DOSING REGIMENS OF ANTI-CD38 ANTIBODIES FOR TREATMENT OF SUBJECTS WITH IMMUNE THROMBOCYTOPENIA

Cross Reference to Related Applications

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application Serial No. 63/564,458 filed on March 12, 2024, U.S. Provisional Application Serial No. 63/647,966 filed on May 15, 2024, U.S. Provisional Application Serial No. 63/661,008 filed on June 17, 2024, U.S. Provisional Application Serial No. 63/713,022 filed on October 28, 2024, and U.S. Provisional Application Serial No. 63/745,261 filed on January 14, 2025, the entire disclosures of which are incorporated herein by reference.

Incorporation By Reference Of Material Submitted Electronically

[0002] The instant application contains a Sequence Listing which has been submitted electronically in XML file format and is hereby incorporated by reference in its entirety. Said XML file, created on March 10, 2025, is named 101588-5018-WO Sequence Listing.xml and is 14,814 bytes in size.

Field

[0003] Methods for treating subjects with autoimmune diseases such as immune thrombocytopenia (ITP) by administering isolated anti-CD38 antibodies are disclosed. Also disclosed are unit dosage forms for the anti-CD38 antibodies used in treating subjects with autoimmune diseases such as ITP.

Background

[0004] Immune thrombocytopenia (ITP), also known as immune thrombocytopenic purpura, is an autoimmune disorder that results in a decreased platelet count and may lead to bleeding events, some of which can be severe or life-threatening. Approximately 20% of subjects with ITP do not respond to currently available treatments, and an additional 20% to 30% of subjects who have an initial response experience relapse, resulting in increased bleeding-related morbidity and diminished quality of life. As such, there is an unmet need for a new safe and effective therapy for treating ITP, with a favorable safety profile, rapid onset of action, the

potential to achieve disease remission and a new standard of long-term durable platelet response, off therapy.

Summary

[0005] Provided herein are methods and unit dosage forms comprising anti-CD38 antibodies or antigen binding fragments thereof used in treating subjects with autoimmune diseases such as immune thrombocytopenia (ITP). AB79 (the drug substance component of mezagitamab) is a fully human recombinant monoclonal antibody (mAb) directed against CD38, an antigen that is highly expressed on plasma cells, plasmablasts, and natural killer (NK) cells and is induced on activated T cells and B cells. AB79 binds specifically to CD38 with high affinity (Kd = 3.5 nM) (US Patent No. US 8,362,211, the contents of which is hereby incorporated by reference in its entirety). AB79 administration results in depletion of cells expressing high levels of CD38 through a mechanism that involves apoptosis, antibody-dependent cell-mediated cytotoxicity, and complement-dependent cytotoxicity (Smithson *et al.* (2017) J. Immunol. 198(1 Supplement): 224.20). AB79 depletes the cells that produce the pathogenic autoantibodies (plasmablasts, plasma cells, and especially long-lived plasma cells). A reduction in plasmablasts and long-lived plasma cells by mezagitamab is expected to result in a reduction in the levels of pathogenic autoantibodies, thereby improving the autoantibody-mediated pathology in ITP.

[0006] It is an objective of the present invention to provide methods of treating subjects with autoimmune diseases such as ITP by subcutaneous administration of an anti-CD38 antibody (*e.g.*, mezagitamab).

[0007] The present disclosure provides methods and unit dosage forms for subcutaneous administration of a therapeutically effective amount of an isolated anti-CD38 antibody or antigen binding fragment to a subject with ITP. In some embodiments, the antibody or antigen binding fragment for subcutaneous administration comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8. In some embodiments, the antibody or

antigen binding fragment for subcutaneous administration comprises a variable heavy chain (VH) region comprising or consisting of SEQ ID NO: 9 (or a sequence with at least 80%, 85%, 90%, 95%, 97% or 99% sequence identity thereto) and a variable light chain (VL) region comprising or consisting of SEQ ID NO: 10 (or a sequence with at least 80%, 85%, 90%, 95%, 97% or 99% sequence identity thereto). In some embodiments, the antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 mg to about 600 mg.

[0008] In some embodiments, the disclosure provides a method of treating immune thrombocytopenia (ITP) in a subject in need thereof, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof.

[0009] In some embodiments, the disclosure provides a method of treating immune thrombocytopenia (ITP) in a subject in need thereof, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8.

[0010] In some embodiments, the isolated antibody or antigen binding fragment thereof is administered in a dosage of from about 100 mg to about 600 mg.

[0011] In some embodiments, the isolated antibody or antigen binding fragment thereof is administered subcutaneously.

[0012] In some embodiments, the disclosure provides a method of treating immune thrombocytopenia (ITP) in a subject in need thereof, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ

ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

[0013] In some embodiments, the disclosure provides a method of reducing the level of plasmablasts, plasma cells, and/or NK cells in a subject diagnosed with immune thrombocytopenia (ITP), the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

[0014] In some embodiments, the disclosure provides a method of reducing the level of immunoglobulin(s) in a subject diagnosed with immune thrombocytopenia (ITP), the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

[0015] In some embodiments, the immunoglobulin is one or more selected from the group consisting of IgA, IgG, and IgM. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a reduction in immunoglobulin(s) in three weeks or

less, two weeks or less, or one week or less. In some embodiments, the immunoglobulin(s) are reduced by at least about 10%, at least about 20%, at least about 30%, at least about 40%, or at least about 50% relative to baseline levels of the immunoglobulin(s).

[0016] In some embodiments, the disclosure provides a method of increasing platelet counts in a subject in need thereof, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

[0017] In some embodiments, the disclosure provides a method of achieving platelet response in a subject in need thereof, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof.

[0018] In some embodiments, the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

[0019] In some embodiments, the platelet response is defined as a platelet count of $\geq$50,000/μL and/or wherein the platelet response is defined as a platelet count of $\geq$30,000/μL and at least doubled from baseline. In some embodiments, the platelet response is further defined as a platelet count of $\geq$20,000/μL above baseline. In some embodiments, the platelet response is defined as a platelet count of $\geq$50,000/μL at about 16 weeks after the administering.

[0020] In some embodiments, the method achieves a platelet response in three weeks or less, two weeks or less, or one week or less.

[0021] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet response for at least 2 cumulative number of weeks, at least 4 cumulative number of weeks, at least 8 cumulative number of weeks, at least 10 cumulative number of weeks, at least 12 cumulative number of weeks, at least 14 cumulative number of weeks, at least 16 cumulative number of weeks, at least 18 cumulative number of weeks, or at least 20 cumulative number of weeks from baseline to about 24 weeks after the administering.

[0022] In some embodiments, the disclosure provides method of achieving a durable platelet response in a subject in need thereof, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

[0023] In some embodiments, the durable platelet response is defined as a sustained platelet response for at least 4 of 6 biweekly measurements from about 10 weeks to about 24 weeks after the administering, wherein the subject has not received a rescue therapy, and wherein the platelet response is defined at a platelet count of $\geq$50,000/μL. In some embodiments, the durable platelet response is defined as a platelet count of $\geq$50,000/μL on at least 2 of 6 weekly platelet measurements from week 10 to week 24. In some embodiments, the durable platelet response is defined as a platelet count of $\geq$50,000/μL on at least 4 of 6 weekly platelet measurements from about 19 weeks to about 24 weeks after the administering.

[0024] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a durable platelet response, wherein the durable platelet response is measured

as the cumulative number of weeks in which platelet count is sustained (e.g., ≥30,000/μL or ≥50,000/μL).

[0025] In some embodiments, the platelet response is sustained for at least about 2 weeks, at least about 4 weeks, at least about 6 weeks, at least about 8 weeks, at least about 10 weeks, at least about 12 weeks, at least about 14 weeks, or at least about 16 weeks after the administration of the isolated human anti-CD38 antibody or antigen binding fragment thereof.

[0026] In some embodiments, the disclosure provides a method of achieving complete platelet response in a subject in need thereof, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

[0027] In some embodiments, the complete platelet response is defined as a platelet count of ≥100,000/μL in at least one measurement from baseline to about 24 weeks after the administering. In some embodiments, the complete platelet response is defined as a platelet count of ≥100,000/μL in at least two measurements from baseline to about 24 weeks after the administering. In some embodiments, the complete platelet response is measured on at least two visits from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks.

[0028] In some embodiments, the disclosure provides a method of achieving a clinically meaningful platelet response in a subject in need thereof, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a

CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

[0029] In some embodiments, the clinically meaningful platelet response is defined as a platelet count ≥20,000/μL above baseline.

[0030] In some embodiments, the clinically meaningful platelet response is measured in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks.

[0031] In some embodiments, the disclosure provides a method of achieving hemostatic platelet response in a subject in need thereof having a baseline platelet count of <15,000/μL, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

[0032] In some embodiments, the hemostatic platelet response is defined as a platelet count of ≥30,000/μL and ≥20,000/μL above baseline.

[0033] In some embodiments, the hemostatic platelet response is measured in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks.

[0034] In some embodiments, the disclosure provides a method of reducing the level of anti-platelet autoantibodies in a subject diagnosed with immune thrombocytopenia (ITP), the method

comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO:8 ; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

[0035] In some embodiments, the disclosure provides a method of reducing immune thrombocytopenia (ITP) disease activity and/or progression in a subject diagnosed with ITP, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

[0036] In some embodiments, the ITP disease activity and/or progression is measured by one or more assessments selected from the group consisting of World Health Organization (WHO) Bleeding Scale, Immune Thrombocytopenic Purpura Subject Assessment Questionnaire (ITP-PAQ), and 5-Level EuroQol Five Dimensions (EQ-5D-5L). In some embodiments, the ITP disease activity and/or progression is measured by a change from baseline in Symptoms, Fatigue/Sleep, Physical Health-Activity, Physical Health-Bother, Psychological Health, Overall Quality of Life, Social Activity, and/or Work scales scores of the ITP-PAQ from baseline to about 24 weeks after the administering. In some embodiments, the ITP disease activity and/or progression is measured by a change from baseline in the Menstrual Symptoms subscale scores of the ITP-PAQ from baseline to about 24 weeks after the administering in a female subject who

had at least one menstrual period within 12 months before the receiving the isolated antibody. In some embodiments, the ITP disease activity and/or progression is measured by a change from baseline in the Fertility subscale scores of the ITP-PAQ in a female subject from baseline to about 24 weeks after the administering. In some embodiments, wherein the ITP disease activity and/or progression is measured by a change from baseline in the EQ-5D-5L utility index score and/or VAS score from baseline to about 24 weeks after the administering. In some embodiments, the ITP disease activity and/or progression is measured by a change in a Symptoms Scale Score of ITP-PAQ from baseline to about 24 weeks after the administering.

[0037] In some embodiments, the disclosure provides a method of reducing bleeding events in a subject diagnosed with immune thrombocytopenia (ITP), the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

[0038] In some embodiments, the bleed events are measured by Immune Thrombocytopenia-specific Bleeding Assessment Tool (ITP-BAT). In some embodiments, the bleeding events comprise Grade $\geq$2 in the Skin domain, Grade $\geq$1 in the Mucosal domain, and/or Grade $\geq$1 in the Organ domain.

[0039] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in ITP remission. In some embodiments, ITP remission is defined as all platelet counts $\geq$50,000/μL for at least about 12 or at least about 24 weeks after any treatment cycle with the isolated antibody or antigen binding fragment thereof in the absence of other therapy for ITP.

[0040] In some embodiments, the disclosure provides a method of treating immune thrombocytopenia (ITP) in a subject diagnosed with ITP, the method comprising administering

to the subject an isolated human anti-CD38 antibody, wherein the isolated antibody comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8, wherein: the ITP is chronic primary ITP or persistent primary ITP; the subject has had an insufficient response or intolerance to other therapy; the other therapy is a first-line ITP therapy and/or a second-line ITP therapy, the other therapy comprises one or more of a corticosteroid, immunoglobulins, splenectomy, a thrombopoietin receptor agonist (TPO-RA) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag), rituximab, fostamatinib, and background ITP medication(s) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag, methotrexate, azathioprine, leflunomide, cyclosporine, fostamatinib, mycophenolate, danazol, dapsone, methylprednisolone, hydrocortisone, cortisone, prednisolone, prednisone, and/or dexamethasone); the isolated antibody is subcutaneously administered in a dosage of about 600 mg in a course of once per week for 8 weeks; optionally wherein the isolated antibody is further administered in more than one course of once per week for 8 weeks; and/or optionally wherein the isolated antibody is not further administered for a period of 8 weeks.

[0041] In some embodiments, the subject in need thereof is diagnosed with immune thrombocytopenia (ITP). In some embodiments, the ITP is primary ITP. In some embodiments, the ITP is persistent ITP. In some embodiments, the ITP is chronic ITP. In some embodiments, the ITP is persistent primary ITP. In some embodiments, the ITP is chronic primary ITP. In some embodiments, the primary ITP has persisted for at least about 3 months.

[0042] In some embodiments, the subject has had a prior response to other therapy excluding a thrombopoietin receptor agonist (TPO-RA), wherein the prior response is defined as achieving a platelet count of $\geq$50,000/mL.

[0043] In some embodiments, wherein the subject has a baseline mean platelet count of $<$30,000/μL from at least 2 consecutive measurements taken at least about 5 days apart; optionally wherein the baseline mean platelet count comprises individual values $\leq$35,000/μL.

[0044] In some embodiments, the subject has had an insufficient response or intolerance to other therapy. In some embodiments, the other therapy is a first-line ITP therapy and/or a second-line ITP therapy. In some embodiments, the other therapy comprises one or more of a corticosteroid, immunoglobulins, splenectomy, a thrombopoietin receptor agonist (TPO-RA) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag), rituximab, fostamatinib, and background ITP medication(s) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag, methotrexate, azathioprine, leflunomide, cyclosporine, fostamatinib, mycophenolate, danazol, dapsone, methylprednisolone, hydrocortisone, cortisone, prednisolone, prednisone, and/or dexamethasone). In some embodiments, the insufficient response to other treatment is defined as failure to achieve a sustained platelet count of at least 50,000/μL or doubling of baseline platelet count after an appropriate course of the other therapy. In some embodiments, the intolerance to other therapy is defined as a documented side effect causing discontinuation of the therapy.

[0045] In some embodiments, the subject in need thereof has an ITP disease duration (*e.g.*, mean ITP disease duration) of at least about 0.1 years, at least about 0.3 years, at least about 0.5 years, at least about 1 year, at least about 5 years, or at least about 10 years.

[0046] In some embodiments, the subject in need thereof has received a mean of about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, or about 13 prior ITP treatments.

[0047] In some embodiments, the other therapy comprises one or more of a corticosteroid, immunoglobulins, splenectomy, a thrombopoietin receptor agonist (TPO-RA), and background ITP medication(s) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag, methotrexate, azathioprine, leflunomide, cyclosporine, fostamatinib, mycophenolate, danazol, dapsone, methylprednisolone, hydrocortisone, cortisone, prednisolone, prednisone, and/or dexamethasone).

[0048] In some embodiments, the isolated antibody or antigen binding fragment thereof further comprises one or more engineered glycoforms, wherein the engineered glycoform comprises glycosylation of one or more polypeptides. In some embodiments, the glycosylation is N-linked glycosylation or O-linked glycosylation. In some embodiments, the glycosylation is N-linked glycosylation.

[0049] In some embodiments, the variable heavy chain region of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 90% to SEQ ID NO: 9, and/or the variable light chain region of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 90% to SEQ ID NO: 10.

[0050] In some embodiments, the variable heavy chain region of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 9, and/or the variable light chain region of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 10.

[0051] In some embodiments, the variable heavy chain region of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 99% to SEQ ID NO: 9, and/or the variable light chain region of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 99% to SEQ ID NO: 10.

[0052] In some embodiments, the heavy chain of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 11; and/or the light chain of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 12.

[0053] In some embodiments, the heavy chain of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 14; and/or the light chain of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 12.

[0054] In some embodiments, the isolated antibody or antigen binding fragment thereof interacts with at least K121, F135, Q139, D141, E239, W241, C275, K276, F284, P291 and E292 of SEQ ID NO: 1 and SEQ ID NO: 2, based on human sequence numbering.

[0055] In some embodiments, the isolated antibody or antigen binding fragment thereof binds to human CD38 (SEQ ID NO: 1) with a KD of 10^{-8} M or a greater affinity, and wherein the affinity is measured by a standard Biacore® assay.

[0056] In some embodiments, the variable heavy chain region comprises SEQ ID NO: 9 and the variable light chain region comprises SEQ ID NO: 10.

[0057] In some embodiments, the isolated antibody or antigen binding fragment thereof comprises a heavy chain as set forth in SEQ ID NO: 11 and a light chain as set forth in SEQ ID NO: 12.

[0058] In some embodiments, the isolated antibody or antigen binding fragment thereof comprises a heavy chain as set forth in SEQ ID NO: 14 and a light chain as set forth in SEQ ID NO: 12.

[0059] In some embodiments, the isolated antibody or antigen binding fragment thereof further comprises an Fc domain. In some embodiments, the Fc domain is a human Fc domain or a variant Fc domain. In some embodiments, the isolated antibody or antigen binding fragment is a human IgG antibody. In some embodiments, the human IgG antibody is a human IgG1 antibody.

[0060] In some embodiments, the subject receives background ITP medication(s). In some embodiments, the background ITP medication(s) is one or more selected from the group consisting of a thrombopoietin receptor agonist (TPO-RA), a corticosteroid, an immunosuppressant, and an inhibitor. In some embodiments, the background ITP medication(s) is one or more selected from the group consisting of romiplostim, eltrombopag, avatrombopag, hetrombopag, methotrexate, azathioprine, leflunomide, cyclosporine, fostamatinib, mycophenolate, danazol, dapsone, methylprednisolone, hydrocortisone, cortisone, prednisolone, prednisone, and dexamethasone. In some embodiments, the background ITP medication(s) is administered in combination with the isolated antibody or antigen binding fragment thereof.

[0061] In some embodiments, the subject in need thereof has a baseline mean platelet count of less than or equal to about 40×10^9/L, less than or equal to about 35×10^9/L, less than or equal to about 30×10^9/L, less than or equal to about 25×10^9/L, or less than or equal to about 20×10^9/L.

[0062] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a length of platelet response of at least about 1 week, at least about 5 weeks, at least about 10 weeks, at least about 15 weeks, at least about 20 weeks, or at least about 25 weeks, wherein the length of the platelet response is defined as the sum of all weeks in which the subject

achieves a platelet response, and wherein the platelet response is defined as a platelet count of ≥50,000/μL.

[0063] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet response, wherein the platelet response is defined as a platelet count of ≥50,000/μL and/or wherein the platelet response is defined as a platelet count of ≥30,000/μL and at least doubled from baseline. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet response, wherein the platelet response is defined as a platelet count of ≥50,000/μL at about 16 weeks after the administering. In some embodiments, the platelet response is further defined as a platelet count of ≥20,000/μL above baseline.

[0064] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet response in three weeks or less, two weeks or less, or one week or less.

[0065] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet response for at least 2 cumulative number of weeks, at least 4 cumulative number of weeks, at least 8 cumulative number of weeks, at least 10 cumulative number of weeks, at least 12 cumulative number of weeks, at least 14 cumulative number of weeks, at least 16 cumulative number of weeks, at least 18 cumulative number of weeks, or at least 20 cumulative number of weeks from baseline to about 24 weeks after the administering.

[0066] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a durable platelet response, wherein the durable platelet response is defined as a sustained platelet response for at least 4 of 6 biweekly measurements from about 10 weeks to about 24 weeks after the administering, wherein the subject has not received a rescue therapy, and wherein the platelet response is defined at a platelet count of ≥50,000/μL. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a durable platelet response, wherein the durable platelet response is defined as a platelet count of ≥50,000/μL on at least 2 of 6 weekly platelet measurements from about 10 weeks to about 24 weeks after the administering. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a durable platelet response, wherein the durable

platelet response is defined as a platelet count of ≥50,000/μL on at least 4 of 6 weekly platelet measurements from about 19 weeks to about 24 weeks after the administering.

[0067] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a durable platelet response, wherein the durable platelet response is measured as the cumulative number of weeks in which platelet count is sustained (e.g., ≥30,000/μL or ≥50,000/μL).

[0068] In some embodiments, the platelet response is sustained for at least about 2 weeks, at least about 4 weeks, at least about 6 weeks, at least about 8 weeks, at least about 10 weeks, at least about 12 weeks, at least about 14 weeks, or at least about 16 weeks after the administration of the isolated human anti-CD38 antibody or antigen binding fragment thereof.

[0069] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a complete platelet response, wherein the complete platelet response is defined as a platelet count of ≥100,000/μL in at least one measurement from baseline to about 24 weeks after the administering. In some embodiments, the subject has not received a rescue therapy in the previous four weeks. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a complete platelet response, wherein the complete platelet response is defined as a platelet count of ≥100,000/μL in at least two measurements from baseline to about 24 weeks after the administering.

[0070] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a clinically meaningful platelet response, wherein the clinically meaningful platelet response is defined as a platelet count of ≥20,000/μL above baseline in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks.

[0071] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a hemostatic platelet response, wherein the hemostatic platelet response is defined as a platelet count of ≥30,000/μL and ≥20,000/μL above baseline in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a in the previous four weeks and the subject has a baseline platelet count of <15,000/μL.

[0072] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet count of >10,000/μL, >20,000/μL, >30,000/μL, >40,000/μL, >50,000/μL, >60,000/μL, >70,000/μL, >80,000/μL, >90,000/μL, or >100,000/μL. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet count of >50,000/μL. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet count of >100,000/μL.

[0073] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in less than 75%, less than 50%, or less than 25% incidence of use of a rescue therapy. In some embodiments, the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the method does not include the use of a rescue therapy.

[0074] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a reduction in ITP disease activity and/or progression in a subject diagnosed with ITP. In some embodiments, the ITP disease activity and/or progression is measured by one or more assessments selected from the group consisting of World Health Organization (WHO) Bleeding Scale, Immune Thrombocytopenic Purpura Subject Assessment Questionnaire (ITP-PAQ), and 5-Level EuroQol Five Dimensions (EQ-5D-5L); optionally wherein the ITP disease activity and/or progression is measured by a change in a Symptoms Scale Score of ITP-PAQ from baseline to about 24 weeks after the administering. In some embodiments, the ITP disease activity and/or progression is measured by a change from baseline in Symptoms, Fatigue/Sleep, Physical Health-Activity, Physical Health-Bother, Psychological Health, Overall Quality of Life, Social Activity, and/or Work scales scores of the ITP-PAQ from baseline to about 24 weeks after the administering. In some embodiments, the ITP disease activity and/or progression is measured by a change from baseline in the Menstrual Symptoms subscale scores of the ITP-PAQ from baseline to about 24 weeks after the administering in a female subject who had at least one menstrual period within 12 months before the receiving the isolated antibody. In some embodiments, the ITP disease activity and/or progression is measured by a change from baseline in the Fertility subscale scores of the ITP-PAQ in a female subject from baseline to about 24 weeks after the administering. In some embodiments, the ITP disease activity and/or progression is measured by a change from baseline in the EQ-5D-5L utility index score and/or VAS score from baseline to about 24 weeks after the administering. In some embodiments, the ITP disease

activity and/or progression is measured by a change in a Symptoms Scale Score of ITP-PAQ from baseline to about 24 weeks after the administering.

[0075] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a reduction in bleeding events in the subject. In some embodiments, the bleed events are measured by Immune Thrombocytopenia-specific Bleeding Assessment Tool (ITP-BAT). In some embodiments, the bleeding events comprise Grade $\geq$2 in the Skin domain, Grade $\geq$1 in the Mucosal domain, and/or Grade $\geq$1 in the Organ domain.

[0076] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in ITP remission. In some embodiments, ITP remission is defined as all platelet counts $\geq$50,000/μL for at least about 12 or at least about 24 weeks after any treatment cycle with the isolated antibody or antigen binding fragment thereof in the absence of other therapy for ITP.

[0077] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a reduction in immunoglobulin(s). In some embodiments, the immunoglobulin is one or more selected from the group consisting of IgA, IgG, and IgM. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a reduction in immunoglobulin(s) in three weeks or less, two weeks or less, or one week or less. In some embodiments, the immunoglobulin(s) are reduced by at least about 10%, at least about 20%, at least about 30%, at least about 40%, or at least about 50% relative to baseline levels of the immunoglobulin(s).

[0078] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in less than 10% incidence of grade 3 or 4 of one or more treatment-related adverse events (TRAEs) or treatment-emergent adverse events (TEAEs). In some embodiments, the TRAEs or TEAEs are selected from the group consisting of gingival bleeding, heavy menstrual bleeding, haematochezia, mouth haemorrhage, haematoma, traumatic haematoma, epistaxis, petechiae, ecchymosis, conjunctival haemorrhage, blood urine, and haemorrhagic ovarian cyst. In some embodiments, a TRAE or TEAE resulting from administering the isolated antibody or antigen binding fragment thereof has a maximum intensity of Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or Grade 2. In some embodiments, administering

the isolated antibody or antigen binding fragment thereof results in a reduction in ITP-associated bleeding adverse events (AEs) relative to placebo.

[0079] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a reduction in dose and/or frequency of use of background ITP medication(s).

[0080] In some embodiments, the isolated antibody or antigen binding fragment thereof is administered in a dosage selected from the group consisting of about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, and about 600 mg. In some embodiments, the isolated antibody or antigen binding fragment thereof is administered in a dosage of about 100 mg. In some embodiments, the isolated antibody or antigen binding fragment thereof is administered in a dosage of about 300 mg. In some embodiments, the isolated antibody or antigen binding fragment thereof is administered in a dosage of about 600 mg.

[0081] In some embodiments, the isolated antibody or antigen binding fragment thereof is administered once every week, once every two weeks, once every three weeks or once every four weeks.

[0082] In some embodiments, (a) the isolated antibody is administered once per week for from 1 week to 16 weeks; (b) the isolated antibody is not administered for a period of from 1 week to 16 weeks; and (c) the isolated antibody is administered once per week for from 1 week to 16 weeks. In some embodiments, (a) the isolated antibody is administered once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; and (c) the isolated antibody is administered once per week for 8 weeks. In some embodiments, (a) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; and (c) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks. In some embodiments, (a) the isolated antibody is administered once per week for from 1 week to 16 weeks; (b) the isolated antibody is not administered for a period of from 1 week to 16 weeks; (c) the isolated antibody is administered once per week for from 1 week to 16 weeks; and (d) the

isolated antibody is not administered for a period of from 1 week to 16 weeks. In some embodiments, (a) the isolated antibody is administered once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; (c) the isolated antibody is administered once per week for 8 weeks; and (d) the isolated antibody is not administered for a period of 8 weeks. In some embodiments, (a) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; (c) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks; and (d) the isolated antibody is not administered for a period of 8 weeks.

[0083] In some embodiments, the isolated antibody or antigen binding fragment thereof is administered in the form of a pharmaceutically acceptable composition. In some embodiments, the pharmaceutically acceptable composition comprises the isolated antibody or antigen binding fragment thereof and at least one pharmaceutically acceptable carrier, excipient, or stabilizer.

[0084] In some embodiments, the isolated antibody or antigen binding fragment thereof comprises a heavy chain as set forth in SEQ ID NO: 11 and a light chain as set forth in SEQ ID NO: 12; and wherein the antibody or antigen binding fragment thereof is subcutaneously administered once per week for 8 weeks.

[0085] In some embodiments, the isolated antibody or antigen binding fragment thereof comprises a heavy chain as set forth in SEQ ID NO: 14 and a light chain as set forth in SEQ ID NO: 12; and wherein the antibody or antigen binding fragment thereof is subcutaneously administered once per week for 8 weeks.

[0086] In some embodiments, the isolated antibody or antigen binding fragment thereof is mezagitamab.

[0087] In some embodiments, the isolated antibody or antigen binding fragment thereof is from about 2 times to about 4 times more efficacious than fostamatinib and/or efgartigimod. In some embodiments, the isolated antibody or antigen binding fragment thereof results in from about 2 times to about 4 times more durable platelet response as compared to fostamatinib and/or efgartigimod.

[0088] In some embodiments, the disclosure provides a unit dosage form comprising an isolated antibody or antigen binding fragment thereof that comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; wherein the isolated antibody or antigen binding fragment thereof binds to human CD38 (SEQ ID NO: 1), and the unit dosage form is formulated for subcutaneous administration of the isolated antibody or antigen binding fragment thereof at a dosage of from about 100 mg to about 600 mg in the treatment of ITP.

[0089] In some embodiments, the disclosure provides a unit dosage form comprising an isolated human anti-CD38 antibody that comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; wherein the isolated antibody or antigen binding fragment thereof binds to human CD38 (SEQ ID NO: 1), and the unit dosage form is formulated for subcutaneous administration of the isolated antibody or antigen binding fragment thereof at a dosage of about 600 mg in a course of once per week for 8 weeks in the treatment of chronic primary ITP or persistent primary ITP in a subject that has had an insufficient response or intolerance to other therapy; wherein the other therapy is a first-line ITP therapy and/or a second-line ITP therapy, wherein the other therapy comprises one or more of a corticosteroid, immunoglobulins, splenectomy, a thrombopoietin receptor agonist (TPO-RA) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag), rituximab, fostamatinib, and background ITP medication(s) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag, methotrexate, azathioprine, leflunomide, cyclosporine, fostamatinib, mycophenolate, danazol, dapsone, methylprednisolone, hydrocortisone, cortisone, prednisolone, prednisone, and/or dexamethasone); optionally wherein the isolated antibody is further administered in more than

one course of once per week for 8 weeks, and/or optionally wherein the isolated antibody is not further administered for a period of 8 weeks.

[0090] In some embodiments, the isolated antibody or antigen binding fragment thereof further comprises one or more engineered glycoforms, wherein the engineered glycoform comprises glycosylation of one or more polypeptides. In some embodiments, the glycosylation is N-linked glycosylation or O-linked glycosylation. In some embodiments, the glycosylation is N-linked glycosylation.

[0091] In some embodiments, the variable heavy chain region of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 90% to SEQ ID NO: 9, and/or the variable light chain region of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 90% to SEQ ID NO: 10.

[0092] In some embodiments, the variable heavy chain region comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 9, and/or the variable light chain region comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 10.

[0093] In some embodiments, the variable heavy chain region comprises an amino acid sequence having an identity of at least 99% to SEQ ID NO: 9, and/or the variable light chain region comprises an amino acid sequence having an identity of at least 99% to SEQ ID NO: 10.

[0094] In some embodiments, the heavy chain of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 11, and/or the light chain of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 12.

[0095] In some embodiments, the heavy chain of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 14, and/or the light chain of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 12.

[0096] In some embodiments, the isolated antibody or antigen binding fragment thereof interacts with at least K121, F135, Q139, D141, E239, W241, C275, K276, F284, P291 and E292 of SEQ ID NO: 1 and SEQ ID NO: 2, based on human sequence numbering.

[0097] In some embodiments, the isolated antibody or antigen binding fragment thereof binds to human CD38 (SEQ ID NO: 1) with a KD of 10^{-8} M or a greater affinity, and wherein the affinity is measured by a standard Biacore® assay.

[0098] In some embodiments, the variable heavy chain region comprises SEQ ID NO: 9 and the variable light chain region comprises SEQ ID NO: 10.

[0099] In some embodiments, the isolated antibody or antigen binding fragment thereof comprises a heavy chain as set forth in SEQ ID NO: 11 and a light chain as set forth in SEQ ID NO: 12.

[0100] In some embodiments, the isolated antibody or antigen binding fragment thereof comprises a heavy chain as set forth in SEQ ID NO: 14 and a light chain as set forth in SEQ ID NO: 12.

[0101] In some embodiments, wherein the isolated antibody or antigen binding fragment thereof further comprises an Fc domain. In some embodiments, the Fc domain is a human Fc domain or a variant Fc domain. In some embodiments, the isolated antibody or antigen binding fragment is a human IgG antibody. In some embodiments, the human IgG antibody is a human IgG1 antibody.

[0102] In some embodiments, wherein the isolated antibody or antigen binding fragment thereof is used in combination with one or more background ITP medication(s). In some embodiments, the background ITP medication(s) is one or more selected from the group consisting of a thrombopoietin receptor agonist (TPO-RA), a corticosteroid, an immunosuppressant, and an inhibitor. In some embodiments, the background ITP medication(s) is one or more selected from the group consisting of romiplostim, eltrombopag, avatrombopag, hetrombopag, methotrexate, azathioprine, leflunomide, cyclosporine, fostamatinib, mycophenolate, danazol, dapsone, methylprednisolone, hydrocortisone, cortisone, prednisolone, prednisone, and dexamethasone.

[0103] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a length of platelet response of at least about 1 week, at least about 5 weeks, at least about 10 weeks, at least about 15 weeks, at least about 20 weeks, or at least about 25 weeks, wherein the length of the platelet response is defined as the sum of all weeks in which the subject achieves a platelet response, and wherein the platelet response is defined as a platelet count of ≥50,000/μL.

[0104] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet response, wherein the platelet response is defined as a platelet count of ≥50,000/μL and/or wherein the platelet response is defined as a platelet count of ≥30,000/μL and at least doubled from baseline. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet response, wherein the platelet response is further defined as a platelet count of ≥20,000/μL above baseline. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet response, wherein the platelet response is defined as a platelet count of ≥50,000/μL at about 16 weeks after the administering.

[0105] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet response, wherein the platelet response is achieved in three weeks or less, two weeks or less, or one week or less. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet response for at least 2 cumulative number of weeks, at least 4 cumulative number of weeks, at least 8 cumulative number of weeks, at least 10 cumulative number of weeks, at least 12 cumulative number of weeks, at least 14 cumulative number of weeks, at least 16 cumulative number of weeks, at least 18 cumulative number of weeks, or at least 20 cumulative number of weeks from baseline to about 24 weeks after the administering.

[0106] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a durable platelet response, wherein the durable platelet response is defined as a durable platelet response for at least 4 of 6 biweekly measurements from about 10 weeks to about 24 weeks after the administering, wherein the subject has not received a rescue therapy, and wherein the platelet response is defined at a platelet count of ≥50,000/μL. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in

a durable platelet response, wherein the durable platelet response is defined as a platelet count of ≥50,000/μL on at least 2 of 6 weekly platelet measurements from about 10 weeks to about 24 weeks after the administering. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a durable platelet response, wherein the durable platelet response is defined as a platelet count of ≥50,000/μL on at least 4 of 6 weekly platelet measurements from about 19 weeks to about 24 weeks after the administering.

[0107] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a durable platelet response, wherein the durable platelet response is measured as the cumulative number of weeks in which platelet count is sustained (e.g., ≥30,000/μL or ≥50,000/μL).

[0108] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a durable platelet response, wherein the platelet response is sustained for at least about 2 weeks, at least about 4 weeks, at least about 6 weeks, at least about 8 weeks, at least about 10 weeks, at least about 12 weeks, at least about 14 weeks, or at least about 16 weeks after the administration of the isolated human anti-CD38 antibody or antigen binding fragment thereof.

[0109] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a complete platelet response, wherein the complete platelet response is defined as a platelet count of ≥100,000/μL on at least two visits from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a complete platelet response, wherein the complete platelet response is defined as a platelet count of ≥100,000/μL in at least one measurement from baseline to about 24 weeks after the administering. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a complete platelet response, wherein the complete platelet response is defined as a platelet count of ≥100,000/μL in at least two measurements from baseline to about 24 weeks after the administering.

[0110] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a clinically meaningful platelet response, wherein the clinically meaningful

platelet response is defined as a platelet count of ≥20,000/μL above baseline in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks.

[0111] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a hemostatic platelet response, wherein the hemostatic platelet response is defined as a platelet count of ≥30,000/μL and ≥20,000/μL above baseline in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks and the subject has a baseline platelet count of <15,000/μL.

[0112] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet count of >10,000/μL, >20,000/μL, >30,000/μL, >40,000/μL, >50,000/μL, >60,000/μL, >70,000/μL, >80,000/μL, >90,000/μL, or >100,000/μL. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet count of >50,000/μL. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet count of >100,000/μL.

[0113] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in less than 75%, less than 50%, or less than 25% incidence of use of a rescue therapy. In some embodiments, the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the unit dosage form does not include the use of a rescue therapy.

[0114] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a reduction in ITP disease activity and/or progression in a subject diagnosed with ITP. In some embodiments, the ITP disease activity and/or progression is measured by one or more assessments selected from the group consisting of World Health Organization (WHO) Bleeding Scale, Immune Thrombocytopenic Purpura Subject Assessment Questionnaire (ITP-PAQ), and 5-Level EuroQol Five Dimensions (EQ-5D-5L); optionally wherein the ITP disease activity and/or progression is measured by a change in a Symptoms Scale Score of ITP-PAQ from baseline to about 24 weeks after the administering. In some embodiments, the ITP disease activity and/or progression is measured by a change from baseline in Symptoms, Fatigue/Sleep, Physical Health-Activity, Physical Health-Bother, Psychological Health, Overall Quality of Life,

Social Activity, and/or Work scales scores of the ITP-PAQ from baseline to about 24 weeks after the administering. In some embodiments, the ITP disease activity and/or progression is measured by a change from baseline in the Menstrual Symptoms subscale scores of the ITP-PAQ from baseline to about 24 weeks after the administering in a female subject who had at least one menstrual period within 12 months before the receiving the isolated antibody. In some embodiments, the ITP disease activity and/or progression is measured by a change from baseline in the Fertility subscale scores of the ITP-PAQ in a female subject from baseline to about 24 weeks after the administering. In some embodiments, the ITP disease activity and/or progression is measured by a change from baseline in the EQ-5D-5L utility index score and/or VAS score from baseline to about 24 weeks after the administering. In some embodiments, the ITP disease activity and/or progression is measured by a change in a Symptoms Scale Score of ITP-PAQ from baseline to about 24 weeks after the administering.

[0115] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a reduction in bleeding events in the subject. In some embodiments, the bleed events are measured by Immune Thrombocytopenia-specific Bleeding Assessment Tool (ITP-BAT). In some embodiments, the bleeding events comprise Grade $\geq$2 in the Skin domain, Grade $\geq$1 in the Mucosal domain, and/or Grade $\geq$1 in the Organ domain.

[0116] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in ITP remission. In some embodiments, ITP remission is defined as all platelet counts $\geq$50,000/μL for at least about 12 or at least about 24 weeks after any treatment cycle with the isolated antibody or antigen binding fragment thereof in the absence of other therapy for ITP.

[0117] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a reduction in immunoglobulin(s). In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a reduction in immunoglobulin(s), wherein the immunoglobulin is one or more selected from the group consisting of IgA, IgG, and IgM. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a reduction in immunoglobulin(s), wherein the reduction in immunoglobulin(s) is achieved in three weeks or less, two weeks or less, or one week or less. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a reduction in immunoglobulin(s), wherein the immunoglobulin(s) are

reduced by at least about 10%, at least about 20%, at least about 30%, at least about 40%, or at least about 50% relative to baseline levels of the immunoglobulin(s).

[0118] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in less than 10% incidence of grade 3 or 4 of one or more treatment-related adverse events (TRAEs) or treatment-emergent adverse events (TEAEs). In some embodiments, the TRAEs or TEAEs are selected from the group consisting of gingival bleeding, heavy menstrual bleeding, haematochezia, mouth haemorrhage, haematoma, traumatic haematoma, epistaxis, petechiae, ecchymosis, conjunctival haemorrhage, blood urine, and haemorrhagic ovarian cyst. In some embodiments, a TRAE or TEAE resulting from administering the isolated antibody or antigen binding fragment thereof has a maximum intensity of Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or Grade 2. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results a reduction in ITP-associated bleeding adverse events (AEs) relative to placebo.

[0119] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a reduction in dose and/or frequency of use of background ITP medication(s).

[0120] In some embodiments, the isolated antibody or antigen binding fragment thereof is administered in a dosage selected from the group consisting of about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, and about 600 mg. In some embodiments, the isolated antibody or antigen binding fragment thereof is administered in a dosage of about 100 mg. In some embodiments, the isolated antibody or antigen binding fragment thereof is administered in a dosage of about 300 mg. In some embodiments, the isolated antibody or antigen binding fragment thereof is administered in a dosage of about 600 mg.

[0121] In some embodiments, the dosage is a dosage administered once every week, once every two weeks, once every three weeks or once every four weeks.

[0122] In some embodiments, (a) the isolated antibody is administered once per week for from 1 week to 16 weeks; (b) the isolated antibody is not administered for a period of from 1 week to 16

weeks; and (c) the isolated antibody is administered once per week for from 1 week to 16 weeks. In some embodiments, (a) the isolated antibody is administered once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; and (c) the isolated antibody is administered once per week for 8 weeks. In some embodiments, (a) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; and (c) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks. In some embodiments, (a) the isolated antibody is administered once per week for from 1 week to 16 weeks; (b) the isolated antibody is not administered for a period of from 1 week to 16 weeks; (c) the isolated antibody is administered once per week for from 1 week to 16 weeks; and (d) the isolated antibody is not administered for a period of from 1 week to 16 weeks. In some embodiments, (a) the isolated antibody is administered once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; (c) the isolated antibody is administered once per week for 8 weeks; and (d) the isolated antibody is not administered for a period of 8 weeks. In some embodiments, (a) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; (c) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks; and (d) the isolated antibody is not administered for a period of 8 weeks.

[0123] In some embodiments, the unit dosage form further comprises at least one pharmaceutically acceptable carrier, excipient, or stabilizer.

[0124] In some embodiments, the isolated antibody or antigen binding fragment thereof comprises a heavy chain as set forth in SEQ ID NO: 11 and a light chain as set forth in SEQ ID NO: 12; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered once per week for 8 weeks.

[0125] In some embodiments, the isolated antibody or antigen binding fragment thereof comprises a heavy chain as set forth in SEQ ID NO: 14 and a light chain as set forth in SEQ ID NO: 12; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered once per week for 8 weeks.

[0126] In some embodiments, the isolated antibody or antigen binding fragment thereof is administered to a subject once a week for 8 weeks.

[0127] In some embodiments, the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of about 600 mg.

[0128] In some embodiments, the isolated antibody or antigen binding fragment thereof is mezagitamab.

[0129] In some embodiments, the ITP is persistent or chronic ITP in an adult human.

[0130] In some embodiments, the subject is an adult.

[0131] In some embodiments, the subject has had an insufficient response or intolerance to other therapy.

[0132] In some embodiments, the isolated antibody or antigen binding fragment thereof is mezagitamab.

[0133] In some embodiments, the ITP is primary ITP. In some embodiments, the ITP is persistent ITP. In some embodiments, the ITP is chronic ITP. In some embodiments, the ITP is persistent or chronic primary ITP. In some embodiments, the primary ITP has persisted for at least about 3 months. In some embodiments, wherein the subject has had a prior response to other therapy excluding a thrombopoietin receptor agonist (TPO-RA), wherein the prior response is defined as achieving a platelet count of $\geq$50,000/mL. In some embodiments, the subject has a baseline mean platelet count of $<$30,000/μL from at least 2 consecutive measurements taken at least about 5 days apart; optionally wherein the baseline mean platelet count comprises individual values $\leq$35,000/μL.

[0134] In some embodiments, the unit dosage form is administered to a subject having an insufficient response or intolerance to other therapy. In some embodiments, wherein the other therapy is a first-line ITP therapy and/or a second-line ITP therapy. In some embodiments, the other therapy comprises one or more of a corticosteroid, immunoglobulins, splenectomy, a thrombopoietin receptor agonist (TPO-RA) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag), rituximab, fostamatinib, and background ITP medication(s) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag, methotrexate, azathioprine, leflunomide,

cyclosporine, fostamatinib, mycophenolate, danazol, dapsone, methylprednisolone, hydrocortisone, cortisone, prednisolone, prednisone, and/or dexamethasone). In some embodiments, the insufficient response to other treatment is defined as failure to achieve a sustained platelet count of at least 50,000/μL or doubling of baseline platelet count after an appropriate course of the other therapy. In some embodiments, the intolerance to other therapy is defined as a documented side effect causing discontinuation of the therapy.

[0135] In some embodiments, the unit dosage form is administered to a subject having an ITP disease duration (*e.g.*, mean ITP disease duration) of at least about 0.1 years, at least about 0.3 years, at least about 0.5 years, at least about 1 year, at least about 5 years, or at least about 10 years.

[0136] In some embodiments, the unit dosage form is administered to a subject having received a mean of about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, or about 13 prior ITP treatments.

[0137] In some embodiments, the disclosure provides an isolated human anti-CD38 antibody or antigen binding fragment thereof for use in the treatment of immune thrombocytopenia (ITP), wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8.

[0138] In some embodiments, the disclosure provides a pharmaceutical composition comprising an isolated human anti-CD38 antibody or antigen binding fragment thereof for treating immune thrombocytopenia (ITP) comprising an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a

CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8.

[0139] In some embodiments, the disclosure provides a medicament for treating immune thrombocytopenia (ITP) comprising an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8.

[0140] In some embodiments, the disclosure provides a use of an isolated human anti-CD38 antibody or antigen binding fragment thereof in the manufacture of a medicament for treating immunoglobulin A nephropathy (IgAN), wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8.

Brief Description of the Drawings

[0141] The objects and features of the invention may be better understood by reference to the drawings described below.

[0142] **Figure 1** shows the mechanism of action of various pharmacological agents in treating ITP.

[0143] **Figure 2A** shows the Phase 2 study design. The primary objective was to evaluate the safety and tolerability of mezagitamab in subjects with persistent/chronic primary ITP. The secondary objective was to assess the effects of mezagitamab administration on platelet counts in subjects with persistent/chronic primary ITP.

[0144] Figure 2B shows the Phase 2 study schematic. LFP: long-term follow-up period; SFP: safety follow-up period.

[0145] Figure 2C shows the two part, Phase 2, randomized, double-blind, placebo-controlled study that evaluated the safety and efficacy of mezagitamab.

[0146] Figure 3A shows the subject disposition of the main study (enrolled set, *i.e.*, all randomized subjects).

Figure 3B shows the participant flow diagram from the phase 2 study. IP, investigational product. *Due to adverse event. **After completion of the main study but before enrolment in the open-label extension. †Due to withdrawal by participant or other reason. ‡Due to withdrawal by participant.

[0147] Figure 4A shows platelet response (PR) by week 16. >60% PR was observed at all three dose levels; 600 mg mezagitamab reached to >90% PR. *Without a dosing period-permitted rescue treatment in the previous 4 weeks and without any other previous rescue therapy. For hemostatic platelet response, the percentages are based on all subjects in the full analysis set with baseline platelet count <15,000/μL. n = number of subjects with the response; N = number of total subjects; BL = baseline; p-value based on Bernard's test.

[0148] Figure 4B shows platelet responses at week 16 (secondary endpoints, efficacy). PR, platelet response; n, number of patients with the response; N, number of total patients. PR defined as PC ≥50,000/μL and ≥20,000/μL above BL on ≥2 visits*; Complete PR defined as PC ≥100,000/μL on ≥2 visits*; Clinically meaningful PR defined as PC ≥20,000/μL above BL on ≥2 visits*; Hemostatic PR defined as PC ≥30,000/μL and ≥20,000/μL above BL on ≥2 visits* (*without a dosing period–permitted rescue treatment in the previous 4 weeks and without other previous rescue therapy; for hemostatic platelet response, the percentages are based on all patients in the full analysis set with baseline platelet count <15,000/μL; P-value based on Barnard's test).

[0149] Figure 5 shows platelet count (10^9/L) change from baseline over time through week 16: dose-dependent increase over time with mezagitamab treatment (Mixed Effects Model for Repeated Measures). LS: least squares; SEM: standard error of the mean.

[0150] Figure 6 shows the change from baseline platelet counts (10^9/L) in mezagitamab cohorts (combined) versus placebo cohort.

[0151] Figure 7 shows mezagitamab demonstrated favorable durable platelet (PLT) response off therapy in comparison with the platelet responses achieved in clinical trials of fostamatinib (Syk Inhibitor, approved in 2018 for ITP) and efgartigimod (anti-FcRn) on therapy. Durable platelet response: mezagitamab, subjects achieving PLT counts of at least $50x10^9$/L for at least 4 out of the last 6 visits between study week 10 and week 24 of the main study period for the mezagitamab group; placebo, subjects for at least 2 of the last 3 visits between week 12 and week 16 for the placebo group (the use of rescue therapy was considered for this ad hoc analysis). For the interim analysis, in the TAK-079 600 mg cohort, 7/11 subjects completed week 20 and 4/11 subjects completed week 24.

[0152] Figure 8 shows the distribution of observed post dose serum concentrations (C_{trough}) resulting from multiple SC administrations of mezagitamab (100 mg, 300 mg, and 600 mg) in subjects with ITP (Phase 2 Study; interim analysis). The figure shows a sustained dose-exposure relationship, less than moderate variability, and no impact of key intrinsic factors (age, sex, and race). Mezagitamab follows target-mediated drug disposition, and observed PK exposures were generally consistent with previously completed studies (*i.e.*, RRMM, MG, and SLE).

[0153] Figure 9 shows dose dependent serum immunoglobulins reductions (observed mean change from baseline) resulting from multiple SC administrations of mezagitamab (100 mg, 300 mg, and 600 mg) in subjects with ITP (Phase 2 study, interim analysis). The figure shows rapid, profound, and sustained dose-dependent immunoglobulin reductions (including IgG) closely pertinent to ITP pathogenesis. At the highest dose of 600 mg, immunoglobulin reductions were generally consistent with other studies, and levels gradually returned to baseline starting from study week 20.

[0154] Figure 10 shows the exposure-response analysis. Exposure-dependent improvement in platelet count and extended duration of response were observed, and the effect appears to be saturated at the higher end of drug exposures.

[0155] Figure 11 shows the trial schema for the Phase 3 study in Example 2. Subjects who meet all eligibility criteria during screening are randomly assigned in a 2:1 ratio to receive mezagitamab 600 mg or placebo QW for 8 weeks.

[0156] Figure 12 shows the trial schema for the Phase 3 study in Example 3.

[0157] Figure 13 shows the duration of platelet response through week 16. Data are presented as mean + SD. *Duration of platelet response is defined as the number of weeks with platelet count ≥50,000/μL.

[0158] Figure 14 shows the change from baseline in ITP-PAQ scale scores at week 16. The data are presented as model-based mean and standard error of the mean.

[0159] Figure 15 shows the mean change from baseline in ITP-PAQ scale scores at week 16. The data are presented as model-based mean and standard error of the mean.

[0160] Figure 16A shows the observed mean percentage change from baseline in total plasmablasts.

[0161] Figure 16B shows the observed mean percentage change from baseline in total CD38+ B cells.

[0162] Figure 16C shows the observed mean percentage change from baseline in total NK cells.

[0163] Figure 16D shows the observed mean percentage change from baseline in total CD38+ NK cells.

[0164] Figure 16E shows the percentage change from baseline in IgG.

Detailed Description

[0165] Increased expression of CD38 has been documented in a variety of diseases, including autoimmune diseases such as immune thrombocytopenia (ITP). CD38 is a type II glycoprotein that is highly and uniformly expressed on antibody-producing plasmablasts and plasma cells, making it a potential target for treatment of ITP. The significantly higher CD38 expression on plasma cells and plasmablasts compared with other immune cells suggests the potential for selectively depleting these cells with an anti-CD38 antibody.

[0166] Mezagitamab is a full-length, human IgG1 monoclonal antibody (mAb) directed against human CD38. Mezagitamab selectively depletes cells expressing high levels of the CD38 target by antibody-dependent cell mediated cytotoxicity, complement-dependent cytotoxicity (CDC), antibody-dependent phagocytosis, and apoptosis. CD38 is uniformly and constitutively highly expressed on antibody-producing plasma cells and plasmablasts as well as on subsets of natural killer (NK) cells, B cells, and T cells. Sensitivity of cells to lysis by mezagitamab depends, in part, on the level of cell-surface CD38 expression such that cells having high levels of CD38 expression are depleted more effectively than cells with low levels of CD38 expression. The depletion of plasma cells and plasmablasts by mezagitamab in patients with ITP is expected to reduce the production of antiplatelet antibodies, thereby decreasing disease activity.

[0167] Daratumumab (DARZALEX®), a commercially available anti-CD38 antibody, showed encouraging preliminary data for the treatment of ITP in three patients (Tsykunova *et al.* HemaSphere, 2022 Jun; 6(Suppl): 2182-2183). Two of the three patients responded to the study treatment at week 12, and one relapsed by week 24. The results demonstrated only a slight decrease in immunoglobulin G levels and no serious adverse events >grade 2 were reported. Daratumumab was also demonstrated to successfully treat thrombocytopenia in a patient after an allogenic transplant (Migdady, Y. *et al.*, Blood Advances, 2020, 4(5): 815-818). Intravenous daratumumab has been approved for subjects with multiple myeloma (relapsed and newly diagnosed). However, the most frequent adverse reactions (≥20%) with daratumumab monotherapy or in combination with standard anti-myeloma regimens are infusion-related reactions (IRRs), neutropenia, thrombocytopenia, fatigue, nausea, diarrhea, constipation, vomiting, muscle spasms, arthralgia, back pain, pyrexia, chills, dizziness, insomnia, cough, dyspnea, peripheral edema, peripheral sensory neuropathy, and upper respiratory tract infections (DARZALEX® USPI). Daratumumab can cause severe and/or serious infusion reactions including anaphylactic reactions and have been reported in approximately half of all subjects (DARZALEX® USPI). Attention must also be paid to daratumumab interference with certain laboratory assays, which importantly may complicate blood compatibility testing.

[0168] Other antibodies targeting CD38 are known (*see*, *e.g.,* WO 2006/125640 incorporated herein by reference in its entirety, which discloses four human antibodies: MOR03077, MOR03079, MOR03080, and MOR03100 and two murine antibodies: OKT10 and IB4). These

prior art antibodies are inferior to mezagitamab for a variety of reasons. MOR03080 binds to human CD38 and cynomolgus CD38 but with a low affinity to human CD38 (Biacore KD = 27.5 nm). OKT10 binds to human CD38 and cynomolgus CD38 but with a low/moderate affinity to human CD38 (Biacore KD = 8.28 nm). MOR03079 binds to human CD38 with a high affinity (Biacore KD = 2.4 nm) but does not bind to cynomolgus CD38. MOR03100 and MOR03077 bind to human CD38 with moderate or low affinity (Biacore KD = 10 nm and 56 nm, respectively). By comparison, mezagitamab binds to human and cynomolgus CD38 with a high affinity (to human CD38 with Biacore KD = 5.4 nm). Moreover, the prior art antibodies have poor antibody dependent cellular cytotoxicity (ADCC) as well as complement dependent cytotoxicity (CDC) activity.

[0169] An advantage of more efficient ADCC is the ability to deliver an anti-CD38 therapeutic as a low volume injection. A safety profile and pharmacodynamic (PD) target effect was observed after mezagitamab, at a dose up to 0.6 mg/kg dose was subcutaneously administered to healthy subjects. A single subcutaneous dose of 0.6 mg/kg mezagitamab reduced the level of plasmablasts (PBs) in peripheral blood >90% and natural killer (NK) cells >80% without comparable reductions in monocytes and B and T cells. Levels of PBs and NK cells recovered to 50% of baseline levels 21 days after administration, on average. At this dose, there were no Serious Adverse Events (SAEs), on-study deaths, or Adverse Events (AEs) that led to study discontinuation (WO 2019/140410, incorporated herein by reference in its entirety). In studies with subjects with relapsed and/or refractory multiple myeloma (RRMM), after mezagitamab was subcutaneously administered at a dosage of 45 mg, 135 mg, 300 mg, or 600 mg, no drug-related SAEs, on-study deaths, or AEs that led to study discontinuation were reported. Administration of mezagitamab was shown to achieve ~50% reduction of the plasma cells resident in the bone marrow and ~80% reduction of plasmablasts in the peripheral blood. In subjects with advanced RRMM, mezagitamab also showed early signs of anti-tumor activity as evidenced by at least 50% reduction in disease burden in some subjects and prolonged disease stabilization in others (WO 2019/186273; incorporated herein by reference in its entirety). In studies with subjects with moderate to severe systemic lupus erythematosus (SLE), subcutaneously administered dosages of 45 mg, 90 mg, and 135 mg were found to be well tolerated, with no substantial imbalances in AEs between the placebo and treatments groups and

no dose-dependent effects or safety concerns were identified (PCT Application No. PCT/US2023/073238, incorporated herein by reference in its entirety). In studies with subjects with myasthenia gravis (MG) receiving concomitant stable background therapy, weekly doses of mezagitamab up to 600 mg had a favorable safety profile and showed improvements in MG symptom severity and persistent and durable reductions in both IgG and autoantibody levels (PCT Application No. PCT/US2023/085225, incorporated herein by reference in its entirety). Moreover, at clinically achievable doses of mezagitamab, the depletion of plasma cells and plasmablasts has been associated with a substantial reduction in the levels of various immunoglobulins, specifically between 20%-40% and 40-60% reductions in levels of IgG and IgA, respectively, which have both been linked to the causation of various autoimmune diseases. However, the feasibility and efficacy of administering mezagitamab in treating subjects with immune thrombocytopenia (ITP) is unknown.

[0170] The methods and unit dosages of the present disclosure provide, for the first time, subcutaneous administration of therapeutically effective dosages of anti-CD38 antibodies in treating subjects with ITP.

[0171] The present disclosure provides methods and unit dosage forms for subcutaneous administration of a therapeutically effective amount of an isolated anti-CD38 antibody or antigen binding fragment to a subject with ITP. In some embodiments, the antibody or antigen binding fragment for subcutaneous administration comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8. In some embodiments, the antibody or antigen binding fragment for subcutaneous administration comprises a variable heavy chain (VH) region comprising or consisting of SEQ ID NO: 9 (or a sequence with at least 80%, 85%, 90%, 95%, 97% or 99% sequence identity thereto) and a variable light chain (VL) region comprising or consisting of SEQ ID NO: 10 (or a sequence with at least 80%, 85%, 90%, 95%, 97% or 99% sequence identity thereto). In some embodiments, the antibody or antigen binding

fragment thereof is subcutaneously administered in a dosage of from about 100 mg to about 600 mg.

[0172] Unless otherwise defined herein, scientific and technical terms used in connection with the present disclosure shall have the meanings that are commonly understood by those of ordinary skill in the art. The meaning and scope of the terms should be clear. However, in the event of any latent ambiguity, definitions provided herein take precedence over any dictionary or extrinsic definition. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. The term "or" includes "and/or" unless stated otherwise. Furthermore, the use of the term "including," "includes," or "included" is not limiting. Terms such as "element" and "component" encompass both elements and components comprising one unit and elements and components that comprise more than one subunit unless specifically stated otherwise.

[0173] The methods and techniques of the present disclosure are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, delivery, and treatment of subjects. Commercial enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein.

[0174] All headings and section designations are used for clarity and reference purposes only and are not to be considered limiting in any way. For example, those of skill in the art will appreciate the usefulness of combining various aspects of the disclosure from different headings and sections as appropriate according to the spirit and scope of the disclosure described herein.

[0175] Select terms are defined below in order for the present disclosure to be more readily understood.

[0176] The terms "human CD38" and "human CD38 antigen" refer to the amino acid sequence of SEQ ID NO: 1, or a functional fraction thereof, such as an epitope, as defined herein (Table 1). In general, CD38 possesses a short intracytoplasmic tail, a transmembrane domain, and an extracellular domain. The terms "cynomolgus CD38" and "cynomolgus CD38 antigen" refer to

the amino acid sequence of SEQ ID NO: 2, which is 92% identical to the amino acid sequence of human CD38 (**Table 1**). Synonyms for CD38 include cyclic ADP ribose hydrolase; cyclic ADP ribose-hydrolase 1; ADP ribosyl cyclase; ADP-ribosyl cyclase 1; cADPr hydrolase 1; CD38-rs1; I-19; NIM-R5 antigen; 2'- phospho-cyclic-ADP-ribose transferase; 2'-phospho-ADP-ribosyl cyclase; 2'-phospho-cyclic-ADP- ribose transferase; 2'-phospho-ADP-ribosyl cyclase; and T10.

Table 1. Amino Acid Sequence of Human and Cynomolgus Monkey CD38

Species	**Amino Acid Sequence** 12345678901234567890123456789012345678901234567890	**SEQ ID NO**
Human CD38	MANCEFSPVSGDKPCCRLSRRAQLCLGVSILVLILVVVLAVVVPRWRQQW SGPGTTKRFPETVLARCVKYTEIHPEMRHVDCQSVWDAFKGAFISKHPCN ITEEDYQPLMKLGTQTVPCNKILLWSRIKDLAHQFTQVQRDMFTLEDTLL GYLADDLTWCGEFNTSKINYQSCPDWRKDCSNNPVSVFWKTVSRRFAEAA CDVVHVMLNGSRSKIFDKNSTFGSVEVHNLQPEKVQTLEAWVIHGGREDS RDLCQDPTIKELESIISKRNIQFSCKNIYRPDKFLQCVKNPEDSSCTSEI	1
Cyno CD38	MANCEFSPVSGDKPCCRLSRRAQVCLGVCLLVLLILVVVVAVVLPRWRQQ WSGSGTTSRFPETVLARCVKYTEVHPEMRHVDCQSVWDAFKGAFISKYPC NITEEDYQPLVKLGTQTVPCNKTLLWSRIKDLAHQFTQVQRDMFTLEDML LGYLADDLTWCGEFNTFEINYQSCPDWRKDCSNNPVSVFWKTVSRRFAET ACGVVHVMLNGSRSKIFDKNSTFGSVEVHNLQPEKVQALEAWVIHGGRED SRDLCQDPTIKELESIISKRNIRFFCKNIYRPDKFLQCVKNPEDSSCLSG I	2
Human CD157	MAAQGCAASRLLQLLLQLLLLLLLLAAGGARARWRGEGTSAHLRDIFLGR CAEYRALLSPEQRNKNCTAIWEAFKVALDKDPCSVLPSDYDLFINLSRHS IPRDKSLFWENSHLLVNSFADNTRRFMPLSDVLYGRVADFLSWCRQKNDS GLDYQSCPTSEDCENNPVDSFWKRASIQYSKDSSGVIHVMLNGSEPTGAY PIKGFFADYEIPNLQKEKITRIEIWVMHEIGGPNVESCGEGSMKVLEKRL KDMGFQYSCINDYRPVKLLQCVDHSTHPDCALKSAAAATQRKAPSLYTEQ RAGLIIPLFLVLASRTQL	13

[0177] The terms "therapeutically effective amount" and "therapeutically effective dosage" refer to an amount of a therapy that is sufficient to reduce or ameliorate the severity and/or duration of a disorder or one or more symptoms thereof; prevent the advancement of a disorder; cause regression of a disorder; prevent the recurrence, development, onset, or progression of one or

more symptoms associated with a disorder; or enhance or improve the prophylactic or therapeutic effect(s) of another therapy (*e.g.*, prophylactic or therapeutic agent), at dosages and for periods of time necessary to achieve a desired therapeutic result. A therapeutically effective amount may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the medicaments to elicit a desired response in the individual. A therapeutically effective amount of an antibody or antigen binding fragment thereof is one in which any toxic or detrimental effects of the antibody or antigen binding fragment thereof are outweighed by the therapeutically beneficial effects.

[0178] The terms "subject" and "subject" include both humans and other animals. Thus, the compositions, dosages, and methods disclosed herein are applicable to both human and veterinary therapies. In one embodiment, the subject is a mammal, for example, a human.

[0179] The term "isolated antibody" refers to an antibody that is substantially free of other antibodies having different antigenic specificities. For instance, an isolated antibody that specifically binds to CD38 is substantially free of antibodies that specifically bind antigens other than CD38. An isolated antibody that specifically binds to an epitope, isoform, or variant of human CD38 or cynomolgus CD38 may, however, have cross-reactivity to other related antigens, for instance from other species, such as CD38 species homologs. Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

[0180] The term "about" refers to an extent near in number, degree, volume, time, *etc.*, with only minor variations in dimension of up to about 10%.

[0181] The term "pharmaceutically acceptable carrier" refers to a pharmaceutically acceptable material, composition, or vehicle, suitable for administering compounds of the present disclosure to mammals. The carriers include liquid or solid filler, diluent, excipient, solvent, or encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject. In one embodiment, the pharmaceutically acceptable carrier is suitable for subcutaneous administration.

[0182] The term "pharmaceutical composition" refers to preparations suitable for administration to a subject and treatment of disease. When the anti-CD38 antibodies of the present disclosure are administered as pharmaceuticals to mammals, *e.g.*, humans, they can be administered "as is" or as a pharmaceutical composition containing the anti-CD38 antibody in combination with a pharmaceutically acceptable carrier, excipient, and/or stabilizer. The pharmaceutical composition can be in the form of a unit dosage form for administration of a particular dosage of the anti-CD38 antibody at a particular concentration, a particular amount, or a particular volume. Pharmaceutical compositions comprising the anti-CD38 antibodies, either alone or in combination with prophylactic agents, therapeutic agents, and/or pharmaceutically acceptable carriers are provided. Suitably, the pharmaceutical composition may comprise a unit dosage form according to the present disclosure either alone or in combination with prophylactic agents, therapeutic agents, and/or pharmaceutically acceptable carriers. Suitably, the pharmaceutical composition may comprise a human anti-CD38 antibody as described herein either alone or in combination with prophylactic agents, therapeutic agents, and/or pharmaceutically acceptable carriers.

[0183] Traditional antibody structural units typically comprise a tetramer. Each tetramer is typically composed of two identical pairs of polypeptide chains, each pair having one "light" chain (typically having a molecular weight of about 25 kDa) and one "heavy" chain (typically having a molecular weight of about 50-70 kDa). Human light chains (LC) are classified as kappa and lambda light chains. Heavy chains (HC) are classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. IgG has several subclasses, including, but not limited to IgG1, IgG2, IgG3, and IgG4. IgM has subclasses, including, but not limited to, IgM1 and IgM2. Thus, "isotype" refers to any of the subclasses of immunoglobulins defined by the chemical and antigenic characteristics of their constant regions. The known human immunoglobulin isotypes are IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgM1, IgM2, IgD, and IgE. Therapeutic antibodies can also comprise hybrids of isotypes and/or subclasses.

[0184] Each variable heavy (VH) chain and variable light (VL) chain region (about 100 to 110 amino acids in length) is composed of three hypervariable regions called "complementarity determining regions" (CDRs) and four framework regions (FRs) (about 15-30 amino acids in

length), arranged from amino-terminus to carboxy-terminus in the following order: FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4. "Variable" refers to the fact that the CDRs differ extensively in sequence among antibodies and thereby determines a unique antigen binding site.

[0185] The hypervariable region generally encompasses amino acid residues from about amino acid residues 24-34 (LCDR1; "L" denotes light chain), 50-56 (LCDR2) and 89-97 (LCDR3) in the VL region and around about 31-35B (HCDR1; "H" denotes heavy chain), 50-65 (HCDR2), and 95-102 (HCDR3) in the VL region (Kabat *et al.* (1991) Sequences Of Proteins Of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD; incorporated herein by reference in its entirety) and/or those residues forming a hypervariable loop (*e.g.*, residues 26-32 (LCDR1), 50-52 (LCDR2) and 91-96 (LCDR3) in the VL region and 26-32 (HCDR1), 53-55 (HCDR2) and 96-101 (HCDR3) in the VH region (Chothia and Lesk (1987) J. Mol. Biol. 196: 901-917; incorporated herein by reference in its entirety)

[0186] The Kabat numbering system is generally used when referring to a residue in the variable domain (approximately, residues 1-107 of the VL region and residues 1-113 of the VH region) (*e.g.*, Kabat *et al.* (1991) Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD; incorporated herein by reference in its entirety), with the EU number system used for the Fc region.

[0187] The term "immunoglobulin (Ig) domain" refers to a region of an immunoglobulin having a distinct tertiary structure. Ig domains include VH and VL regions, CDRs, framework regions, constant region domains, and hinge regions. Each HC and LC has constant region domains referred to as constant heavy (CH) domains and constant light (CL) domains. In the context of IgG antibodies, the IgG isotypes each have a constant region comprising three CH domains. The carboxy-terminal portion of each HC and LC defines a constant region primarily responsible for effector function. Accordingly, "CH" domains in the context of IgG are as follows: "CH1" refers to positions 118-220 according to the EU index as in Kabat. "CH2" refers to positions 237-340 according to the EU index as in Kabat, and "CH3" refers to positions 341-447 according to the EU index as in Kabat.

[0188] Another type of Ig domain of the HC is the hinge region. The term "hinge region" refers to the flexible polypeptide comprising the amino acids between the first and second constant domains of an antibody. Structurally, the IgG CH1 domain ends at EU position 220, and the IgG CH2 domain begins at residue EU position 237. Thus, for IgG the antibody hinge is herein defined to include positions 221 (D221 in IgG1) to 236 (G236 in IgG1), wherein the numbering is according to the EU index as in Kabat. In some embodiments, for example in the context of an Fc region, the lower hinge is included, with the "lower hinge" generally referring to positions 226 or 230.

[0189] The term "Fc region" refers to the polypeptide comprising the constant region of an antibody excluding the CH1 domain and in some cases, part of the hinge. Thus, Fc refers to the last two constant region Ig domains (CH2 and CH3) of IgA, IgD, and IgG, the last three constant region Ig domains of IgE and IgM, and the flexible hinge N-terminal to these domains. For IgA and IgM, Fc may include the J chain. For IgG, the Fc domain comprises Ig domains Cγ2 and Cγ3 (Cγ2 and Cγ3) and the lower hinge region between Cγ1 (Cγ1) and Cγ2 (Cγ2). Although the boundaries of the Fc region may vary, the human IgG HC Fc region is usually defined to include residues C226 or P230 to its carboxyl-terminus, wherein the numbering is according to the EU index as in Kabat. In some embodiments, as is more fully described below, amino acid modifications are made to the Fc region, for example to alter binding to one or more FcγR receptors or to the FcRn receptor.

CD38 Antibodies

[0190] Accordingly, the present disclosure provides isolated anti-CD38 antibodies that specifically bind human and primate CD38 protein that find use in subcutaneous administration methods and unit dosage forms in treating subjects with ITP. The antibodies or antigen binding fragments thereof used in the present disclosure bind to both the human and primate CD38 proteins, particularly primates used in clinical testing, such as cynomolgus monkeys (*Macaca fascicularis,* Crab eating macaque, also referred to herein as "cyno").

[0191] "Mezagitamab" or "TAK-079" is a therapeutic protein comprising a fully human IgG1 monoclonal antibody that binds specifically to human CD38 with high affinity (Kd = 3.5 nM) referred to herein as "AB79" (US Patent No. 8,362,211, the contents of which is hereby

incorporated by reference in its entirety) which binds to and depletes plasma cells/plasmablasts expressing the glycoprotein CD38, a specific biomarker, on their cell surface. CD38 is highly expressed on the cell surfaces of various components of the immune system including plasma cells and plasmablasts, which produce immunoglobulins. It is also expressed on subsets of natural killer (NK) cells, T-cells, and B-cells. The amino acid sequences of mezagitamab are shown in **Table 2**.

Table 2: Amino Acid Sequences of Mezagitamab

	Sequence 12345678901234567890123456789012345678901234567890	**SEQ ID NO**
HCDR1	GFTFDDYG	3
HCDR2	ISWNGGKT	4
HCDR3	ARGSLFHDSSGFYFGH	5
LCDR1	SSNIGDNY	6
LCDR2	RDS	7
LCDR3	QSYDSSLSGS	8
VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSD ISWNGGKTHYVDSVKGQFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGS LFHDSSGFYFGHWGQGTLVTVSSASTKGPSVFPLA	9
VL	QSVLTQPPSASGTPGQRVTISCSGSSSNIGDNYVSWYQQLPGTAPKLLIY RDSQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCQSYDSSLSGSV FGGGTKLTVLGQPKANPTVTLFPPSSEEL	10
HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSD ISWNGGKTHYVDSVKGQFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGS LFHDSSGFYFGHWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR EPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PGK	11
HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSD ISWNGGKTHYVDSVKGQFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGS LFHDSSGFYFGHWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR EPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG	14
LC	QSVLTQPPSASGTPGQRVTISCSGSSSNIGDNYVSWYQQLPGTAPKLLIY RDSQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCQSYDSSLSGSV FGGGTKLTVLGQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTV AWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVT HEGSTVEKTVAPTECS	12

[0192] Mezagitamab inhibits the growth of tumor cells expressing CD38 by cell depletion via ADCC and CDC. Mezagitamab also reduces the level of plasma cells and plasmablasts in blood isolated from healthy subjects and subjects with autoimmune diseases. The anti-human CD38 mAb daratumumab also depletes CD38-expressing plasmablasts and plasma cells in samples from subjects with autoimmune diseases in a dose-dependent manner *in vitro*. For example, daratumumab provided a clinically relevant depletion of autoreactive long-lived plasma cells in subjects with treatment-refractory autoantibody-mediated neurological diseases such as myasthenia gravis (Scheibe *et al.* (2022) Eur. J. Neurol. 29(6): 1847-1854).

[0193] In contrast to daratumumab, mezagitamab cross-reacts with CD38 expressed by cynomolgus monkeys providing a unique opportunity to determine if reducing the level of cells expressing CD38 would affect inflammation and tissue damage in a non-human primate model of autoimmune disease. In healthy cynomolgus monkeys, the efficiency of depletion for lymphocytes, and B, T and NK cells correlated positively with level of CD38 expression and AB79 dose level (PCT Application No. PCT/US2017/042128; US Patent No. 8,362,211, incorporated herein by reference in their entirety).

[0194] In some embodiments, the anti-CD38 antibodies or antigen binding fragments thereof of the disclosure interact with CD38 at a number of amino acid residues including K121, F135, Q139, D141, M142, E239, W241, S274, C275, K276, F284, V288, K289, N290, P291, E292, D293 and S294 based on human sequence numbering. Suitably, the anti-CD38 antibodies or antigen binding fragments thereof of the disclosure may interact with CD38 at a number of amino acid residues including K121, F135, Q139, D141, M142, E239, W241, S274, C275, K276, F284, V288, K289, N290, P291, E292, D293 and S294 of SEQ ID NO: 1, based on human sequence numbering. Suitably, the anti-CD38 antibodies or antigen binding fragments thereof of the disclosure interact with CD38 at a number of amino acid residues including K121, F135, Q139, D141, M142, E239, W241, F274, C275, K276, F284, V288, K289, N290, P291, E292, D293 and S294 of SEQ ID NO: 2. It should be noted that these residues are identical in both human and cynomolgus monkeys, with the exception that S274 is actually F274 in cynomolgus monkeys. These residues may represent the immunodominant epitope and/or residues within the footprint of the specific antigen binding peptide.

[0195] In some embodiments, the anti-CD38 antibody for use according to the disclosure comprises a heavy chain (HC) comprising the following CDR amino acid sequences: GFTFDDYG (SEQ ID NO: 3; HCDR1 mezagitamab), ISWNGGKT (SEQ ID NO: 4; HCDR2 mezagitamab), and ARGSLFHDSSGFYFGH (SEQ ID NO: 5; HCDR3 mezagitamab) or variants of those sequences having up to three amino acid changes. In some embodiments, the antibody for use according to the disclosure comprises a light chain (LC) comprising the following CDR amino acid sequences: SSNIGDNY (SEQ ID NO: 6; LCDR1 mezagitamab), RDS (SEQ ID NO: 7; LCDR2 mezagitamab), and QSYDSSLSGS (SEQ ID NO: 8; LCDR3 mezagitamab) or variants of those sequences having up to three amino acid changes. In some embodiments, the antibody for use according to the disclosure comprises an HC comprising the following CDR amino acid sequences: GFTFDDYG (SEQ ID NO: 3; HCDR1 mezagitamab), ISWNGGKT (SEQ ID NO: 4; HCDR2 mezagitamab), ARGSLFHDSSGFYFGH (SEQ ID NO: 5; HCDR3 mezagitamab) or variants of those sequences having up to three amino acid changes and an LC comprising the following CDR amino acid sequences: SSNIGDNY (SEQ ID NO: 6; LCDR1 mezagitamab), RDS (SEQ ID NO: 7; LCDR2 mezagitamab), and QSYDSSLSGS (SEQ ID NO: 8; LCDR3 mezagitamab) or variants of those sequences having up to three amino acid changes. In some embodiments, the anti-CD38 antibody comprises an HC comprising the following CDR amino acid sequences: GFTFDDYG (SEQ ID NO: 3; HCDR1 mezagitamab), ISWNGGKT (SEQ ID NO: 4; HCDR2 mezagitamab), and ARGSLFHDSSGFYFGH (SEQ ID NO: 5; HCDR3 mezagitamab). In some embodiments, the antibody comprises an LC comprising the following CDR amino acid sequences: SSNIGDNY (SEQ ID NO: 6; LCDR1 mezagitamab), RDS (SEQ ID NO: 7; LCDR2 mezagitamab), and QSYDSSLSGS (SEQ ID NO: 8; LCDR3 mezagitamab). In some embodiments, the antibody comprises an HC comprising the following CDR amino acid sequences: GFTFDDYG (SEQ ID NO: 3; HCDR1 mezagitamab), ISWNGGKT (SEQ ID NO: 4; HCDR2 mezagitamab), ARGSLFHDSSGFYFGH (SEQ ID NO: 5; HCDR3 mezagitamab) and an LC comprising the following CDR amino acid sequences: SSNIGDNY (SEQ ID NO: 6; LCDR1 mezagitamab), RDS (SEQ ID NO: 7; LCDR2 mezagitamab), and QSYDSSLSGS (SEQ ID NO: 8; LCDR3 mezagitamab). In some embodiments, the antibody comprises an HC comprising a VH region amino acid sequence having at least 80% sequence identity to SEQ ID NO: 9. Suitably, the VH region may comprise the CDR sequences as defined by SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 and the remainder of the VH region sequence may have at

least 80% sequence identity to SEQ ID NO: 9. Suitably, the VH region may comprise the CDR sequences as defined by SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 and the remainder of the VH region sequence may have at least 85% sequence identity to SEQ ID NO: 9. Suitably, the VH region may comprise the CDR sequences as defined by SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 and the remainder of the VH region sequence may have at least 90% sequence identity to SEQ ID NO: 9. Suitably, the VH region may comprise the CDR sequences as defined by SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 and the remainder of the VH region sequence may have at least 95% sequence identity to SEQ ID NO: 9. Suitably, the VH region may comprise the CDR sequences as defined by SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 and the remainder of the VH region sequence may have at least 97% sequence identity to SEQ ID NO: 9. Suitably, the VH region may comprise the CDR sequences as defined by SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 and the remainder of the VH region sequence may have at least 99% sequence identity to SEQ ID NO: 9.

[0196] In some embodiments, the antibody comprises an HC comprising the VH region amino acid sequence of SEQ ID NO: 9.

[0197] In some embodiments, the antibody comprises an LC comprising a VL region amino acid sequence having at least 80% sequence identity to SEQ ID NO: 10. Suitably, the VL region may comprise the CDR sequences as defined by SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8 and the remainder of the VL region sequence may have at least 80% sequence identity to SEQ ID NO: 10. Suitably, the VL region may comprise the CDR sequences as defined by SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8 and the remainder of the VL region sequence may have at least 85% sequence identity to SEQ ID NO: 10. Suitably, the VL region may comprise the CDR sequences as defined by SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8 and the remainder of the VL region sequence may have at least 90% sequence identity to SEQ ID NO: 10. Suitably, the VL region may comprise the CDR sequences as defined by SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8 and the remainder of the VL region sequence may have at least 95% sequence identity to SEQ ID NO: 10. Suitably, the VL region may comprise the CDR sequences as defined by SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8 and the remainder of the VL region sequence may have at least 97% sequence identity to SEQ ID NO: 10. Suitably, the VL region may comprise the CDR sequences as defined by SEQ ID NO: 6, SEQ ID NO: 7

and SEQ ID NO: 8 and the remainder of the VL region sequence may have at least 99% sequence identity to SEQ ID NO: 10.

[0198] In some embodiments, the antibody comprises an LC comprising the VL region amino acid sequence of SEQ ID NO: 10.

[0199] In some embodiments, the antibody comprises an HC comprising the VH region amino acid sequence of SEQ ID NO: 9 or a variant thereof as described herein and an LC comprising the VL region amino acid sequence of SEQ ID NO: 10 or a variant thereof as described herein.

[0200] As will be appreciated by those in the art, the VH and VL regions can be joined to human IgG constant domain sequences, generally IgG1, IgG2, or IgG4.

[0201] In some embodiments, the antibody comprises a HC comprising or consisting of an amino acid sequence having at least 80%, 85%, 90%, 95%, 97% or 99% sequence identity to SEQ ID NO: 11. Suitably, the HC may comprise the CDR sequences as defined by SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 and the remainder of the HC may have at least 80% sequence identity to SEQ ID NO 11. Suitably, the HC may comprise the CDR sequences as defined by SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 and the remainder of the HC may have at least 85% sequence identity to SEQ ID NO 11. Suitably, the HC may comprise the CDR sequences as defined by SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 and the remainder of the HC may have at least 90% sequence identity to SEQ ID NO 11. Suitably, the HC may comprise the CDR sequences as defined by SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 and the remainder of the HC may have at least 95% sequence identity to SEQ ID NO 11. Suitably, the HC may comprise the CDR sequences as defined by SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 and the remainder of the HC may have at least 97% sequence identity to SEQ ID NO 11. Suitably, the HC may comprise the CDR sequences as defined by SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 and the remainder of the HC may have at least 99% sequence identity to SEQ ID NO 11.

[0202] In some embodiments, the antibody comprises the HC amino acid sequence of SEQ ID NO: 11.

[0203] In some embodiments, the antibody comprises a HC comprising or consisting of an amino acid sequence having at least 80%, 85%, 90%, 95%, 97% or 99% sequence identity to

SEQ ID NO: 14. Suitably, the HC may comprise the CDR sequences as defined by SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 and the remainder of the HC may have at least 80% sequence identity to SEQ ID NO 14. Suitably, the HC may comprise the CDR sequences as defined by SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 and the remainder of the HC may have at least 85% sequence identity to SEQ ID NO 14. Suitably, the HC may comprise the CDR sequences as defined by SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 and the remainder of the HC may have at least 90% sequence identity to SEQ ID NO 14. Suitably, the HC may comprise the CDR sequences as defined by SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 and the remainder of the HC may have at least 95% sequence identity to SEQ ID NO 14. Suitably, the HC may comprise the CDR sequences as defined by SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 and the remainder of the HC may have at least 97% sequence identity to SEQ ID NO 14. Suitably, the HC may comprise the CDR sequences as defined by SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 and the remainder of the HC may have at least 99% sequence identity to SEQ ID NO 14.

[0204] In some embodiments, the antibody comprises the HC amino acid sequence of SEQ ID NO: 14.

[0205] In some embodiments, the antibody comprises a LC comprising or consisting of an amino acid sequence having at least 80%, 85%, 90%, 95%, 97% or 99% sequence identity to SEQ ID NO: 12. Suitably, the LC may comprise the CDR sequences as defined by SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8 and the remainder of the LC may have at least 80% sequence identity to SEQ ID NO 12. Suitably, the LC may comprise the CDR sequences as defined by SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8 and the remainder of the LC may have at least 85% sequence identity to SEQ ID NO 12. Suitably, the LC may comprise the CDR sequences as defined by SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8 and the remainder of the LC may have at least 90% sequence identity to SEQ ID NO 12. Suitably, the LC may comprise the CDR sequences as defined by SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8 and the remainder of the LC may have at least 95% sequence identity to SEQ ID NO 12. Suitably, the LC may comprise the CDR sequences as defined by SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8 and the remainder of the LC may have at least 97% sequence identity to SEQ ID NO 12. Suitably, the LC may comprise the CDR sequences as defined by SEQ ID NO: 6, SEQ ID NO: 7

and SEQ ID NO: 8 and the remainder of the LC may have at least 99% sequence identity to SEQ ID NO 12.

[0206] In some embodiments, the antibody comprises the LC amino acid sequence of SEQ ID NO: 12.

[0207] In some embodiments, the antibody comprises or consists of the HC amino acid sequence of SEQ ID NO: 11 or a variant thereof as described herein and the LC amino acid sequence of SEQ ID NO: 12 or a variant thereof as described herein.

[0208] In some embodiments, the antibody comprises or consists of the HC amino acid sequence of SEQ ID NO: 14 or a variant thereof as described herein and the LC amino acid sequence of SEQ ID NO: 12 or a variant thereof as described herein.

[0209] The present disclosure encompasses antibodies that bind to both human and cynomolgus CD38 and interact with at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% of the following amino acid residues: K121, F135, Q139, D141, M142, E239, W241, S274, C275, K276, F284, V288, K289, N290, P291, E292, D293 and S294 of SEQ ID NO: 1 and SEQ ID NO: 2, based on human numbering. Suitably, the antibody may interact with at least 90% of these amino acid residues. Suitably, the antibody may interact with at least 95% of these amino acid residues. Suitably, the antibody may interact with at least 97% of these amino acid residues. Suitably, the antibody may interact with at least 98% of these amino acid residues. Suitably, the antibody may interact with at least 99% of these amino acid residues. Suitably, the antibody may interact with at least 14 (*e.g.*, at least 15 or at least 16) of the following amino acids: K121, F135, Q139, D141, M142, E239, W241, S274, C275, K276, F284, V288, K289, N290, P291, E292, D293 and S294 of SEQ ID NO: 1 and SEQ ID NO: 2, based on human numbering.

[0210] In some embodiments, the antibodies are full length. By "full length antibody" herein is meant the structure that constitutes the natural biological form of an antibody, including variable and constant regions, including one or more modifications as outlined herein.

[0211] Alternatively, the antibodies can be a variety of structures, including, but not limited to, antibody fragments, antigen binding fragment, monoclonal antibodies, bispecific antibodies, minibodies, domain antibodies, synthetic antibodies (sometimes referred to herein as "antibody mimetics"), chimeric antibodies, humanized antibodies, antibody fusions (sometimes referred to

as "antibody conjugates"), and fragments of each, respectively. Specific antibody fragments include, but are not limited to, (i) the Fab fragment consisting of VL, VH, CL and CH1 domains, (ii) the Fd fragment consisting of the VH and CH1 domains, (iii) the Fv fragment consisting of the VL and VH domains of a single antibody; (iv) the dAb fragment (Ward *et al.* (1989) Nature 341: 544-546) which consists of a single variable, (v) isolated CDR regions, (vi) F(ab')2 fragments, a bivalent fragment comprising two linked Fab fragments (vii) single chain Fv molecules (scFv), wherein a VH domain and a VL domain are linked by a peptide linker which allows the two domains to associate to form an antigen binding site (Bird *et al.* (1988) Science 242: 423-426, Huston *et al.* (1988) Proc. Natl. Acad. Sci. USA 85: 5879-5883), (viii) bispecific single chain Fv (WO 03/11161) and (ix) "diabodies" or "triabodies", multivalent or multispecific fragments constructed by gene fusion (TomLinson *et al.* (2000) Methods Enzymol. 326: 461-479; WO94/13804; Holliger *et al.* (1993) Proc. Natl. Acad. Sci. USA 90: 6444-6448).

[0212] Suitably, the antibody may be a Fab fragment. Suitably, the antibody may be an Fv fragment. Suitably, the antibody may be an Fd fragment. Suitably, the antibody structure may be isolated CDR regions. Suitably, the antibody may be a F(ab')2 fragment. Suitably, the antibody may be an scFv fragment.

[0213] In some embodiments, the antibody or antigen binding fragment thereof of the present disclosure further comprises one or more engineered glycoforms. In some embodiments, the engineered glycoform comprises glycosylation of one or more polypeptides. In some embodiments, the glycosylation is N-linked glycosylation or O-linked glycosylation. In some embodiments, the glycosylation is N-linked glycosylation. In some embodiments, the glycosylation is O-linked glycosylation.

[0214] In some embodiments, the isolated antibody of the present disclosure is mezagitamab.

Antibody Modifications

[0215] The present disclosure further provides variant anti-CD38 antibodies. That is, there are a number of modifications that can be made to the antibodies of the disclosure, including, but not limited to, amino acid modifications in the CDRs (affinity maturation), amino acid modifications in the VH region and/or VL region, amino acid modifications in the HC and/or LC, amino acid modifications in the Fc region, glycosylation variants, covalent modifications of other types, *etc.*

[0216] The term "variant" means a polypeptide that differs from that of a parent polypeptide. Amino acid variants can include substitutions, insertions, and deletions of amino acids. In general, variants can include any number of modifications, as long as the function of the protein is still present, as described herein. That is, in the case of amino acid variants generated with the CDRs of mezagitamab, for example, the antibody should still specifically bind to both human and cynomolgus CD38. The term "variant Fc region" means an Fc sequence that differs from that of a wild-type or parental Fc sequence by virtue of at least one amino acid modification. Fc variant may refer to the Fc polypeptide itself, compositions comprising the Fc variant polypeptide, or the amino acid sequence. If amino acid variants are generated with the Fc region, for example, the variant antibodies should maintain the required functions for the particular application or indication of the antibody. For example, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid substitutions can be utilized, for example, 1-10, 1-5, 1-4, 1-3, and 1-2 substitutions. Suitable modifications can be made at one or more positions as is generally outlined, for example in US Patent Application Serial Nos. 11/841,654 and 12/341,769; US Patent Publication Nos. 2004013210; 20050054832; 20060024298; 20060121032; 20060235208; and 20070148170; and US Patent Nos. 6,737,056; 7,670,600; 6,086,875; and 8,937,158, all of which are expressly incorporated by reference in their entirety, and in particular for specific amino acid substitutions that increase binding to Fc receptors.

[0217] A variant can be considered in terms of similarity (*i.e.*, amino acid residues having similar chemical properties/functions), but preferably a variant is expressed in terms of sequence identity.

[0218] Sequence comparisons can be conducted by eye, or more usually, with the aid of readily available sequence comparison programs. These publicly and commercially available computer programs can calculate sequence identity between two or more sequences.

[0219] It may be desirable to have from 1-5 modifications in the Fc region of wild-type or engineered proteins, as well as from 1 to 5 modifications in the Fv region, for example. A variant polypeptide sequence will preferably possess at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to the parent sequences (*e.g.*, the VH or VL regions, the constant regions, and/or the HC and LC sequences for mezagitamab). Suitably, the variant may have at least 80% sequence identity to the parent sequence. Suitably, the variant

may have at least 85% sequence identity to the parent sequence. Suitably, the variant may have at least 90% sequence identity to the parent sequence. Suitably, the variant may have at least 92% sequence identity to the parent sequence. Suitably, the variant may have at least 95% sequence identity to the parent sequence. Suitably, the variant may have at least 97% sequence identity to the parent sequence. Suitably, the variant may have at least 98% sequence identity to the parent sequence. Suitably, the variant may have at least 99% sequence identity to the parent sequence.

[0220] In one embodiment, the sequence identity is determined across the entirety of the sequence. In one embodiment, the sequence identity is determined across the entirety of the candidate sequence being compared to a sequence recited herein.

[0221] The term "amino acid substitution" means the replacement of an amino acid at a particular position in a parent polypeptide sequence with another amino acid. For example, the substitution S100A refers to a variant polypeptide in which the serine at position 100 is replaced with alanine. Suitably, the amino acid substitution may be a conservative amino acid substitution. Suitably, a variant may comprise one or more, *e.g.*, two or three conservative amino acid substitutions. A "conservative substitution" is defined as one in which one amino acid is substituted for another having similar biochemical properties.

[0222] Unless otherwise explicitly stated herein by way of reference to a specific, individual amino acid, amino acids may be substituted using conservative substitutions as recited below. An aliphatic, polar uncharged amino may be a cysteine, serine, threonine, methionine, asparagine, or glutamine residue. An aliphatic, polar charged amino acid may be an aspartic acid, glutamic acid, lysine, or arginine residue. An aromatic amino acid may be a histidine, phenylalanine, tryptophan, or tyrosine residue. Conservative substitutions may be made, for example according to **Table 3** below. Amino acids in the same block in the second column and preferably in the same line in the third column may be substituted for each other:

Table 3. Conservative Substitutions

ALIPHATIC	Non-polar	G A P
		I L V
	Polar – uncharged	C S T M

		N Q
	Polar – charged	D E
		K R
AROMATIC		H F W Y

[0223] The term "amino acid insertion" means the addition of an amino acid at a particular position in a parent polypeptide sequence.

[0224] The term "amino acid deletion" means the removal of an amino acid at a particular position in a parent polypeptide sequence.

[0225] The terms "parent antibody" and "precursor antibody" mean an unmodified antibody that is subsequently modified to generate a variant. In an embodiment, the parent antibody herein is mezagitamab. In an embodiment, the parent antibody herein comprises a VH region having the amino acid sequence of SEQ ID NO: 9 and the VL region having the amino acid sequence of SEQ ID NO: 10. In an embodiment, the parent antibody herein comprises an HC amino acid sequence of SEQ ID NO: 11 and an LC amino acid sequence of SEQ ID NO: 12. In an embodiment, the parent antibody herein comprises an HC amino acid sequence of SEQ ID NO: 14 and an LC amino acid sequence of SEQ ID NO: 12. Parent antibody may refer to the polypeptide itself, compositions that comprise the parent antibody, or the amino acid sequence that encodes it. Accordingly, the term "parent Fc polypeptide" means an Fc polypeptide that is modified to generate a variant.

[0226] The terms "wild type," "WT," and "native" mean an amino acid sequence or a nucleotide sequence that is found in nature, including allelic variations. A WT protein, polypeptide, antibody, immunoglobulin, IgG, *etc.*, has an amino acid sequence or a nucleotide sequence that has not been intentionally modified.

[0227] In some embodiments, one or more amino acid modifications are made in one or more of the CDRs of the anti-CD38 antibody. In general, only 1, 2, or 3 amino acids are substituted in any single CDR, and generally no more than from 4, 5, 6, 7, 8 9 or 10 changes are made within a set of CDRs. However, it should be appreciated that any combination of no substitutions, 1, 2 or 3 substitutions in any CDR can be independently and optionally combined with any other substitution.

[0228] In some cases, amino acid modifications in the CDRs are referred to as "affinity maturation". An "affinity matured" antibody is one having one or more alteration(s) in one or more CDRs which results in an improvement in the affinity of the antibody for antigen, compared to a parent antibody which does not possess those alteration(s). In some cases, it may be desirable to decrease the affinity of an antibody to its antigen.

[0229] Affinity maturation can be done to increase the binding affinity of the antibody for the antigen by at least about 10% to 50%, 100%, 150% or more, or from 1- to 5-fold as compared to the "parent" antibody. Preferred affinity matured antibodies will have nanomolar or even picomolar affinities for the target antigen. Affinity matured antibodies are produced by known procedures (*e.g.*, Marks *et al.* (1992) Biotechnol. 10: 779-783; Barbas *et al.* (1994) Proc. Nat. Acad. Sci. USA 91: 3809-3813; Shier *et al.* (1995) Gene 169: 147-155; Yelton *et al.* (1995) J. Immunol. 155: 1994-2004; Jackson *et al.* (1995) J. Immunol. 154(7): 3310-9; and Hawkins *et al.* (1992) J. Mol. Biol. 226: 889-896; incorporated herein by reference in their entirety).

[0230] Alternatively, amino acid modifications can be made, *e.g.*, in one or more of the CDRs of the antibodies of the disclosure that are "silent", *e.g.*, that do not significantly alter the affinity of the antibody for the antigen. These can be made for a number of reasons, including optimizing expression (as can be done for the nucleic acids encoding the antibodies of the disclosure).

[0231] Thus, included within the definition of the CDRs and antibodies of the disclosure are variant CDRs and antibodies; that is, the antibodies of the disclosure can include amino acid modifications in one or more of the CDRs set forth in SEQ ID NOs: 3 to 8. In addition, as outlined below, amino acid modifications can also independently and optionally be made in any region outside the CDRs, including framework and constant regions.

[0232] In some embodiments, variant antibodies of mezagitamab that are specific for human CD38 (SEQ ID NO: 1) and cynomolgus CD38 (SEQ ID NO: 2) is described. This antibody is composed of six CDRs, wherein each CDR of this antibody can differ from SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and/or SEQ ID NO: 8 by 0, 1, or 2 amino acid substitutions.

Glycosylation

[0233] Another type of modification is alterations in glycosylation. In one embodiment, the antibodies disclosed herein can be modified to include one or more engineered glycoforms. By "engineered glycoform" as used herein is meant a carbohydrate composition that is covalently attached to the antibody, wherein said carbohydrate composition differs chemically from that of a parent antibody. Engineered glycoforms may be useful for a variety of purposes, including but not limited to enhancing or reducing effector function. A preferred form of engineered glycoform is afucosylation, which has been shown to be correlated to an increase in ADCC function, presumably through tighter binding to the FcγRIIIa receptor. In this context, "afucosylation" means that the majority of the antibody produced in the host cells is substantially devoid of fucose, *e.g.*, about 90-95-98% of the generated antibodies do not have appreciable fucose as a component of the carbohydrate moiety of the antibody (generally attached at N297 in the Fc region). Defined functionally, afucosylated antibodies generally exhibit at least a 50% or higher affinity to the FcγRIIIa receptor.

[0234] Engineered glycoforms may be generated by a variety of methods known in the art (US Patent No. 8,362,211, incorporated herein by reference in its entirety). "Engineered glycoform" typically refers to the different carbohydrate or oligosaccharide; thus, an antibody can include an engineered glycoform.

[0235] Alternatively, "engineered glycoform" may refer to the IgG variant that comprises the different carbohydrate or oligosaccharide. As is known in the art, glycosylation patterns can depend on both the sequence of the protein (*e.g.*, the presence or absence of particular glycosylation amino acid residues, discussed below), or the host cell or organism in which the protein is produced. Particular expression systems are discussed below.

[0236] Glycosylation of polypeptides is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tri-peptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tri-peptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the

attachment of one of the sugars N-acetylgalactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used.

[0237] Addition of glycosylation sites to the antibody is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tri-peptide sequences (for N-linked glycosylation sites). The alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues to the starting sequence (for O-linked glycosylation sites). For ease, the antibody amino acid sequence is preferably altered through changes at the DNA level, particularly by mutating the DNA encoding the target polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

[0238] Another means of increasing the number of carbohydrate moieties on the antibody is by chemical or enzymatic coupling of glycosides to the protein. These procedures are advantageous in that they do not require production of the protein in a host cell that has glycosylation capabilities for N- and O-linked glycosylation. Depending on the coupling mode used, the sugar(s) may be attached to (a) arginine and histidine, (b) free carboxyl groups, (c) free sulfhydryl groups such as those of cysteine, (d) free hydroxyl groups such as those of serine, threonine, or hydroxyproline, (e) aromatic residues such as those of phenylalanine, tyrosine, or tryptophan, or (f) the amide group of glutamine. These methods are described in WO87/05330 and in Aplin and Wriston (1981) CRC Crit. Rev. Biochem. 10(4): 259-306, both entirely incorporated by reference.

[0239] Removal of carbohydrate moieties present on the starting antibody (*e.g.*, post-translationally) may be accomplished chemically or enzymatically. Chemical deglycosylation requires exposure of the protein to the compound trifluoromethanesulfonic acid, or an equivalent compound. This treatment results in the cleavage of most or all sugars except the linking sugar (N-acetylglucosamine or N-acetylgalactosamine), while leaving the polypeptide intact. Chemical deglycosylation is described by Hakimuddin et al., 1987, Arch. Biochem. Biophys. 259:52 and by Edge et al., 1981, Anal. Biochem. 118: 131, both entirely incorporated by reference. Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura et al., 1987, Meth. Enzymol. 138:350, entirely incorporated by reference. Glycosylation at potential glycosylation

sites may be prevented by the use of the compound tunicamycin as described by Duskin *et al.* (1982) J. Biol. Chem. 257: 3105, entirely incorporated by reference. Tunicamycin blocks the formation of protein-N-glycoside linkages.

[0240] Another type of covalent modification of the antibody comprises linking the antibody to various nonproteinaceous polymers, including, but not limited to, various polyols such as polyethylene glycol, polypropylene glycol or other polyoxyalkylenes, in the manner set forth in, for example, 2005-2006 PEG Catalog from Nektar Therapeutics (available at the Nektar website) US Patents 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337, all entirely incorporated herein by reference. In addition, as is known in the art, amino acid substitutions may be made in various positions within the antibody to facilitate the addition of polymers such as PEG. See for example, U.S. Publication No. 2005/0114037Al, entirely incorporated herein by reference.

[0241] In addition to the modifications outlined above, other modifications can be made. For example, the molecules may be stabilized by the incorporation of disulfide bridges linking the VH and VL domains (Reiter *et al.* (1996) Nature Biotech. 14: 1239-1245; incorporated herein by reference in its entirety). In addition, there are a variety of covalent modifications of antibodies that can be made as outlined below.

[0242] Covalent modifications of antibodies are included within the scope of this disclosure, and are generally, but not always, done post-translationally. For example, several types of covalent modifications of the antibody are introduced into the molecule by reacting specific amino acid residues of the antibody with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C-terminal residues.

[0243] In some embodiments, the anti-CD38 antibody of the present disclosure specifically binds to one or more residues or regions in CD38 but also does not cross-react with other proteins with homology to CD38, such as BST-1 (bone marrow stromal cell antigen-1) and/or Mo5, also called CD157.

[0244] Typically, a lack of cross-reactivity means less than about 5% relative competitive inhibition between the molecules when assessed by ELISA and/or FACS analysis using sufficient amounts of the molecules under suitable assay conditions.

Side Effect Reduction

[0245] An adverse event (AE) was defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it did not necessarily have to have a causal relationship with this treatment. Treatment-emergent adverse events (TEAEs) were defined as AEs that occurred after the first dose of study drug received in the treatment period and until the end of safety follow-up. The terms "serious TEAEs" and "treatment-emergent SAEs" and can be considered interchangeable in this document. PTE and AE verbatim terms were coded by SOC and PT using MedDRA version 24.0. TEAEs are typically referred to by grades 1, 2, 3, 4, and 5, grade 1 being the least severe and grade 5 being the most severe TEAE. Based on FDA and other guidelines for Common Terminology Criteria for Adverse Events (CTCAE) standards for oncology drugs (*see*, *e.g.*, U.S. Department of Health and Human Services, Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03, 2010 and Nilsson and Koke (2001) Drug Inform. J. 35: 1289-1299, incorporated herein by reference in its entirety) the following is how such grades are generally determined. Grade 1 is mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated. Grade 2 is moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living ("ADL"). Grade 3 is severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Grade 4 is life-threatening consequence: urgent intervention indicated. Grade 5 is death related to AE.

[0246] The anti-CD38 antibodies of the present disclosure allow for reduced side effects compared to prior art anti-CD38 antibodies. In some embodiments, the antibody for use according to the present disclosure, *e.g.*, mezagitamab, does not induce TEAEs. In some embodiments, the antibody for use according to the present disclosure, *e.g.*, mezagitamab, allows for a reduction in the incidence of TEAEs in a subject population as compared to other anti-CD38 antibodies, such as MOR202. In some embodiments, the antibody for use according to the present disclosure, *e.g.*, mezagitamab, allows for a reduction in the grade of the TEAEs in a subject population as compared to other anti-CD38 antibodies, such as MOR202. In some embodiments, the antibody for use according to the present disclosure, *e.g.*, mezagitamab, allows for a reduction in the grade of the TEAEs as compared to other anti-CD38 antibodies from grade

5 to grade 4. In some embodiments, the antibody for use according to the present disclosure, *e.g.*, mezagitamab, allows for a reduction in the grade of the TEAEs as compared to other anti-CD38 antibodies from grade 4 to grade 3. In some embodiments, the antibody for use according to the present disclosure, *e.g.*, mezagitamab, allows for a reduction in the grade of the TEAEs as compared to other anti-CD38 antibodies from grade 3 to grade 2. In some embodiments, the antibody for use according to the present disclosure, *e.g.*, mezagitamab, allows for a reduction in the grade of the TEAEs as compared to other anti-CD38 antibodies from grade 2 to grade 1.

[0247] In some embodiments, the antibody for use according to the present disclosure, *e.g.*, mezagitamab allows for a reduction in grade of one or more TEAEs selected from the group consisting of anemia (including hemolytic anemia), thrombocytopenia, fatigue, infusion-related reactions (IRRs), leukopenia, lymphopenia, and nausea. In some embodiments, the antibody for use according to the present disclosure, *e.g.*, mezagitamab, allows for a reduction in the occurrence of one or more TEAEs selected from the group consisting of anemia (including hemolytic anemia), thrombocytopenia, fatigue, infusion-related reactions (IRRs), leukopenia, lymphopenia, and nausea.

[0248] In some embodiments, administering the antibody or antigen binding fragment thereof of the present disclosure results in less than 10% incidence of grade 3 or 4 of one or more TRAEs or TEAEs; optionally wherein the TRAEs or TEAEs are selected from the group consisting of gingival bleeding, heavy menstrual bleeding, haematochezia, mouth haemorrhage, haematoma, traumatic haematoma, epistaxis, petechiae, ecchymosis, conjunctival haemorrhage, blood urine, and haemorrhagic ovarian cyst.

[0249] In some embodiments, a TRAE or TEAE resulting from administering the antibody or antigen binding fragment thereof of the present disclosure has a maximum intensity of Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or Grade 2.

[0250] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a reduction in ITP-associated bleeding adverse events (AEs) relative to placebo. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in at least about 5%, at least about 10%, at least about 15%, at least about 20%, or at least about 25% reduction in ITP-associated bleeding adverse events (AEs) relative to placebo.

Disease Indication

[0251] The antibodies or antigen binding fragment thereof, methods, and dosage units of the disclosure find use in treating subjects with ITP.

Immune Thrombocytopenia (ITP)

[0252] Immune thrombocytopenic purpura (ITP), also referred to as "idiopathic thrombocytopenic purpura," "immune thrombocytopenia," "autoimmune thrombocytopenic purpura," "Werlhof disease," and "autoimmune thrombocytopenia," is a rare, IgG mediated autoimmune disease caused, in part, by the development of autoantibodies to platelets (and/or megakaryocytes), which are blood cells responsible for preventing or stopping bleeding. ITP is characterized by the accelerated destruction of platelets (with or without impaired production), resulting in a decreased platelet count and an increased risk of bleeding, which can be debilitating, or which in severe cases may be life-threatening. (Tsuda *et al.* (2017) Ann. Hematol., 96(11), 1915-1920; Zitek *et al.* (2022) Open Access Emerg. Med. 14, 25-34, incorporated herein by reference in their entireties).

[0253] There are two types of ITP: primary ITP and secondary ITP. Primary ITP is idiopathic, whereas secondary ITP is linked to an underlying condition. The rate of secondary ITP in children has not been studied in detail but is assumed to be rare (2.4%). In adults, ~18-38% of ITP subjects have an underlying disease, comorbid condition, and/or comedication, making the diagnosis of secondary ITP more probable. Secondary ITP is known to be caused by systemic autoimmune disorders, primary or secondary immunodeficiency, infectious diseases, paraneoplastic syndromes (*e.g.*, lymphomas and other malignancies), and drug-dependent antibodies.

[0254] The International Working Group on ITP further defines ITP according to the following clinical phases: (1) newly diagnosed ITP is in the first three months post-diagnosis; (2) persistent ITP is for 3-12 months; (3) chronic ITP is for >1 year; and (4) refractory ITP.

[0255] Refractory ITP was traditionally generally defined based on the absence of response or relapse after splenectomy before the advent of medical alternatives. Approximately 20% of subjects do not attain a hemostatic platelet count after splenectomy or fail to respond to initial or subsequent medical approaches; an additional 20% to 30% of splenectomy responders eventually

relapse. More recently, the definition of refractory ITP has been extended to include subjects who require treatment but are unable or unwilling to undergo splenectomy. In practice, refractory ITP is often defined as the persistence of low platelet counts despite appropriate use of all conventional therapies deemed safe for the specific subject, regardless of hemorrhagic manifestations. The threshold value to identify "low" platelet count is variable depending on the subject's age, comorbidities, and concomitant therapies (*e.g.*, antiplatelet or anticoagulant agents). As used herein, "refractory ITP" refers to subjects who are refractory to other treatments, for example, corticosteroids, immunoglobulins, and/or splenectomy.

[0256] The treatment strategy in ITP is to prevent or stop bleeding by maintaining the platelet count at or above a minimum threshold of $\geq$50,000/μL. Disease remission (or functional restoration to normal) is defined as a platelet count of $\geq$100,000/μL at 1 year after treatment is completed.

[0257] Various pharmacological agents, approved and unapproved, are currently available for treatment of ITP. Surgical removal of the spleen (splenectomy) is an invasive and aggressive treatment available in severe cases. All existing treatments have important limitations including significant adverse events such as chronic immunosuppression and in the case of splenectomy, the potential for overwhelming infections. **Figure 1** shows the mechanism of action of various pharmacological agents.

[0258] The various existing agents for ITP can be loosely categorized into first-line and second-line treatments. In adults, the corticosteroids, namely prednisone and dexamethasone, are the prototypical first line agents. First-line treatment for ITP relies on general immunosuppression with corticosteroids and the initial response rate is 50–90%. However, sustained remission is only achieved for 10–30% of patients and adverse events including infection are a concern. Intravenous immunoglobulin (IVIG) has also been used in the first line setting. Although corticosteroids may be effective in the short term, the response is poorly sustained after drug discontinuation with up to 70% of patients experiencing relapse in the long term. Their utility in ITP is further limited by well-known corticosteroid-related adverse effects such as hypertension, hyperglycemia, sleep and mood disturbances, gastric irritation or ulcer formation, glaucoma, myopathy, and osteoporosis (Al-Samkari *et al.* (2020) Blood Adv., 4(1), 9-18, incorporated herein by reference in its entirety). Approved second line agents include thrombopoietin

receptor agonists (TPO-RAs) (*e.g.,* avatrombopag, eltrombopag, and romiplostim), indicated for patients who have an insufficient response with glucocorticoids, as well as fostamatinib, which is indicated for patients with an insufficient response to previous treatment. Empiric use of rituximab or IVIG is also seen in second-line treatment, with splenectomy being a surgical option.

[0259] Approximately 20% of ITP subjects do not respond at all (do not achieve a platelet count >50,000/μL) to these first- and second-line agents or experience a loss of response or intolerance. An additional 20% to 30% of subjects with an initial response eventually relapse, resulting in increased bleeding-related morbidity and diminished quality of life (Provan *et al.* (2019) Blood Adv., 3(22), 3780-3817; Rodeghiero (2023) Int. J. Hematol., 117(3), 316-330, incorporated herein by reference in their entireties). In addition to the well-known safety and tolerability issues with the first-line treatments (corticosteroids and IVIG), the available second-line therapies (including investigational agents) have significant safety or tolerability risks as outlined in **Table 4**. Of note, each of the second-line therapies have treatment-limiting safety or tolerability concerns per approved US labeling: arterial and venous thrombosis, increase in bone marrow reticulin formation, collagen fibrosis and hepatotoxicity with TPO-RAs as well as hypotension, hepatoxicity, diarrhea, and neutropenia with fostamatinib. These side effects can limit the potential benefits from these treatments. A shared limitation of these existing approved therapies is their inability to deliver long-term sustained responses off treatment. As such, there is an unmet need for improved treatments for treating ITP.

Table 4. Safety and tolerability risks of available 2nd line therapies.

2nd Line Therapy	**Safety and Tolerability Risks**
Rituximab	Black box warning for fatal infusion, severe mucocutaneous reactions and PML
TPO-RA *(Romiplostim Ph3)*	*Mild to moderate AEs were reported in almost all subjects receiving placebo (95%) and all subjects receiving romiplostim (100%).* Clinical significance observed in romiplostim vs placebo: dizziness, insomnia, myalgia, pain in extremity, and abdominal pain, etc.
TPO-RA *(Eltrombopag Ph3)**	14% of subjects withdrew due to AEs, including hepatobiliary, cataracts, DVT, cerebral infarction, headache, myelofibrosis
Anti-FcRn *(Efgartigimod Ph2)*	~69% of subjects treated at 5mg/kg and ~85% of subjects treated at 10mg/kg had at least 1 TEAE, which were mainly mild or moderate in severity

Anti-FcRn *(Efgartigimod Ph3)*	The most common side effects are respiratory tract infection, headache, and urinary tract infection
BTK Inhibitor *(Rilzabrutinib Ph1/2)*	45% of pts experienced grade 1 or 2 TEAEs
Syk Inhibitor *(Fostamatinib)*	The most common AE were diarrhea (31%), hypertension (28%), nausea (19%), dizziness (11%) and ALT increase (11%)

[0260] The available second line therapies include TPO-RAs (*e.g.*, romiplostim, eltrombopag, avatrombopag), the recently approved Syk inhibitor (fostamatinib), a monoclonal antibody (rituximab), a small molecule Syk inhibitor (fostamatinib), splenectomy and an anti-FcRn antagonist (efgartigimod (IV)). In addition, several additional MOAs are in clinical development, including anti-BAFF antibody, BTK inhibitor, and Syk inhibitors.

[0261] Pivotal studies in this indication generally assess response to treatment by measuring durable platelet response, *i.e.*, the proportion of treated subjects that experience a sustained increase in their platelet count over time. In most of the studies performed to date, these assessments were conducted while subjects were still receiving treatment.

[0262] In six pivotal studies for the two approved TPO-RA agents (romiplostim and eltrombopag), initial platelet responses on treatment ranged between 50-90%. However, over time, approximately one third of subjects who remained either on once-daily or weekly treatments would go on to either experience recurrences and/or discontinue TPO-RAs due to lack of response.

[0263] The most recently approved ITP treatment, fostamatinib, prevents platelet destruction by inhibiting Syk-mediated IgG Fcγ receptor signaling, thus interfering with phagocytosis of antibody-covered platelets as well as antibody formation. This is a more downstream effect as it does not affect the upstream production of pathogenic autoantibodies. Fostamatinib is a chronic oral treatment administered twice daily. In its registrational studies the durable platelet response on therapy was 18%. *See* TAVALISSE® FDA Full Prescribing Information, revised November 2020, which is herein incorporated by reference in its entirety.

[0264] Anti-FcRns such as efgartigimod also deplete pathogenic IgGs by interfering with their recycling. They deplete IgG more rapidly and to a greater extent than mezagitamab; however, anti-FcRns do not affect the plasma cells that produce pathogenic autoantibodies (or other

antibodies). This means that the activity of all anti-FcRn therapies is dependent on continuous administration, precluding any potential for a durable off-therapy effect. Efgartigimod ran two Phase 3 studies in subjects with ITP, utilizing a weekly IV formulation in the first study and a weekly subcutaneously administered treatment in the second study. The weekly IV treatment achieved a 22% durable response rate at 12 weeks (on therapy) in comparison to 5% in placebo (Broome, C. M. *et al.*, Lancet, 2023, 402: 1648-1659, which is herein incorporated by reference in its entirety). Similarly, the topline results from the Phase 3 study using weekly subcutaneously administered treatment failed its primary endpoint, achieving a durable platelet response on therapy in 13% of treated subjects (vs 16% in the placebo arm).

[0265] The combination of inadequate/suboptimal efficacy and the serious adverse effects of the available therapies reveals an unmet need for a safe and effective treatment option for long-term treatment of these subjects.

[0266] In some embodiments, the disclosure provides methods of treating ITP in a subject. In some embodiments, the disclosure provides methods of treating primary ITP in a subject. In some embodiments, the disclosure provides methods of treating secondary ITP in a subject.

[0267] In some embodiments, the disclosure provides methods of treating newly diagnosed ITP in a subject. In some embodiments, the disclosure provides methods of treating acute ITP in a subject. In some embodiments, the disclosure provides methods of treating persistent ITP in a subject. In some embodiments, the disclosure provides methods of treating chronic ITP in a subject. In some embodiments, the disclosure provides methods of treating refractory ITP in a subject.

[0268] In some embodiments, the disclosure provides methods of treating newly diagnosed primary ITP in a subject. In some embodiments, the disclosure provides methods of treating acute primary ITP in a subject. In some embodiments, the disclosure provides methods of treating persistent primary ITP in a subject. In some embodiments, the disclosure provides methods of treating chronic primary ITP in a subject. In some embodiments, the disclosure provides methods of treating refractory primary ITP in a subject.

[0269] In some embodiments, the subject is diagnosed with ITP. In some embodiments, the subject is diagnosed with primary ITP. In some embodiments, the subject is diagnosed with

persistent ITP. In some embodiments, the subject is diagnosed with chronic ITP. In some embodiments, the subject is diagnosed with persistent or chronic primary ITP.

[0270] In some embodiments, the primary ITP has persisted for at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, or at least about 12 months. In some embodiments, the primary ITP has persisted for at least about 3 months.

[0271] In some embodiments, some embodiments, the disclosure provides the methods disclosed herein, wherein a subject has had an insufficient response or intolerance to other therapy. As used herein, "other therapy" generally refers to first-line and/or second-line ITP therapies, including standard-of-care therapies and background ITP medication(s). In some embodiments, the other therapy comprises one or more of a corticosteroid, immunoglobulins, splenectomy, a thrombopoietin receptor agonist (TPO-RA) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag), rituximab, fostamatinib, and/or background ITP medication(s). In some embodiments, the other therapy comprises one or more of immunoglobulins, splenectomy, romiplostim, eltrombopag, avatrombopag, hetrombopag, methotrexate, azathioprine, leflunomide, cyclosporine, fostamatinib, mycophenolate, danazol, dapsone, methylprednisolone, hydrocortisone, cortisone, prednisolone, prednisone, and/or dexamethasone. In some embodiments, the insufficient response to other treatment is defined as failure to achieve a sustained platelet count of at least 50,000/μL or doubling of baseline platelet count after an appropriate course of the other therapy. In some embodiments, the intolerance to other therapy is defined as a documented side effect causing discontinuation of the therapy.

[0272] In some embodiments, the subject has had a prior response to other therapy. In some embodiments, the subject has had a prior response to other therapy excluding a thrombopoietin receptor agonist (TPO-RA). In some embodiments, the prior response is defined as achieving a platelet count of ≥10,000/mL, ≥20,000/mL, ≥30,000/mL, ≥40,000/mL, or ≥50,000/mL. In some embodiments, the prior response is defined as achieving a platelet count of ≥50,000/mL.

[0273] In some embodiments, the subject has a baseline mean platelet count of <10,000/μL, <20,000/μL, <30,000/μL, <40,000/μL, or <50,000/μL from at least 2 consecutive measurements taken at least about 1 day apart, at least about 3 days apart, at least about 5 days apart, or at least

about 10 days apart. In some embodiments, the subject has a baseline mean platelet count of <30,000/μL from at least about 2 consecutive measurements taken at least about 5 day apart. In some embodiments, the baseline mean platelet count comprises individual values ≤35,000/μL.

[0274] The therapeutic anti-CD38 antibodies of the present disclosure bind to CD38 positive cells, resulting in depletion of these cells through multiple mechanisms of action, including both CDC and ADCC pathways.

[0275] In some embodiments, the disclosure provides methods of treating ITP in a subject in need thereof, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof. In some embodiments, the isolated human anti-CD38 antibody or antigen binding fragment thereof is administered in a dosage of from about 100 mg to about 600 mg. In some embodiments, the isolated human anti-CD38 antibody or antigen binding fragment thereof is administered subcutaneously.

[0276] In some embodiments, the disclosure provides methods of treating ITP in a subject in need thereof, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8. In some embodiments, the isolated human anti-CD38 antibody or antigen binding fragment thereof is administered in a dosage of from about 100 mg to about 600 mg. In some embodiments, the isolated human anti-CD38 antibody or antigen binding fragment thereof is administered subcutaneously.

[0277] In some embodiments, the disclosure provides methods of treating ITP in a subject in need thereof, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO:

4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

[0278] In some embodiments, the disclosure provides methods of reducing the level of plasmablasts, plasma cells, and/or NK cells in a subject diagnosed with ITP, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof. In some embodiments, the disclosure provides methods of reducing the level of plasmablasts, plasma cells, and/or NK cells in a subject diagnosed with ITP, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

[0279] In some embodiments, the disclosure provides methods of reducing the level of immunoglobulin(s) in a subject diagnosed with ITP, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof. In some embodiments, the disclosure provides methods of reducing the level of immunoglobulin(s) in a subject diagnosed with ITP, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the

amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg. In some embodiments, the immunoglobulin is IgA, IgG and/or IgM. In some embodiments, the immunoglobulin is IgA. In some embodiments, the immunoglobulin is IgG. In some embodiments, the immunoglobulin is IgM.

[0280] In some embodiments, the disclosure provides methods of reducing the level of immunoglobulin(s) in a subject diagnosed with ITP, wherein the immunoglobulin(s) (*e.g.*, IgA, IgG, and/or IgM) are reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 90%, or at least about 95% relative to baseline levels of the immunoglobulin(s). In some embodiments, IgA is reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 90%, or at least about 95% relative to baseline levels of the IgA. In some embodiments, IgG is reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 90%, or at least about 95% relative to baseline levels of the IgG. In some embodiments, IgM is reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 90%, or at least about 95% relative to baseline levels of IgM. In some embodiments, IgA is reduced by at least about 50% relative to baseline levels of IgA. In some embodiments, IgG is reduced by at least about 30% relative to baseline levels of IgG. In some embodiments, IgM is reduced by at least about 40% relative to baseline levels of IgM.

[0281] In some embodiments, the disclosure provides methods of reducing the level of immunoglobulin(s) in a subject diagnosed with ITP, wherein administering the isolated antibody

or antigen binding fragment thereof results in a reduction in immunoglobulin(s) (*e.g.*, IgA, IgG, and/or IgM) in six weeks or less, five weeks or less, four weeks or less, three weeks or less, two weeks or less, or one week or less. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a reduction in immunoglobulin(s) in one week or less.

[0282] In some embodiments, the disclosure provides methods of increasing platelet counts in a subject in need thereof the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof. In some embodiments, the disclosure provides methods of increasing platelet counts in a subject in need thereof, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet count of >10,000/μL, >20,000/μL, >30,000/μL, >40,000/μL, >50,000/μL, >60,000/μL, >70,000/μL, >80,000/μL, >90,000/μL, or >100,000/μL. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet count of >50,000/μL. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet count of >100,000/μL.

[0283] In some embodiments, the disclosure provides methods of achieving platelet response in a subject in need thereof the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof. In some embodiments, the disclosure provides methods of achieving platelet response in a subject in need thereof the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid

sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg. In some embodiments, the platelet response is defined as a platelet count of ≥10,000/μL, ≥20,000/μL, ≥30,000/μL, ≥40,000/μL, ≥50,000/μL, ≥60,000/μL, ≥70,000/μL, ≥80,000/μL, ≥90,000/μL, ≥100,000/μL, ≥110,000/μL, ≥120,000/μL, ≥130,000/μL, ≥140,000/μL, or ≥150,000/μL. In some embodiments, the platelet response is defined as a platelet count of ≥20,000/μL above baseline, for example, ≥30,000/μL, ≥40,000/μL, ≥50,000/μL, ≥60,000/μL, ≥70,000/μL, ≥80,000/μL, ≥90,000/μL, or ≥100,000/μL above baseline. In some embodiments, the platelet response is defined as a platelet count of ≥50,000/μL and ≥20,000/μL above baseline. In some embodiments, the platelet response is defined as a platelet count of ≥50,000/μL and/or the platelet response is defined as a platelet count of ≥30,000/μL and at least doubled from baseline. In some embodiments, the platelet response is defined as a platelet count of ≥50,000/μL. In some embodiments, the platelet response is defined as a platelet count of ≥30,000/μL and at least doubled from baseline. In some embodiments, the platelet response is defined as a platelet count of ≥10,000/μL, ≥20,000/μL, ≥30,000/μL, ≥40,000/μL, or ≥50,000/μL at about 2 weeks, about 4 weeks, about 6 weeks, about 8 weeks, about 10 weeks, about 12 weeks, about 14 weeks, about 16 weeks, about 18 weeks, or about 20 weeks after the administering. In some embodiments, the platelet response is defined as a platelet count of ≥50,000/μL at about 16 weeks after the administering.

[0284] In some embodiments, the disclosure provides methods of achieving platelet response in a subject in need thereof, wherein the method achieves a platelet response in six weeks or less, five weeks or less, four weeks or less, three weeks or less, two weeks or less, or one week or less. In some embodiments, the method achieves a platelet response in one week or less.

[0285] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet response for at least 2 cumulative number of weeks, at least 4 cumulative number of weeks, at least 8 cumulative number of weeks, at least 10 cumulative number of weeks, at least 12 cumulative number of weeks, at least 14 cumulative number of

weeks, at least 16 cumulative number of weeks, at least 18 cumulative number of weeks, or at least 20 cumulative number of weeks from baseline to about 24 weeks after the administering.

[0286] In some embodiments, the disclosure provides methods of achieving durable platelet response in a subject in need thereof the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof. In some embodiments, the disclosure provides methods of achieving durable platelet response in a subject in need thereof the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg. In some embodiments, the durable platelet response is defined as a sustained platelet response for at least 1 of 6 biweekly measurements, at least 2 of 6 biweekly measurements, at least 3 of 6 biweekly measurements, at least 4 of 6 biweekly measurements, or at least 5 of 6 biweekly measurements from about 10 weeks to about 24 weeks after the administering, wherein the subject has not received a rescue therapy. In some embodiments, the durable platelet response is defined as a sustained platelet response for at least 1 of 6 weekly measurements, at least 2 of 6 weekly measurements, at least 3 of 6 weekly measurements, at least 4 of 6 weekly measurements, or at least 5 of 6 weekly platelet measurements from baseline to about 24 weeks after the administering. In some embodiments, the durable platelet response is defined as a sustained platelet response for at least 4 of 6 biweekly measurements from about 10 weeks to about 24 weeks after the administering, wherein the subject has not received a rescue therapy. In some embodiments, the platelet response is defined at a platelet count of $\geq$10,000/μL, $\geq$20,000/μL, $\geq$30,000/μL, $\geq$40,000/μL, $\geq$50,000/μL, $\geq$60,000/μL, $\geq$70,000/μL, $\geq$80,000/μL, $\geq$90,000/μL, $\geq$100,000/μL, $\geq$110,000/μL, $\geq$120,000/μL, $\geq$130,000/μL, $\geq$140,000/μL, or $\geq$150,000/μL. In some embodiments, the platelet response is defined at a platelet count of $\geq$50,000/μL. In some

embodiments, the durable platelet response is defined as a platelet count of ≥10,000/μL, ≥20,000/μL, ≥30,000/μL, ≥40,000/μL, or ≥50,000/μL on at least 1 of 6, at least 2 of 6, at least 3 of 6, or at least 4 of 6 weekly platelet measurements from baseline to about 24 weeks after the administering, from about 5 weeks to about 24 weeks after the administering, from about 10 weeks to about 24 weeks after the administering, from about 15 weeks to about 24 weeks after the administering, or from about 19 weeks to about 24 weeks after the administering. In some embodiments, the durable platelet response is defined as a platelet count of ≥50,000/μL on at least 2 of 6 weekly platelet measurements from about 10 weeks to about 24 weeks after the administering. In some embodiments, the durable platelet response is defined as a platelet count of ≥50,000/μL on at least 4 of 6 weekly platelet measurements from about 19 weeks to about 24 weeks after the administering. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a durable platelet response, wherein the durable platelet response is measured as the cumulative number of weeks in which platelet count is sustained (e.g., ≥30,000/μL or ≥50,000/μL). In some embodiments, the platelet response is sustained for at least about 2 weeks, at least about 4 weeks, at least about 6 weeks, at least about 8 weeks, at least about 10 weeks, at least about 12 weeks, at least about 14 weeks, at least about 16 weeks, at least about 18 weeks, at least about 20 weeks, at least about 25 weeks, at least about 30 weeks, at least about 35 weeks, at least about 40 weeks, at least about 45 weeks, or at least about 50 weeks after the administration of the isolated human anti-CD38 antibody or antigen binding fragment thereof.

[0287] In some embodiments, the disclosure provides methods of achieving complete platelet response in a subject in need thereof the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof. In some embodiments, the disclosure provides methods of achieving complete platelet response in a subject in need thereof the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2

having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg. In some embodiments, the complete platelet response is defined as a platelet count of ≥50,000/μL, ≥60,000/μL, ≥70,000/μL, ≥80,000/μL, ≥90,000/μL, ≥100,000/μL, ≥110,000/μL, ≥120,000/μL, ≥130,000/μL, ≥140,000/μL, ≥150,000/μL, ≥175,000/μL, or ≥200,000/μL. In some embodiments, the complete platelet response is defined as a platelet count of ≥100,000/μL. In some embodiments, the complete platelet response is measured on at least one visit, at least two visits, at least three visits, at least four visits, or at least five visits from baseline to about 10 weeks after the administering, from baseline to about 12 weeks after the administering, from baseline to about 14 weeks after the administering, from baseline to about 16 weeks after the administering, from baseline to about 18 weeks after the administering, from baseline to about 20 weeks after the administering, from baseline to about 22 weeks after the administering, or from baseline to about 24 weeks after the administering, optionally wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the complete platelet response is measured in at least one measurement, at least two measurements, at least three measurements, at least four measurements, or at least five measurements from baseline to about 10 weeks after the administering, from baseline to about 12 weeks after the administering, from baseline to about 14 weeks after the administering, from baseline to about 16 weeks after the administering, from baseline to about 18 weeks after the administering, from baseline to about 20 weeks after the administering, from baseline to about 22 weeks after the administering, or from baseline to about 24 weeks after the administering. In some embodiments, the complete platelet response is measured on at least two visits from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the complete platelet response is defined as a platelet count of ≥100,000/μL in at least one measurement from baseline to about 24 weeks after the administering. In some embodiments, the complete platelet response is defined as a platelet count of ≥100,000/μL in at least two measurements from baseline to about 24 weeks after the administering.

[0288] In some embodiments, the disclosure provides methods of achieving a clinically meaningful platelet response in a subject in need thereof the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof. In some embodiments, the disclosure provides methods of achieving a clinically meaningful platelet response in a subject in need thereof the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg. In some embodiments, the clinically meaningful platelet response is defined as a platelet count ≥20,000/μL, ≥30,000/μL, ≥40,000/μL, ≥50,000/μL, ≥60,000/μL, ≥70,000/μL, ≥80,000/μL, ≥90,000/μL, or ≥100,000/μL above baseline. In some embodiments, the clinically meaningful platelet response is defined as a platelet count ≥20,000/μL above baseline. In some embodiments, the clinically meaningful platelet response is measured on at least one visit, at least two visits, at least three visits, at least four visits, or at least five visits from baseline to about 10 weeks after the administering, from baseline to about 12 weeks after the administering, from baseline to about 14 weeks after the administering, from baseline to about 16 weeks after the administering, from baseline to about 18 weeks after the administering, from baseline to about 20 weeks after the administering, from baseline to about 22 weeks after the administering, from baseline to about 24 weeks after the administering, or from baseline to about 32 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the clinically meaningful platelet response is measured on at least two visits from baseline to about 16 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the clinically meaningful platelet response is measured on at least two visits from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the clinically meaningful platelet response is measured in at

least one measurement, at least two measurements, at least three measurements, at least four measurements, or at least five measurements from baseline to about 10 weeks after the administering, from baseline to about 12 weeks after the administering, from baseline to about 14 weeks after the administering, from baseline to about 16 weeks after the administering, from baseline to about 18 weeks after the administering, from baseline to about 20 weeks after the administering, from baseline to about 22 weeks after the administering, from baseline to about 24 weeks after the administering, or from baseline to about 32 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the clinically meaningful platelet response is measured in at least two measurements from baseline to about 16 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the clinically meaningful platelet response is measured in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a clinically meaningful platelet response, wherein the clinically meaningful platelet response is defined as a platelet count of $\geq$20,000/μL above baseline in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks.

[0289] In some embodiments, the disclosure provides methods of achieving hemostatic platelet response in a subject in need thereof having a baseline platelet count of <15,000/μL, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof. In some embodiments, the disclosure provides methods of achieving hemostatic platelet response in a subject in need thereof having a baseline platelet count of <15,000/μL, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence

of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg. In some embodiments, the baseline platelet count is <12,000/μL, <10,000/μL, <8,000/μL, <5,000/μL, or <1,000/μL. In some embodiments, the hemostatic platelet response is defined as a platelet count of ≥30,000/μL, ≥40,000/μL, ≥50,000/μL, ≥60,000/μL, ≥70,000/μL, ≥80,000/μL, ≥90,000/μL, or ≥100,000/μL. In some embodiments, the hemostatic platelet response is defined as a platelet count of ≥20,000/μL, ≥30,000/μL, ≥40,000/μL, ≥50,000/μL, ≥60,000/μL, ≥70,000/μL, ≥80,000/μL, ≥90,000/μL, or ≥100,000/μL above baseline. In some embodiments, the hemostatic platelet response is defined as a platelet count of ≥30,000/μL and ≥20,000/μL above baseline. In some embodiments, the hemostatic platelet response is measured on at least one visit, at least two visits, at least three visits, at least four visits, or at least five visits from baseline to about 10 weeks after the administering, from baseline to about 12 weeks after the administering, from baseline to about 14 weeks after the administering, from baseline to about 16 weeks after the administering, from baseline to about 18 weeks after the administering, from baseline to about 20 weeks after the administering, from baseline to about 22 weeks after the administering, from baseline to about 24 weeks after the administering, or from baseline to about 32 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the hemostatic platelet response is measured on at least two visits from baseline to about 18 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the hemostatic platelet response is measured on at least two visits from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the hemostatic platelet response is measured in at least one measurement, at least two measurements, at least three measurements, at least four measurements, or at least five measurements from baseline to about 10 weeks after the administering, from baseline to about 12 weeks after the administering, from baseline to about 14 weeks after the administering, from baseline to about 16 weeks after the administering, from baseline to about 18 weeks after the administering, from baseline to about 20 weeks after the administering, from baseline to about 22 weeks after the administering, from baseline to about 24 weeks after the administering, or from baseline to about 32 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks and the subject has a baseline platelet count of <15,000/μL.

In some embodiments, the hemostatic platelet response is measured in at least two measurements from baseline to about 18 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks and the subject has a baseline platelet count of <15,000/μL. In some embodiments, the hemostatic platelet response is measured in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks and the subject has a baseline platelet count of <15,000/μL. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a hemostatic platelet response, wherein the hemostatic platelet response is defined as a platelet count of ≥30,000/μL and ≥20,000/μL above baseline in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks and the subject has a baseline platelet count of <15,000/μL.

[0290] In some embodiments, the disclosure provides methods of reducing the level of autoantibodies in a subject diagnosed with ITP, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof. In some embodiments, the disclosure provides methods of reducing the level of autoantibodies in a subject diagnosed with ITP, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg. In some embodiments, the disclosure provides the methods as disclosed herein, wherein the autoantibodies are anti-platelet autoantibodies.

[0291] In some embodiments, the disclosure provides methods of reducing ITP disease activity and/or progression in a subject diagnosed with ITP, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the

isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

[0292] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the ITP disease activity and/or progression is measured one or more assessments selected from the group consisting of World Health Organization (WHO) Bleeding Scale, Immune Thrombocytopenic Purpura Subject Assessment Questionnaire (ITP-PAQ), and/or 5-Level EuroQol Five Dimensions (EQ-5D-5L). In some embodiments, the ITP disease activity and/or progression is measured by World Health Organization (WHO) Bleeding Scale. In some embodiments, the ITP disease activity and/or progression is measured by Immune Thrombocytopenic Purpura Subject Assessment Questionnaire (ITP-PAQ). In some embodiments, the ITP disease activity and/or progression is measured by 5-Level EuroQol Five Dimensions (EQ-5D-5L). In some embodiments, the ITP disease activity and/or progression is measured by a change from baseline in Symptoms, Fatigue/Sleep, Physical Health-Activity, Physical Health-Bother, Psychological Health, Overall Quality of Life, Social Activity, and/or Work scales scores of the ITP-PAQ from baseline to about 24 weeks after the administering. In some embodiments, the ITP disease activity and/or progression is measured by a change from baseline in the Menstrual Symptoms subscale scores of the ITP-PAQ from baseline to about 24 weeks after the administering in a female subject who had at least one menstrual period within 12 months before the receiving the isolated antibody. In some embodiments, the ITP disease activity and/or progression is measured by a change from baseline in the Fertility subscale scores of the ITP-PAQ in a female subject from baseline to about 24 weeks after the administering. In some embodiments, the ITP disease activity and/or progression is measured by a change from baseline in the EQ-5D-5L utility index score and/or VAS score from baseline to about 24 weeks after the administering. In some embodiments, the ITP disease activity and/or progression is

measured by a change in a Symptoms Scale Score of ITP-PAQ from baseline to about 24 weeks after the administering.

[0293] In some embodiments, the disclosure provides methods of reducing bleeding events in a subject diagnosed with immune thrombocytopenia (ITP), the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg. In some embodiments, bleed events are measured by Immune Thrombocytopenia-specific Bleeding Assessment Tool (ITP-BAT). In some embodiments, the bleeding events comprise Grade ≥2 in the Skin domain, Grade ≥1 in the Mucosal domain, and/or Grade ≥1 in the Organ domain.

[0294] In some embodiments, the disclosure provides methods of achieving immune thrombocytopenia (ITP) remission in a subject diagnosed with ITP, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg. In some embodiments, ITP remission is defined as all platelet counts ≥10,000/μL, ≥20,000/μL, ≥30,000/μL, ≥40,000/μL, or ≥50,000/μL for at least about 12 weeks, at least about 14 weeks, at least about 16 weeks, at least about 18 weeks, at least about 20 weeks, at least about 25 weeks, at least about 30 weeks, at least about 35 weeks, at least about 40

weeks, at least about 45 weeks, or at least about 50 weeks after any treatment cycle with isolated antibody or antigen binding fragment thereof in the absence of other therapy for ITP. In some embodiments, ITP remission is defined as all platelet counts ≥50,000/μL for at least about 12 or at least about 24 weeks after any treatment cycle with the isolated antibody or antigen binding fragment thereof in the absence of other therapy for ITP. In some embodiments, ITP remission is defined as all platelet counts ≥50,000/μL for at least about 24 weeks after any treatment cycle with the isolated antibody or antigen binding fragment thereof in the absence of other therapy for ITP.

[0295] In some embodiments, the disclosure provides methods of treating immune thrombocytopenia (ITP) in a subject diagnosed with ITP, the method comprising administering to the subject an isolated human anti-CD38 antibody, wherein the isolated antibody comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8, wherein the ITP is chronic primary ITP or persistent primary ITP, the subject has had an insufficient response or intolerance to other therapy, the other therapy is a first-line ITP therapy and/or a second-line ITP therapy, the other therapy comprises one or more of a corticosteroid, immunoglobulins, splenectomy, a thrombopoietin receptor agonist (TPO-RA) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag), rituximab, fostamatinib, and background ITP medication(s) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag, methotrexate, azathioprine, leflunomide, cyclosporine, fostamatinib, mycophenolate, danazol, dapsone, methylprednisolone, hydrocortisone, cortisone, prednisolone, prednisone, and/or dexamethasone), the isolated antibody is subcutaneously administered in a dosage of about 600 mg in a course of once per week for 8 weeks, optionally wherein the isolated antibody is further administered in more than one (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 courses, *etc.*) course of once per week for 8 weeks; and/or optionally wherein the isolated antibody is not further administered for a period of 8 weeks.

[0296] In some embodiments, the disclosure provides the methods as disclosed herein, wherein (a) the isolated antibody is administered once per week for from 1 week to 16 weeks; (b) the isolated antibody is not administered for a period of from 1 week to 16 weeks; and (c) the isolated antibody is administered once per week for from 1 week to 16 weeks. In some embodiments, (a) the isolated antibody is administered once per week for from 1 week to 16 weeks, from 2 weeks to 16 weeks, from 3 weeks to 16 weeks, from 4 weeks to 16 weeks, from 5 weeks to 16 weeks, from 6 weeks to 16 weeks, from 7 weeks to 16 weeks, from 8 weeks to 16 weeks, from 1 week to 15 weeks, from 1 week to 14 weeks, from 1 week to 13 weeks, from 1 week to 12 weeks, from 1 week to 11 weeks, from 1 week to 10 weeks, from 1 week to 9 weeks, from 1 week to 8 weeks, from 7 weeks to 9 weeks, from 6 weeks to 10 weeks, from 5 weeks to 11 weeks, from 4 weeks to 12 weeks, from 3 weeks to 13 weeks, or from 2 weeks to 14 weeks. In some embodiments, (b) the isolated antibody is not administered for a period of from 1 week to 16 weeks, from 2 weeks to 16 weeks, from 3 weeks to 16 weeks, from 4 weeks to 16 weeks, from 5 weeks to 16 weeks, from 6 weeks to 16 weeks, from 7 weeks to 16 weeks, from 8 weeks to 16 weeks, from 1 week to 15 weeks, from 1 week to 14 weeks, from 1 week to 13 weeks, from 1 week to 12 weeks, from 1 week to 11 weeks, from 1 week to 10 weeks, from 1 week to 9 weeks, from 1 week to 8 weeks, from 7 weeks to 9 weeks, from 6 weeks to 10 weeks, from 5 weeks to 11 weeks, from 4 weeks to 12 weeks, from 3 weeks to 13 weeks, or from 2 weeks to 14 weeks. In some embodiments, (c) the isolated antibody is administered once per week for from 1 week to 16 weeks, from 2 weeks to 16 weeks, from 3 weeks to 16 weeks, from 4 weeks to 16 weeks, from 5 weeks to 16 weeks, from 6 weeks to 16 weeks, from 7 weeks to 16 weeks, from 8 weeks to 16 weeks, from 1 week to 15 weeks, from 1 week to 14 weeks, from 1 week to 13 weeks, from 1 week to 12 weeks, from 1 week to 11 weeks, from 1 week to 10 weeks, from 1 week to 9 weeks, from 1 week to 8 weeks, from 7 weeks to 9 weeks, from 6 weeks to 10 weeks, from 5 weeks to 11 weeks, from 4 weeks to 12 weeks, from 3 weeks to 13 weeks, or from 2 weeks to 14 weeks. In some embodiments, (a) the isolated antibody is administered once per week for 8 weeks. In some embodiments, (b) the isolated antibody is not administered for a period of 8 weeks. In some embodiments, (c) the isolated antibody is administered once per week for 8 weeks. In some embodiments, the disclosure provides the methods as disclosed herein, wherein (a) the isolated antibody is administered once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; and (c) the isolated antibody is

administered once per week for 8 weeks. In some embodiments, the disclosure provides the methods as disclosed herein, wherein (a) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; and (c) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks. In some embodiments, the disclosure provides the methods as disclosed herein, further comprising (d) the isolated antibody is not administered for a period of from 1 week to 16 weeks. In some embodiments, (d) the isolated antibody is not administered for a period of from 1 week to 16 weeks, from 2 weeks to 16 weeks, from 3 weeks to 16 weeks, from 4 weeks to 16 weeks, from 5 weeks to 16 weeks, from 6 weeks to 16 weeks, from 7 weeks to 16 weeks, from 8 weeks to 16 weeks, from 1 week to 15 weeks, from 1 week to 14 weeks, from 1 week to 13 weeks, from 1 week to 12 weeks, from 1 week to 11 weeks, from 1 week to 10 weeks, from 1 week to 9 weeks, from 1 week to 8 weeks, from 7 weeks to 9 weeks, from 6 weeks to 10 weeks, from 5 weeks to 11 weeks, from 4 weeks to 12 weeks, from 3 weeks to 13 weeks, or from 2 weeks to 14 weeks. In some embodiments, (d) the isolated antibody is not administered for a period of 8 weeks. In some embodiments, the disclosure provides the methods as disclosed herein, wherein (a) the isolated antibody is administered once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; (c) the isolated antibody is administered once per week for 8 weeks; and (d) the isolated antibody is not administered for a period of 8 weeks. In some embodiments, the disclosure provides the methods as disclosed herein, wherein (a) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; (c) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks; and (d) the isolated antibody is not administered for a period of 8 weeks. In some embodiments, the disclosure provides the methods as disclosed herein, wherein the antibody or antigen binding fragment thereof is administered in a dosage of from about 100 mg to about 600 mg, for example, about 100 mg, about 300 mg, or about 600 mg. In some embodiments, the disclosure provides the methods as disclosed herein, wherein the isolated antibody is subcutaneously administered.

[0297] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the subject in need thereof has a baseline mean platelet count of less than or equal to about 100×10^9/L, less than or equal to about 50×10^9/L, less than or equal to about 45×10^9/L, less than or equal to about 40×10^9/L, less than or equal to about 35×10^9/L, less than or equal to about 30×10^9/L, less than or equal to about 25×10^9/L, less than or equal to about 20×10^9/L, less than or equal to about 15×10^9/L, or less than or equal to about 10×10^9/L.

[0298] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the subject in need thereof has an ITP disease duration (*e.g.*, mean ITP disease duration) of at least about 0.1 years, at least about 0.2 years, at least about 0.3 years, at least about 0.4 years, at least about 0.5 years, at least about 0.6 years, at least about 0.7 years, at least about 0.8 years, at least about 0.9 years, at least about 1 year, at least about 2 years, at least about 3 years, at least about 4 years, at least about 5 years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, at least about 10 years, at least about 11 years, at least about 12 years, at least about 13 years, at least about 14 years, at least about 15 years, at least about 20 years, at least about 25 years, at least about 30 years, or at least about 35 years.

[0299] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the subject in need thereof has received a mean of about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, or about 13 prior ITP treatments.

[0300] In some embodiments, the disclosure provides the methods as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in a length of platelet response of at least about 1 week, at least about 5 weeks, at least about 10 weeks, at least about 15 weeks, at least about 20 weeks, at least about 25 weeks, at least about 30 weeks, at least about 35 weeks, at least about 40 weeks, at least about 45 weeks, or at least about 50 weeks, wherein the length of the platelet response is defined as the sum of all weeks in which the subject achieves a platelet response, and wherein the platelet response is defined as a platelet count of ≥10,000/μL, ≥20,000/μL, ≥30,000/μL, ≥40,000/μL, ≥50,000/μL, ≥60,000/μL, ≥70,000/μL, ≥80,000/μL, ≥90,000/μL, ≥100,000/μL, ≥110,000/μL, ≥120,000/μL, ≥130,000/μL, ≥140,000/μL, or ≥150,000/μL. In some embodiments, the length of platelet response is at least about 1 week, at least about 5 weeks, at least about 10 weeks, at least about 15 weeks, at least about 20 weeks, at least about 25 weeks, at least about 30 weeks, at least about 35 weeks, at least about 40 weeks,

at least about 45 weeks, or at least about 50 weeks, wherein the length of the platelet response is defined as the sum of all weeks in which the subject achieves a platelet response, and wherein the platelet response is defined as a platelet count of ≥50,000/μL.

[0301] In some embodiments, the disclosure provides the methods as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in a platelet response, wherein the platelet response is defined as a platelet count of ≥10,000/μL, ≥20,000/μL, ≥30,000/μL, ≥40,000/μL, ≥50,000/μL, ≥60,000/μL, ≥70,000/μL, ≥80,000/μL, ≥90,000/μL, ≥100,000/μL, ≥110,000/μL, ≥120,000/μL, ≥130,000/μL, ≥140,000/μL, or ≥150,000/μL. In some embodiments, the platelet response is defined as a platelet count of ≥20,000/μL above baseline, for example, ≥30,000/μL, ≥40,000/μL, ≥50,000/μL, ≥60,000/μL, ≥70,000/μL, ≥80,000/μL, ≥90,000/μL, or ≥100,000/μL above baseline. In some embodiments, the platelet response is defined as a platelet count of ≥50,000/μL and ≥20,000/μL above baseline. In some embodiments, the platelet response is defined as a platelet count of ≥50,000/μL and/or the platelet response is defined as a platelet count of ≥30,000/μL and at least doubled from baseline. In some embodiments, the platelet response is defined as a platelet count of ≥50,000/μL. In some embodiments, the platelet response is defined as a platelet count of ≥30,000/μL and at least doubled from baseline. In some embodiments, the platelet response is defined as a platelet count of ≥10,000/μL, ≥20,000/μL, ≥30,000/μL, ≥40,000/μL, or ≥50,000/μL at about 2 weeks after the administering, about 4 weeks after the administering, about 6 weeks after the administering, about 8 weeks after the administering, about 10 weeks after the administering, about 12 weeks after the administering, about 14 weeks after the administering, about 16 weeks after the administering, about 18 weeks after the administering, or about 20 weeks after the administering. In some embodiments, the platelet response is defined as a platelet count of ≥50,000/μL at about 16 weeks after the administering.

[0302] In some embodiments, the disclosure provides the methods as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in a platelet response in six weeks or less, five weeks or less, four weeks or less, three weeks or less, two weeks or less, or one week or less. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet response in one week or less.

[0303] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet response for at least 2 cumulative number of weeks, at least 4 cumulative number of weeks, at least 8 cumulative number of weeks, at least 10 cumulative number of weeks, at least 12 cumulative number of weeks, at least 14 cumulative number of weeks, at least 16 cumulative number of weeks, at least 18 cumulative number of weeks, or at least 20 cumulative number of weeks from baseline to about 24 weeks after the administering.

[0304] In some embodiments, the disclosure provides the methods as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in a durable platelet response, wherein the durable platelet response is defined as a durable platelet response for at least 1 of 6 biweekly measurements, at least 2 of 6 biweekly measurements, at least 3 of 6 biweekly measurements, at least 4 of 6 biweekly measurements, or at least 5 of 6 biweekly measurements from about 10 weeks to about 24 weeks after the administering, optionally wherein the subject has not received a rescue therapy. In some embodiments, the durable platelet response is defined as a durable platelet response for at least 1 of 6 weekly measurements, at least 2 of 6 weekly measurements, at least 3 of 6 weekly measurements, at least 4 of 6 weekly measurements, or at least 5 of 6 weekly platelet measurements from baseline to about 24 weeks after the administering. In some embodiments, the durable platelet response is defined as a durable platelet response for at least 4 of 6 biweekly measurements from about 10 weeks to about 24 weeks after the administering, wherein the subject has not received a rescue therapy. In some embodiments, the platelet response is defined at a platelet count of $\geq$10,000/μL, $\geq$20,000/μL, $\geq$30,000/μL, $\geq$40,000/μL, $\geq$50,000/μL, $\geq$60,000/μL, $\geq$70,000/μL, $\geq$80,000/μL, $\geq$90,000/μL, $\geq$100,000/μL, $\geq$110,000/μL, $\geq$120,000/μL, $\geq$130,000/μL, $\geq$140,000/μL, or $\geq$150,000/μL. In some embodiments, the platelet response is defined at a platelet count of $\geq$50,000/μL. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a durable platelet response, wherein the durable platelet response is measured as the cumulative number of weeks in which platelet count is sustained (e.g., $\geq$30,000/μL or $\geq$50,000/μL). In some embodiments, the platelet response is sustained for at least about 2 weeks, at least about 4 weeks, at least about 6 weeks, at least about 8 weeks, at least about 10 weeks, at least about 12 weeks, at least about 14 weeks, at least about 16 weeks, at least about 18 weeks, at least about 20 weeks, at least about 25 weeks, at least about 30 weeks, at least

about 35 weeks, at least about 40 weeks, at least about 45 weeks, or at least about 50 weeks after the administration of the isolated human anti-CD38 antibody or antigen binding fragment thereof. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a durable platelet response, wherein the durable platelet response is defined as a durable platelet response for at least 4 of 6 biweekly measurements from about 10 weeks to about 24 weeks after the administering, wherein the subject has not received a rescue therapy, and wherein the platelet response is defined at a platelet count of ≥50,000/μL. In some embodiments, the durable platelet response is defined as a platelet count of ≥10,000/μL, ≥20,000/μL, ≥30,000/μL, ≥40,000/μL, or ≥50,000/μL on at least 1 of 6, at least 2 of 6, or at least 3 of 6 weekly platelet measurements from baseline to about 24 weeks after the administering, from about 5 weeks to about 24 weeks after the administering, from about 10 weeks to about 24 weeks after the administering, from about 15 weeks to about 24 weeks after the administering, or from about 19 weeks to about 24 weeks after the administering. In some embodiments, the durable platelet response is defined as a platelet count of ≥50,000/μL on at least 2 of 6 weekly platelet measurements from about 10 weeks to about 24 weeks after the administering. In some embodiments, the durable platelet response is defined as a platelet count of ≥50,000/μL on at least 4 of 6 weekly platelet measurements from about 19 weeks to about 24 weeks after the administering.

[0305] In some embodiments, the disclosure provides the methods as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in a complete platelet response, wherein the complete platelet response is defined as a platelet count of ≥50,000/μL, ≥60,000/μL, ≥70,000/μL, ≥80,000/μL, ≥90,000/μL, ≥100,000/μL, ≥110,000/μL, ≥120,000/μL, ≥130,000/μL, ≥140,000/μL, ≥150,000/μL, ≥175,000/μL, or ≥200,000/μL. In some embodiments, the complete platelet response is defined as a platelet count of ≥100,000/μL. In some embodiments, the complete platelet response is measured on at least one visit, at least two visits, at least three visits, at least four visits, or at least five visits from baseline to about 10 weeks after the administering, from baseline to about 12 weeks after the administering, from baseline to about 14 weeks after the administering, from baseline to about 16 weeks after the administering, from baseline to about 18 weeks after the administering, from baseline to about 20 weeks after the administering, from baseline to about 22 weeks after the administering, or from

baseline to about 24 weeks after the administering, optionally wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the complete platelet response is measured in at least one measurement, at least two measurements, at least three measurements, at least four measurements, or at least five measurements from baseline to about 10 weeks after the administering, from baseline to about 12 weeks after the administering, from baseline to about 14 weeks after the administering, from baseline to about 16 weeks after the administering, from baseline to about 18 weeks after the administering, from baseline to about 20 weeks after the administering, from baseline to about 22 weeks after the administering, or from baseline to about 24 weeks after the administering. In some embodiments, the complete platelet response is measured on at least two visits from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the complete platelet response is defined as a platelet count of ≥100,000/μL on at least two visits from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the complete platelet response is defined as a platelet count of ≥100,000/μL in at least one measurement from baseline to about 24 weeks after the administering. In some embodiments, the complete platelet response is defined as a platelet count of ≥100,000/μL in at least two measurements from baseline to about 24 weeks after the administering.

[0306] In some embodiments, the disclosure provides the methods as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in a clinically meaningful platelet response, wherein the clinically meaningful platelet response is defined as a platelet count ≥20,000/μL, ≥30,000/μL, ≥40,000/μL, ≥50,000/μL, ≥60,000/μL, ≥70,000/μL, ≥80,000/μL, ≥90,000/μL, or ≥100,000/μL above baseline. In some embodiments, the clinically meaningful platelet response is defined as a platelet count ≥20,000/μL above baseline. In some embodiments, the clinically meaningful platelet response is measured on at least one visit, at least two visits, at least three visits, at least four visits, or at least five visits from baseline to about 10 weeks after the administering, from baseline to about 12 weeks after the administering, from baseline to about 14 weeks after the administering, from baseline to about 16 weeks after the administering, from baseline to about 18 weeks after the administering, from baseline to about 20 weeks after the administering, from baseline to about 22 weeks after the administering,

or from baseline to about 24 weeks after the administering, or from baseline to about 32 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the clinically meaningful platelet response is measured on at least two visits from baseline to about 16 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the clinically meaningful platelet response is measured on at least two visits from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a clinically meaningful platelet response, wherein the clinically meaningful platelet response is defined as a platelet count of ≥20,000/μL above baseline on at least two visits from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the clinically meaningful platelet response is measured in at least one measurement, at least two measurements, at least three measurements, at least four measurements, or at least five measurements from baseline to about 10 weeks after the administering, from baseline to about 12 weeks after the administering, from baseline to about 14 weeks after the administering, from baseline to about 16 weeks after the administering, from baseline to about 18 weeks after the administering, from baseline to about 20 weeks after the administering, from baseline to about 22 weeks after the administering, or from baseline to about 24 weeks after the administering, or from baseline to about 32 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the clinically meaningful platelet response is measured in at least two measurements from baseline to about 16 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the clinically meaningful platelet response is measured in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a clinically meaningful platelet response, wherein the clinically meaningful platelet response is defined as a platelet count of ≥20,000/μL above baseline in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks.

[0307] In some embodiments, the disclosure provides the methods as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in a hemostatic platelet response, wherein the hemostatic platelet response is defined as a platelet count of ≥30,000/μL, ≥40,000/μL, ≥50,000/μL, ≥60,000/μL, ≥70,000/μL, ≥80,000/μL, ≥90,000/μL, or ≥100,000/μL. In some embodiments, the hemostatic platelet response is defined as a platelet count of ≥20,000/μL, ≥30,000/μL, ≥40,000/μL, ≥50,000/μL, ≥60,000/μL, ≥70,000/μL, ≥80,000/μL, ≥90,000/μL, or ≥100,000/μL above baseline. In some embodiments, the hemostatic platelet response is defined as a platelet count of ≥30,000/μL and ≥20,000/μL above baseline. In some embodiments, the hemostatic platelet response is measured on at least one visit, at least two visits, at least three visits, at least four visits, or at least five visits from baseline to about 10 weeks after the administering, from baseline to about 12 weeks after the administering, from baseline to about 14 weeks after the administering, from baseline to about 16 weeks after the administering, from baseline to about 18 weeks after the administering, from baseline to about 20 weeks after the administering, from baseline to about 22 weeks after the administering, from baseline to about 24 weeks after the administering, or from baseline to about 32 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks and the subject has a baseline platelet count of <15,000/μL. In some embodiments, the hemostatic platelet response is measured on at least two visits from baseline to about 18 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks and the subject has a baseline platelet count of <15,000/μL. In some embodiments, the hemostatic platelet response is measured on at least two visits from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks and the subject has a baseline platelet count of <15,000/μL. In some embodiments, the hemostatic platelet response is measured in at least one measurement, at least two measurements, at least three measurements, at least four measurements, or at least five measurements from baseline to about 10 weeks after the administering, from baseline to about 12 weeks after the administering, from baseline to about 14 weeks after the administering, from baseline to about 16 weeks after the administering, from baseline to about 18 weeks after the administering, from baseline to about 20 weeks after the administering, from baseline to about 22 weeks after the administering, from baseline to about 24 weeks after the administering, or from baseline to about 32 weeks after the administering, wherein the subject has not received a rescue therapy in the

previous four weeks and the subject has a baseline platelet count of <15,000/μL. In some embodiments, the hemostatic platelet response is measured in at least two measurements from baseline to about 18 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks and the subject has a baseline platelet count of <15,000/μL. In some embodiments, the hemostatic platelet response is measured in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks and the subject has a baseline platelet count of <15,000/μL. In some embodiments, the baseline platelet count is <12,000/μL, <10,000/μL, <8,000/μL, <5,000/μL, or <1,000/μL. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a hemostatic platelet response, wherein the hemostatic platelet response is defined as a platelet count of ≥30,000/μL and ≥20,000/μL above baseline on at least two visits from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks and the subject has a baseline platelet count of <15,000/μL. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a hemostatic platelet response, wherein the hemostatic platelet response is defined as a platelet count of ≥30,000/μL and ≥20,000/μL above baseline in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks and the subject has a baseline platelet count of <15,000/μL.

[0308] In some embodiments, the disclosure provides the methods as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in a platelet count of >10,000/μL, >20,000/μL, >30,000/μL, >40,000/μL, >50,000/μL, >60,000/μL, >70,000/μL, >80,000/μL, >90,000/μL, or >100,000/μL. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet count of >50,000/μL. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet count of >100,000/μL.

[0309] In some embodiments, the disclosure provides the methods as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in less than 75%, less than 50%, less than 40%, less than 30%, less than 25%, less than 20%, less than 15%, less

than 10%, or less than 5% incidence of use of a rescue therapy. In some embodiments, the method does not include the use of a rescue therapy.

[0310] As used herein, "rescue therapy" refers to a dosing of concomitant medications (except for a bridging therapy) in accordance with institutional practices or the physician's best medical judgment to control and manage ITP during or after administration of the isolated anti-CD38 antibody or antigen binding fragment thereof. Rescue therapies include, but are not limited to, high-dose corticosteroids, high-dose IVIg, and/or increased or added SOC ITP therapies.

[0311] Because platelet counts may not be affected until several weeks after initiation of treatment with the isolated anti-CD38 antibody or antigen binding fragment thereof, subjects may receive a "bridging therapy." Bridging therapies include, but are not limited to, a one-time infusion of platelets; a single dose of IVIg (up to 1 g/kg); or an additional 20 mg of prednisone (or equivalent) per day for up to 7 days.

[0312] In some embodiments, the disclosure provides the methods as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in a reduction in ITP disease activity and/or progression in a subject diagnosed with ITP. In some embodiments, the ITP disease activity and/or progression is measured one or more assessments selected from the group consisting of World Health Organization (WHO) Bleeding Scale, Immune Thrombocytopenic Purpura Subject Assessment Questionnaire (ITP-PAQ), and/or 5-Level EuroQol Five Dimensions (EQ-5D-5L). In some embodiments, the ITP disease activity and/or progression is measured by World Health Organization (WHO) Bleeding Scale. In some embodiments, the ITP disease activity and/or progression is measured by Immune Thrombocytopenic Purpura Subject Assessment Questionnaire (ITP-PAQ). In some embodiments, the ITP disease activity and/or progression is measured by 5-Level EuroQol Five Dimensions (EQ-5D-5L). In some embodiments, the ITP disease activity and/or progression is measured by a change from baseline in Symptoms, Fatigue/Sleep, Physical Health-Activity, Physical Health-Bother, Psychological Health, Overall Quality of Life, Social Activity, and/or Work scales scores of the ITP-PAQ from baseline to about 24 weeks after the administering. In some embodiments, the ITP disease activity and/or progression is measured by a change from baseline in the Menstrual Symptoms subscale scores of the ITP-PAQ from baseline to about 24 weeks after the administering in a female subject who had at least one menstrual period within

12 months before the receiving the isolated antibody. In some embodiments, the ITP disease activity and/or progression is measured by a change from baseline in the Fertility subscale scores of the ITP-PAQ in a female subject from baseline to about 24 weeks after the administering. In some embodiments, the ITP disease activity and/or progression is measured by a change from baseline in the EQ-5D-5L utility index score and/or VAS score from baseline to about 24 weeks after the administering. In some embodiments, the ITP disease activity and/or progression is measured by a change in a Symptoms Scale Score of ITP-PAQ from baseline to about 24 weeks after the administering.

[0313] In some embodiments, the disclosure provides the methods as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in in a reduction in bleeding events in the subject. In some embodiments, bleed events are measured by Immune Thrombocytopenia-specific Bleeding Assessment Tool (ITP-BAT). In some embodiments, the bleeding events comprise Grade ≥2 in the Skin domain, Grade ≥1 in the Mucosal domain, and/or Grade ≥1 in the Organ domain.

[0314] In some embodiments, the disclosure provides the methods as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in ITP remission. In some embodiments, ITP remission is defined as all platelet counts ≥50,000/μL for at least about 12 or at least about 24 weeks after any treatment cycle with the isolated antibody or antigen binding fragment thereof in the absence of other therapy for ITP.

[0315] In some embodiments, the disclosure provides the methods as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in a reduction in immunoglobulin(s). In some embodiments, the immunoglobulin is one or more selected from the group consisting of IgA, IgG, and IgM. In some embodiments, the immunoglobulin(s) (*e.g.*, IgA, IgG, and/or IgM) are reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 90%, or at least about 95% relative to baseline levels of the immunoglobulin(s). In some embodiments, IgA is reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about

55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 90%, or at least about 95% relative to baseline levels of the IgA. In some embodiments, IgG is reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 90%, or at least about 95% relative to baseline levels of the IgG. In some embodiments, IgM is reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 90%, or at least about 95% relative to baseline levels of IgM. In some embodiments, IgA is reduced by at least about 50% relative to baseline levels of IgA. In some embodiments, IgG is reduced by at least about 30% relative to baseline levels of IgG. In some embodiments, IgM is reduced by at least about 40% relative to baseline levels of IgM.

[0316] In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a reduction in immunoglobulin(s) (*e.g.*, IgA, IgG, and/or IgM) in six weeks or less, five weeks or less, four weeks or less, three weeks or less, two weeks or less, or one week or less. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a reduction in immunoglobulin(s) in one week or less.

[0317] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the antibody or antigen binding fragment thereof further comprises one or more engineered glycoforms.

[0318] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the engineered glycoform comprises glycosylation of one or more polypeptides, and wherein the glycosylation is N-linked glycosylation or O-linked glycosylation.

[0319] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the glycosylation is N-linked glycosylation.

[0320] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the glycosylation is O-linked glycosylation.

[0321] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the VH region of the antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 90% to SEQ ID NO: 9, and/or the VL region of the antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 90% to SEQ ID NO: 10.

[0322] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the VH region comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 9.

[0323] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the VL region comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 10.

[0324] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the VH region comprises an amino acid sequence having an identity of at least 99% to SEQ ID NO: 9.

[0325] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the VL region comprises an amino acid sequence having an identity of at least 99% to SEQ ID NO: 10.

[0326] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the HC of the antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 11.

[0327] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the HC of the antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 14.

[0328] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the LC of the antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 12.

[0329] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the isolated antibody or antigen binding fragment thereof interacts with at least K121, F135,

Q139, D141, E239, W241, C275, K276, F284, P291 and E292 of SEQ ID NO: 1 and SEQ ID NO: 2, based on human sequence numbering.

[0330] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the isolated antibody or antigen binding fragment thereof binds to human CD38 (SEQ ID NO: 1) with a KD of 10^{-8} M or a greater affinity, and wherein the affinity is measured by a standard Biacore assay.

[0331] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the VH region comprises SEQ ID NO: 9 and the VL region comprises SEQ ID NO: 10.

[0332] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the isolated antibody or antigen binding fragment thereof comprises an HC as set forth in SEQ ID NO: 11 and an LC as set forth in SEQ ID NO: 12.

[0333] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the isolated antibody or antigen binding fragment thereof comprises an HC as set forth in SEQ ID NO: 14 and an LC as set forth in SEQ ID NO: 12.

[0334] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the antibody or antigen binding fragment thereof further comprises an Fc domain.

[0335] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the Fc domain is a human Fc domain. In some embodiments, the Fc domain is a variant Fc domain.

[0336] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the isolated antibody or antigen binding fragment is a human IgG antibody. In some embodiments, the human IgG antibody is a human IgG1 antibody.

[0337] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the subject receives background ITP medication(s).

[0338] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the background ITP medication(s) is one or more selected from the group consisting of a thrombopoietin receptor agonist (TPO-RA), a corticosteroid, an immunosuppressant, and/or an

inhibitor. In some embodiments, the disclosure provides the methods as disclosed herein, wherein the background ITP medication(s) is one or more selected from the group consisting of romiplostim, eltrombopag, avatrombopag, hetrombopag, methotrexate, azathioprine, leflunomide, cyclosporine, fostamatinib, mycophenolate, danazol, dapsone, methylprednisolone, hydrocortisone, cortisone, prednisolone, prednisone, and dexamethasone.

[0339] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the background ITP medication(s) is administered in combination with the antibody or antigen binding fragment thereof.

[0340] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the antibody or antigen binding fragment thereof is administered in a dosage of about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, or 600 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 100 mg to about 600 mg, from about 100 mg to about 575 mg, from about 100 mg to about 550 mg, from about 100 mg to about 525 mg, from about 100 mg to about 500 mg, from about 100 mg to about 475 mg, from about 100 mg to about 450 mg, from about 100 mg to about 425 mg, from about 100 mg to about 400 mg, from about 100 mg to about 375 mg, from about 100 mg to about 350 mg, from about 100 mg to about 325 mg, from about 100 mg to about 300 mg, from about 300 mg to about 600 mg, from about 300 mg to about 575 mg, from about 300 mg to about 550 mg, from about 300 mg to about 525 mg, from about 300 mg to about 500 mg, from about 300 mg to about 475 mg, from about 300 mg to about 450 mg, from about 300 mg to about 425 mg, from about 300 mg to about 400 mg, from about 300 mg to about 375 mg, from about 300 mg to about 350 mg, from about 300 mg to about 325 mg, from about 125 mg to about 600 mg, from about 150 mg to about 600 mg, from about 175 mg to about 600 mg, from about 200 mg to about 600 mg, from about 225 mg to about 600 mg, from about 250 mg to about 600 mg, from about 275 mg to about 600 mg, from about 325 mg to about 600 mg, from about 350 mg to about 600 mg, from about 375 mg to about 600 mg, from about 400 mg to about 600 mg, from about 425 mg to about 600 mg, from about 450 mg to about 600 mg, from about 475 mg to about 600 mg, from about 500 mg to about 600 mg, from about 525 mg to about 600

mg, from about 550 mg to about 600 mg, or from about 575 mg to about 600 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of about 100 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of about 300 mg. In some embodiments, wherein the antibody or antigen binding fragment thereof is administered in a dosage of about 600 mg.

[0341] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the dosage is a dosage administered once every week, once every two weeks, once every three weeks or once every four weeks.

[0342] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the antibody or antigen binding fragment thereof is administered in the form of a pharmaceutically acceptable composition.

[0343] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the pharmaceutically acceptable composition comprises the isolated antibody or antibody fragment thereof and at least one pharmaceutically acceptable carrier, excipient, and/or stabilizer.

[0344] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the isolated antibody or antigen binding fragment thereof comprises an HC as set forth in SEQ ID NO: 11 and an LC as set forth in SEQ ID NO: 12; and wherein the antibody or antigen binding fragment thereof is subcutaneously administered once weekly for 8 weeks. In some embodiments, the disclosure provides the methods as disclosed herein, wherein the isolated antibody or antigen binding fragment thereof further comprises one or more engineered glycoforms, wherein the engineered glycoform comprises glycosylation of one or more polypeptides and the glycosylation is N-linked glycosylation.

[0345] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the isolated antibody or antigen binding fragment thereof comprises an HC as set forth in SEQ ID NO: 14 and an LC as set forth in SEQ ID NO: 12; and wherein the antibody or antigen binding fragment thereof is subcutaneously administered once weekly for 8 weeks. In some embodiments, the disclosure provides the methods as disclosed herein, wherein the isolated antibody or antigen binding fragment thereof further comprises one or more engineered

glycoforms, wherein the engineered glycoform comprises glycosylation of one or more polypeptides and the glycosylation is N-linked glycosylation.

[0346] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the isolated antibody or antigen binding fragment thereof is mezagitamab.

[0347] In some embodiments, the disclosure provides the methods as disclosed herein, wherein administering the antibody or antigen binding fragment thereof results in less than 10% incidence of grade 3 or 4 of one or more treatment-related adverse events (TRAEs) or treatment-emergent adverse events (TEAEs). In some embodiments, the TRAEs or TEAEs are selected from the group consisting of gingival bleeding, heavy menstrual bleeding, haematochezia, mouth haemorrhage, haematoma, traumatic haematoma, epistaxis, petechiae, ecchymosis, conjunctival haemorrhage, blood urine, and haemorrhagic ovarian cyst.

[0348] In some embodiments, the disclosure provides the methods as disclosed herein, wherein a TRAE or TEAE resulting from administering the antibody or antigen binding fragment thereof has a maximum intensity of Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or Grade 2.

[0349] In some embodiments, the disclosure provides the methods as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in a reduction in dose and/or frequency of use of background ITP medication(s).

[0350] In some embodiments, the disclosure provides the methods as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in a reduction in ITP-associated bleeding adverse events (AEs) relative to placebo. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in at least about 5%, at least about 10%, at least about 15%, at least about 20%, or at least about 25% reduction in ITP-associated bleeding adverse events (AEs) relative to placebo.

[0351] In some embodiments, the disclosure provides the methods as disclosed herein, wherein the isolated antibody or antigen binding fragment thereof is from about 2 times to about 4 times more efficacious than fostamatinib and/or efgartigimod. In some embodiments, the isolated antibody or antigen binding fragment thereof results in from about 2 times to about 4 times more durable or sustained platelet response as compared to fostamatinib and/or efgartigimod.

[0352] In some embodiments, the disclosure provides an isolated human anti-CD38 antibody or antigen binding fragment thereof for use in the treatment of immune thrombocytopenia (ITP), wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8.

[0353] In some embodiments, the disclosure provides a pharmaceutical composition comprising an isolated human anti-CD38 antibody or antigen binding fragment thereof for treating immune thrombocytopenia (ITP) comprising an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8.

[0354] In some embodiments, the disclosure provides a medicament for treating immune thrombocytopenia (ITP) comprising an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8.

[0355] In some embodiments, the disclosure provides a use of an isolated human anti-CD38 antibody or antigen binding fragment thereof in the manufacture of a medicament for treating immunoglobulin A nephropathy (IgAN), wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO:

4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8.

Antibody Compositions for *In Vivo* Administration

[0356] Formulations of the antibodies or antigen binding fragments thereof used in accordance with the present disclosure are prepared for storage by mixing an antibody having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients, or stabilizers (Remington's Pharmaceutical Sciences 16th edition (1980) Osol, A. Ed.; incorporated herein by reference in its entirety), in the form of lyophilized formulations or aqueous solutions.

[0357] The formulations herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. For example, it may be desirable to provide antibodies or antigen binding fragments thereof with other specificities. Alternatively, or in addition, the composition may comprise a cytotoxic agent, cytokine, growth inhibitory agent and/or small molecule antagonist. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

[0358] In some embodiments, two mezagitamab drug product formulations have been developed, referred to as Process A and Process B as disclosed herein.

[0359] In one embodiment, the Process A mezagitamab drug product is a clear-to-opalescent, colorless solution containing AB79 (20 mg/mL) aqueous solution of arginine hydrochloride, anhydrous citric acid, sodium citrate, polysorbate 80, and water for injection at approximately pH 6.5. The Process A placebo is a clear, colorless solution containing an aqueous solution of arginine hydrochloride, anhydrous citric acid, sodium citrate, polysorbate 80, and water for injection at approximately pH 6.5. The Process A mezagitamab drug product and placebo are supplied in aseptically filled, single-use, clear, type I borosilicate glass vials with fluoropolymer coated butyl rubber stoppers and aluminum crimp seals with flip-off caps.

[0360] In another embodiment, the Process B mezagitamab drug product is made in 2 strengths, 5 mg/mL or 100 mg/mL. Each strength is a clear-to-opalescent, colorless-to-brownish-yellow

solution containing mezagitamab in an aqueous solution of histidine, histidine hydrochloride monohydrate, sucrose, polysorbate 20, and water for injection at approximately pH 5.9. The Process B placebo is a clear, colorless solution containing an aqueous solution of histidine, histidine hydrochloride monohydrate, sucrose, polysorbate 20, and water for injection at approximately pH 5.9. The Process B mezagitamab drug product and placebo are supplied in aseptically filled, single use, clear, type I, borosilicate glass vials with fluoropolymer coated butyl rubber stoppers and aluminum crimp seals with flip-off caps.

Subcutaneous Administration

[0361] The anti-CD38 antibodies described herein, such as mezagitamab, can be administered at sufficiently dosages that are therapeutically effective, thereby allowing for subcutaneous administration. Subcutaneous administration is a minimally invasive mode of administration and is considered the most versatile and therefore desirable mode of administration that can be used for short-term and long-term therapies. In some embodiments, subcutaneous administration can be performed by injection. In some embodiments, the site of the injection or device can be rotated when multiple injections or devices are needed.

[0362] Accordingly, subcutaneous formulations are much easier for a subject to self-administer, especially since the formulation may have to be taken regularly during the subject's entire life. Furthermore, the ease and speed of subcutaneous delivery allows increased subject compliance and quicker access to medication when needed. Thus, the subcutaneous formulations of the anti-CD38 antibodies provided herein provide a substantial benefit over the prior art and solve certain unmet needs.

[0363] In some embodiments, the antibodies of the disclosure are administered to a subject in accordance with known methods via a subcutaneous route. In some embodiments, antibodies of the present disclosure can be administered by subcutaneous injection. In specific embodiments, the subcutaneous formulation is subcutaneously injected into the same site of a subject (*e.g.*, administered to the upper arm, anterior surface of the thigh, lower portion of the abdomen, or upper back) for repeat or continuous injections. In other embodiments, the subcutaneous formulation is subcutaneously injected into a different or rotating site of a subject. Single or multiple administrations of the formulations may be employed.

[0364] In some embodiments, the subcutaneous unit dosage forms described herein can be used for the treatment of ITP. In some embodiments, the subcutaneous unit dosage forms described herein can be used for the treatment of chronic or persistent primary ITP.

[0365] In some embodiments, the antibodies or antigen binding fragments thereof of the disclosure lead to depletion of plasmablasts, plasma cells, NK cells, B cells and/or T cells after subcutaneous administration to a subject. In some embodiments, the antibodies or antigen binding fragments thereof of the disclosure lead to depletion of plasmablasts. In some embodiments, the antibodies or antigen binding fragments thereof of the disclosure lead to depletion of plasma cells. In some embodiments, the antibodies or antigen binding fragments thereof of the disclosure allow for increased depletion of NK cells as compared to the depletion of B cells or T cells. In some embodiments, the antibodies or antigen binding fragments thereof of the disclosure allow for increased depletion of NK cells as compared to B cells, as well as increased depletion of NK cells as compared to T cells. In some embodiments, the antibodies or antigen binding fragments thereof of the disclosure allow for increased depletion of NK cells as compared to B cells, as well as increased depletion of B cells as compared to T cells. In some embodiments, the antibodies or antigen binding fragments thereof of the disclosure allow for increased depletion of NK cells as compared to B cells and increased depletion of B cells as compared to T cells. Suitably, the antibodies or antigen binding fragments thereof of the disclosure may allow for increased depletion of CD38+ cells as compared to $CD38^-$ cells.

[0366] In some embodiments, the antibodies or antigen binding fragments thereof of the disclosure lead to a decrease in the level of immunoglobulin(s) after subcutaneous administration to a subject. In some embodiments, the immunoglobulin is IgA, IgG and/or IgM. In some embodiments, the immunoglobulin is IgA. In some embodiments, the immunoglobulin is IgG. In some embodiments, the immunoglobulin is IgM.

[0367] In some embodiments, the antibodies or antigen binding fragments thereof of the disclosure lead to a decrease in autoantibodies after subcutaneous administration to a subject. In some embodiments, the autoantibodies are anti-platelet autoantibodies.

[0368] In certain embodiments, the bioavailability of the anti-CD38 antibodies described herein after subcutaneous administration is between at least about 50% and at least about 80% as

compared to intravenous administration normalized for the same dose. In certain embodiments, the bioavailability of the anti-CD38 antibodies described herein after subcutaneous administration is between at least about 60% and at least about 80% as compared to intravenous administration normalized for the same dose. In certain embodiments, the bioavailability of the anti-CD38 antibodies described herein after subcutaneous administration is between at least about 50% and 70% as compared to intravenous administration normalized for the same dose. In certain embodiments, the bioavailability of the anti-CD38 antibodies described herein after subcutaneous administration is between at least about 55% and 65% as compared to intravenous administration normalized for the same dose. In certain embodiments, the bioavailability of the anti-CD38 antibodies described herein after subcutaneous administration is between at least about 55% and 70% as compared to intravenous administration normalized for the same dose.

[0369] In certain embodiments, the bioavailability of the anti-CD38 antibodies described herein after subcutaneous administration is at least about 40%, at least about 45%, at least about 50%, at least about 51%, at least about 52%, at least about 53%, at least about 54%, at least about 55%, at least about 56%, at least about 57%, at least about 58%, at least about 59%, at least about 60%, at least about 61%, at least about 62%, at least about 63%, at least about 64%, at least about 65%, at least about 66%, at least about 67%, at least about 68%, at least about 69%, at least about 70%, at least about 71%, at least about 72%, at least about 73%, at least about 74%, at least about 75%, at least about 76%, at least about 77%, at least about 78%, at least about 79%, at least about 80%, at least about 81%, at least about 82%, at least about 83%, at least about 84%, or at least about 85% as compared to intravenous administration normalized for the same dose. Suitably the bioavailability may be at least about 50% as compared to intravenous administration normalized for the same dose. Suitably the bioavailability may be at least about 60% as compared to intravenous administration normalized for the same dose. Suitably the bioavailability may be at least about 70% as compared to intravenous administration normalized for the same dose. Suitably the bioavailability may be at least about 80% as compared to intravenous administration normalized for the same dose. Suitably the bioavailability may be at least about 90% as compared to intravenous administration normalized for the same dose.

[0370] In some embodiments, the present disclosure provides a method wherein the bioavailability of the antibodies of the disclosure after subcutaneous administration is 50%-80% as compared to intravenous administration normalized for the same dose.

[0371] In some embodiments, the present disclosure provides a method wherein the bioavailability of the antibodies of the disclosure after subcutaneous administration is at least about 50% as compared to intravenous administration normalized for the same dose.

[0372] In some embodiments, the present disclosure provides a method wherein the bioavailability of the antibodies of the disclosure after subcutaneous administration is at least about 55% as compared to intravenous administration normalized for the same dose.

[0373] In some embodiments, the present disclosure provides a method wherein the bioavailability of the antibodies of the disclosure after subcutaneous administration is at least about 60% as compared to intravenous administration normalized for the same dose.

[0374] In some embodiments, the present disclosure provides a method wherein the bioavailability of the antibodies of the disclosure after subcutaneous administration is at least about 65% as compared to intravenous administration normalized for the same dose.

[0375] In some embodiments, the present disclosure provides a method wherein the bioavailability of the antibodies of the disclosure after subcutaneous administration is at least about 70% as compared to intravenous administration normalized for the same dose.

[0376] In some embodiments, the present disclosure provides a method wherein the bioavailability of the antibodies of the disclosure after subcutaneous administration is at least about 75% as compared to intravenous administration normalized for the same dose.

[0377] In some embodiments, the present disclosure provides a method wherein the bioavailability of the antibodies of the disclosure after subcutaneous administration is at least about 80% as compared to intravenous administration normalized for the same dose.

[0378] In certain embodiments, the anti-CD38 antibodies or antigen binding fragments thereof as described herein are subcutaneously administered in a single bolus injection. In certain embodiments, the anti-CD38 antibodies or antigen binding fragments thereof as described herein are subcutaneously administered monthly. In certain embodiments, the anti-CD38 antibodies or

antigen binding fragments thereof as described herein are subcutaneously administered every two weeks. In certain embodiments, the anti-CD38 antibodies or antigen binding fragments thereof as described herein are subcutaneously administered weekly. In certain embodiments, the anti-CD38 antibodies or antigen binding fragments thereof as described herein are subcutaneously administered twice a week. In certain embodiments, the anti-CD38 antibodies or antigen binding fragments thereof as described herein are subcutaneously administered daily. In certain embodiments, the anti-CD38 antibodies or antigen binding fragments thereof as described herein are subcutaneously administered every 12 hours. In certain embodiments, the anti-CD38 antibodies or antigen binding fragments thereof as described herein are subcutaneously administered every 8 hours. In certain embodiments, the anti-CD38 antibodies or antigen binding fragments thereof as described herein are subcutaneously administered every 6 hours. In certain embodiments, the anti-CD38 antibodies or antigen binding fragments thereof as described herein are subcutaneously administered every 4 hours. In certain embodiments, the anti-CD38 antibodies or antigen binding fragments thereof as described herein are subcutaneously administered every 2 hours. In certain embodiments, the anti-CD38 antibodies or antigen binding fragments thereof as described herein are subcutaneously administered every hour. In some embodiments, the antibodies or antigen binding fragments thereof as disclosed herein is subcutaneously administered once weekly for 8 weeks.

[0379] In some embodiments, the anti-CD38 antibodies or antigen binding fragments thereof as disclosed herein are subcutaneously administered at a dosage of from about 100 mg to about 600 mg. In some embodiments, the anti-CD38 antibodies or antigen binding fragments thereof as disclosed herein are subcutaneously administered at a dosage of about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, or about 600 mg. In some embodiments, the anti-CD38 antibodies or antigen binding fragments thereof as disclosed herein are subcutaneously administered at a dosage of from about 100 mg to about 600 mg, from about 100 mg to about 575 mg, from about 100 mg to about 550 mg, from about 100 mg to about 525 mg, from about 100 mg to about 500 mg, from about 100 mg to about 475 mg, from about 100 mg to about 450 mg, from about 100 mg to about 425 mg, from about 100 mg to

about 400 mg, from about 100 mg to about 375 mg, from about 100 mg to about 350 mg, from about 100 mg to about 325 mg, from about 100 mg to about 300 mg, from about 300 mg to about 600 mg, from about 300 mg to about 575 mg, from about 300 mg to about 550 mg, from about 300 mg to about 525 mg, from about 300 mg to about 500 mg, from about 300 mg to about 475 mg, from about 300 mg to about 450 mg, from about 300 mg to about 425 mg, from about 300 mg to about 400 mg, from about 300 mg to about 375 mg, from about 300 mg to about 350 mg, from about 300 mg to about 325 mg, from about 125 mg to about 600 mg, from about 150 mg to about 600 mg, from about 175 mg to about 600 mg, from about 200 mg to about 600 mg, from about 225 mg to about 600 mg, from about 250 mg to about 600 mg, from about 275 mg to about 600 mg, from about 325 mg to about 600 mg, from about 350 mg to about 600 mg, from about 375 mg to about 600 mg, from about 400 mg to about 600 mg, from about 425 mg to about 600 mg, from about 450 mg to about 600 mg, from about 475 mg to about 600 mg, from about 500 mg to about 600 mg, from about 525 mg to about 600 mg, from about 550 mg to about 600 mg, or from about 575 mg to about 600 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of about 100 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of about 300 mg. In some embodiments, wherein the antibody or antigen binding fragment thereof is administered in a dosage of about 600 mg.

Unit Dosage Forms

[0380] In some embodiments, the therapeutic anti-CD38 antibodies or antigen binding fragments thereof are formulated as part of a unit dosage form. In some embodiments, the anti-CD38 antibody or antigen binding fragment thereof comprises an HC comprising the following CDR amino acid sequences: GFTFDDYG (SEQ ID NO: 3; HCDR1 mezagitamab), ISWNGGKT (SEQ ID NO: 4; HCDR2 mezagitamab), and ARGSLFHDSSGFYFGH (SEQ ID NO: 5; HCDR3 mezagitamab) or variants of those sequences having up to three amino acid changes. In some embodiments, the antibody or antigen binding fragment thereof comprises an LC comprising the following CDR amino acid sequences: SSNIGDNY (SEQ ID NO: 6; LCDR1 mezagitamab), RDS (SEQ ID NO: 7; LCDR2 mezagitamab), and QSYDSSLSGS (SEQ ID NO: 8; LCDR3 mezagitamab) or variants of those sequences having up to three amino acid changes. In some embodiments, the antibody comprises an HC comprising the following CDR amino acid

sequences: GFTFDDYG (SEQ ID NO: 3; HCDR1 mezagitamab), ISWNGGKT (SEQ ID NO: 4; HCDR2 mezagitamab), ARGSLFHDSSGFYFGH (SEQ ID NO: 5; HCDR3 mezagitamab) or variants of those sequences having up to three amino acid changes and an LC comprising the following CDR amino acid sequences: SSNIGDNY (SEQ ID NO: 6; LCDR1 mezagitamab), RDS (SEQ ID NO: 7; LCDR2 mezagitamab), and QSYDSSLSGS (SEQ ID NO: 8; LCDR3 mezagitamab) or variants of those sequences having up to three amino acid changes. In some embodiments, the antibody comprises an HC comprising the following CDR amino acid sequences: GFTFDDYG (SEQ ID NO: 3; HCDR1 mezagitamab), ISWNGGKT (SEQ ID NO: 4; HCDR2 mezagitamab), and ARGSLFHDSSGFYFGH (SEQ ID NO: 5; HCDR3 mezagitamab). In some embodiments, the antibody comprises an LC comprising the following CDR amino acid sequences: SSNIGDNY (SEQ ID NO: 6; LCDR1 mezagitamab), RDS (SEQ ID NO: 7; LCDR2 mezagitamab), and QSYDSSLSGS (SEQ ID NO: 8; LCDR3 mezagitamab). In some embodiments, the antibody comprises an HC comprising the following CDR amino acid sequences: GFTFDDYG (SEQ ID NO: 3; HCDR1 mezagitamab), ISWNGGKT (SEQ ID NO: 4; HCDR2 mezagitamab), ARGSLFHDSSGFYFGH (SEQ ID NO: 5; HCDR3 mezagitamab) and an LC comprising the following CDR amino acid sequences: SSNIGDNY (SEQ ID NO: 6; LCDR1 mezagitamab), RDS (SEQ ID NO: 7; LCDR2 mezagitamab), and QSYDSSLSGS (SEQ ID NO: 8; LCDR3 mezagitamab). In some embodiments, the antibody or antigen binding fragment thereof comprises an HC comprising an amino acid sequence having at least 80% sequence identity to SEQ ID NO: 9. Suitably, the HC may comprise the following CDR amino acid sequences: GFTFDDYG (SEQ ID NO: 3; HCDR1 mezagitamab), ISWNGGKT (SEQ ID NO: 4; HCDR2 mezagitamab), and ARGSLFHDSSGFYFGH (SEQ ID NO: 5; HCDR3 mezagitamab) and the remainder of the HC may have at least 80% sequence identity to SEQ ID NO 9. In some embodiments, the antibody comprises an HC comprising the VH region amino acid sequence of SEQ ID NO: 9.

EVQLLESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSDISWNGGK THYVDSVKGQFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGSLFHDSSGFYFGHWGQ GTLVTVSSASTKGPSVFPLA (SEQ ID NO: 9).

[0381] In some embodiments, the antibody comprises an LC comprising an amino acid sequence having at least 80% sequence identity to SEQ ID NO: 10. Suitably, the LC may comprise the

following CDR sequences: SSNIGDNY (SEQ ID NO: 6; LCDR1 mezagitamab), RDS (SEQ ID NO: 7; LCDR2 mezagitamab), and QSYDSSLSGS (SEQ ID NO: 8; LCDR3 mezagitamab) and the remainder of the LC may have at least 80% sequence identity to SEQ ID NO: 10. In some embodiments, the antibody comprises an LC comprising the VL region amino acid sequence of SEQ ID NO: 10.

QSVLTQPPSASGTPGQRVTISCSGSSSNIGDNYVSWYQQLPGTAPKLLIYRDSQRPSGVP DRFSGSKSGTSASLAISGLRSEDEADYYCQSYDSSLSGSVFGGGTKLTVLGQPKANPTVT LFPPSSEEL (SEQ ID NO: 10).

[0382] In some embodiments, the antibody comprises an HC comprising the VH region amino acid sequence of SEQ ID NO: 9 or a variant thereof as described herein and an LC comprising the VL region amino acid sequence of SEQ ID NO: 10 or a variant thereof as described herein.

[0383] As will be appreciated by those in the art, the VH region and VL region can be joined to human IgG constant domain sequences, generally IgG1, IgG2 or IgG4. In some embodiments, the antibody comprises an HC having amino acid sequence with at least 80% sequence identity to SEQ ID NO: 11. Suitably, the HC may comprise the CDR sequences as defined by SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 and the remainder of the HC may have at least 80% sequence identity to SEQ ID NO 11. In some embodiments, the antibody comprises the HC amino acid sequence of SEQ ID NO: 11.

EVQLLESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSDISWNGGK THYVDSVKGQFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGSLFHDSSGFYFGHWGQ GTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPC PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 11).

[0384] In some embodiments, the antibody comprises an HC having amino acid sequence with at least 80% sequence identity to SEQ ID NO: 14. Suitably, the HC may comprise the CDR sequences as defined by SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 and the remainder of

the HC may have at least 80% sequence identity to SEQ ID NO 14. In some embodiments, the antibody comprises the HC amino acid sequence of SEQ ID NO: 14.

EVQLLESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSDISWNGGK THYVDSVKGQFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGSLFHDSSGFYFGHWGQ GTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPC PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 14).

[0385] In some embodiments, the antibody comprises an LC having amino acid sequence with at least 80% sequence identity to SEQ ID NO: 12. Suitably, the LC may comprise the CDR sequences as defined by SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8 and the remainder of the LC may have at least 80% sequence identity to SEQ ID NO 12. In some embodiments, the antibody comprises the LC amino acid sequence of SEQ ID NO: 12.

QSVLTQPPSASGTPGQRVTISCSGSSSNIGDNYVSWYQQLPGTAPKLLIYRDSQRPSGVP DRFSGSKSGTSASLAISGLRSEDEADYYCQSYDSSLSGSVFGGGTKLTVLGQPKANPTVT LFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAAS SYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS (SEQ ID NO: 12).

[0386] In some embodiments, the antibody comprises the HC amino acid sequence of SEQ ID NO: 11 or a variant thereof as described herein and the LC amino acid sequence of SEQ ID NO: 12 or a variant thereof as described herein.

[0387] In some embodiments, the antibody comprises the HC amino acid sequence of SEQ ID NO: 14 or a variant thereof as described herein and the LC amino acid sequence of SEQ ID NO: 12 or a variant thereof as described herein.

[0388] In some embodiments, the formulation comprising the anti-CD38 antibody is a unit dosage form. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of from about 100 mg to about 600 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 100 mg, about 125

mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, or about 600 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of from about 100 mg to about 600 mg, from about 100 mg to about 575 mg, from about 100 mg to about 550 mg, from about 100 mg to about 525 mg, from about 100 mg to about 500 mg, from about 100 mg to about 475 mg, from about 100 mg to about 450 mg, from about 100 mg to about 425 mg, from about 100 mg to about 400 mg, from about 100 mg to about 375 mg, from about 100 mg to about 350 mg, from about 100 mg to about 325 mg, from about 100 mg to about 300 mg, from about 300 mg to about 600 mg, from about 300 mg to about 575 mg, from about 300 mg to about 550 mg, from about 300 mg to about 525 mg, from about 300 mg to about 500 mg, from about 300 mg to about 475 mg, from about 300 mg to about 450 mg, from about 300 mg to about 425 mg, from about 300 mg to about 400 mg, from about 300 mg to about 375 mg, from about 300 mg to about 350 mg, from about 300 mg to about 325 mg, from about 125 mg to about 600 mg, from about 150 mg to about 600 mg, from about 175 mg to about 600 mg, from about 200 mg to about 600 mg, from about 225 mg to about 600 mg, from about 250 mg to about 600 mg, from about 275 mg to about 600 mg, from about 325 mg to about 600 mg, from about 350 mg to about 600 mg, from about 375 mg to about 600 mg, from about 400 mg to about 600 mg, from about 425 mg to about 600 mg, from about 450 mg to about 600 mg, from about 475 mg to about 600 mg, from about 500 mg to about 600 mg, from about 525 mg to about 600 mg, from about 550 mg to about 600 mg, or from about 575 mg to about 600 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 100 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 300 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 600 mg.

[0389] In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 100 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 125 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 150 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 175 mg. In

some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 200 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 225 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 250 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 275 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 300 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 325 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 350 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 375 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 400 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 425 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 450 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 475 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 500 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 525 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 550 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 575 mg. In some embodiments, the unit dosage form comprises an amount sufficient to administer a dosage of about 600 mg.

[0390] In some embodiments, the disclosure provides a unit dosage form comprising an isolated human anti-CD38 antibody that comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; wherein the isolated antibody or antigen binding fragment thereof binds to human CD38 (SEQ ID NO: 1), and the unit dosage form is formulated

for subcutaneous administration of the isolated antibody or antigen binding fragment thereof at a dosage of about 600 mg in a course of once per week for 8 weeks in the treatment of chronic primary ITP or persistent primary ITP in a subject that has had an insufficient response or intolerance to other therapy; wherein the other therapy is a first-line ITP therapy and/or a second-line ITP therapy, wherein the other therapy comprises one or more of a corticosteroid, immunoglobulins, splenectomy, a thrombopoietin receptor agonist (TPO-RA) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag), rituximab, fostamatinib, and background ITP medication(s) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag, methotrexate, azathioprine, leflunomide, cyclosporine, fostamatinib, mycophenolate, danazol, dapsone, methylprednisolone, hydrocortisone, cortisone, prednisolone, prednisone, and/or dexamethasone); optionally wherein the isolated antibody is further administered in more than one (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 courses, *etc.*) course of once per week for 8 weeks; and/or optionally wherein the isolated antibody is not further administered for a period of 8 weeks.

[0391] In some embodiments, the disclosure provides a unit dosage form wherein (a) the isolated antibody is administered once per week for from 1 week to 16 weeks; (b) the isolated antibody is not administered for a period of from 1 week to 16 weeks; and (c) the isolated antibody is administered once per week for from 1 week to 16 weeks. In some embodiments, (a) the isolated antibody is administered once per week for from 1 week to 16 weeks, from 2 weeks to 16 weeks, from 3 weeks to 16 weeks, from 4 weeks to 16 weeks, from 5 weeks to 16 weeks, from 6 weeks to 16 weeks, from 7 weeks to 16 weeks, from 8 weeks to 16 weeks, from 1 week to 15 weeks, from 1 week to 14 weeks, from 1 week to 13 weeks, from 1 week to 12 weeks, from 1 week to 11 weeks, from 1 week to 10 weeks, from 1 week to 9 weeks, from 1 week to 8 weeks, from 7 weeks to 9 weeks, from 6 weeks to 10 weeks, from 5 weeks to 11 weeks, from 4 weeks to 12 weeks, from 3 weeks to 13 weeks, or from 2 weeks to 14 weeks. In some embodiments, (b) the isolated antibody is not administered for a period of from 1 week to 16 weeks, from 2 weeks to 16 weeks, from 3 weeks to 16 weeks, from 4 weeks to 16 weeks, from 5 weeks to 16 weeks, from 6 weeks to 16 weeks, from 7 weeks to 16 weeks, from 8 weeks to 16 weeks, from 1 week to 15 weeks, from 1 week to 14 weeks, from 1 week to 13 weeks, from 1 week to 12 weeks, from 1 week to 11 weeks, from 1 week to 10 weeks, from 1 week to 9 weeks, from 1 week to 8 weeks, from 7 weeks to 9 weeks, from 6 weeks to 10 weeks, from 5 weeks to 11 weeks, from 4 weeks to

12 weeks, from 3 weeks to 13 weeks, or from 2 weeks to 14 weeks. In some embodiments, (c) the isolated antibody is administered once per week for from 1 week to 16 weeks, from 2 weeks to 16 weeks, from 3 weeks to 16 weeks, from 4 weeks to 16 weeks, from 5 weeks to 16 weeks, from 6 weeks to 16 weeks, from 7 weeks to 16 weeks, from 8 weeks to 16 weeks, from 1 week to 15 weeks, from 1 week to 14 weeks, from 1 week to 13 weeks, from 1 week to 12 weeks, from 1 week to 11 weeks, from 1 week to 10 weeks, from 1 week to 9 weeks, from 1 week to 8 weeks, from 7 weeks to 9 weeks, from 6 weeks to 10 weeks, from 5 weeks to 11 weeks, from 4 weeks to 12 weeks, from 3 weeks to 13 weeks, or from 2 weeks to 14 weeks. In some embodiments, (a) the isolated antibody is administered once per week for 8 weeks. In some embodiments, (b) the isolated antibody is not administered for a period of 8 weeks. In some embodiments, (c) the isolated antibody is administered once per week for 8 weeks. In some embodiments, the disclosure provides a unit dosage form wherein (a) the isolated antibody is administered once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; and (c) the isolated antibody is administered once per week for 8 weeks. In some embodiments, disclosure provides a unit dosage form wherein (a) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; and (c) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks. In some embodiments, disclosure provides a unit dosage form wherein (a) the isolated antibody is subcutaneously administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; and (c) the isolated antibody is subcutaneously administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks. In some embodiments, the disclosure provides a unit dosage form further comprising (d) the isolated antibody is not administered for a period of from 1 week to 16 weeks. In some embodiments, (d) the isolated antibody is not administered for a period of from 1 week to 16 weeks, from 2 weeks to 16 weeks, from 3 weeks to 16 weeks, from 4 weeks to 16 weeks, from 5 weeks to 16 weeks, from 6 weeks to 16 weeks, from 7 weeks to 16 weeks, from 8 weeks to 16 weeks, from 1 week to 15 weeks, from 1 week to 14 weeks, from 1 week to 13 weeks, from 1 week to 12 weeks, from 1 week to 11 weeks, from 1 week to 10 weeks, from 1 week to 9 weeks, from 1 week to 8 weeks, from 7 weeks to 9 weeks, from 6 weeks to 10 weeks, from 5 weeks to 11 weeks, from 4 weeks to 12 weeks, from 3 weeks to 13 weeks, or from 2

weeks to 14 weeks. In some embodiments, (d) the isolated antibody is not administered for a period of 8 weeks. In some embodiments, the disclosure provides a unit dosage form wherein (a) the isolated antibody is administered once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; (c) the isolated antibody is administered once per week for 8 weeks; and (d) the isolated antibody is not administered for a period of 8 weeks. In some embodiments, the disclosure provides a unit dosage form wherein (a) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; (c) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks; and (d) the isolated antibody is not administered for a period of 8 weeks. In some embodiments, the disclosure provides a unit dosage form wherein (a) the isolated antibody is subcutaneously administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; (c) the isolated antibody is subcutaneously administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks; and (d) the isolated antibody is not administered for a period of 8 weeks. In some embodiments, the disclosure provides a unit dosage form wherein the antibody or antigen binding fragment thereof is administered in a dosage of from about 100 mg to about 600 mg, for example, about 100 mg, about 300 mg, or about 600 mg. In some embodiments, the disclosure provides a unit dosage form wherein the isolated antibody is administered subcutaneously.

[0392] In some embodiments, the anti-CD38 antibody unit dosage forms provided herein may further comprise one or more pharmaceutically acceptable excipients, carriers, and/or diluents. In some embodiments, the anti-CD38 antibody is provided as a pharmaceutical composition which comprises a unit dosage form according to the present disclosure. Suitably, the pharmaceutical composition may further comprise one or more pharmaceutically acceptable excipients, carriers, and/or diluents.

[0393] Dosage regimens are adjusted to provide the optimum desired response (*e.g.*, a therapeutic response). For example, a single bolus may be administered, several divided doses may be administered over time, or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. Compositions may be formulated in dosage unit form for ease of administration and uniformity of dosage. Dosage unit forms as used

herein can, in some embodiments, refer to physically discrete units suited as unitary dosages for the subjects to be treated, each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

[0394] The specification for the dosage unit forms of the present disclosure is dictated by and is directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of an individual.

[0395] The efficient dosages and the dosage regimens for the anti-CD38 antibodies or antigen binding fragments thereof used in the present disclosure depend on the severity of the disease or condition to be treated and may be determined by persons skilled in the art.

[0396] In some embodiments, the anti-CD38 antibody or antigen binding fragments thereof is administered by subcutaneous administration once every week, once every two weeks, once every three weeks or once every four weeks in a dosage of about 100 mg to about 600 mg. In some embodiments, the anti-CD38 antibody or antigen binding fragments thereof is administered by subcutaneous administration once every week in a dosage of about 100 mg to about 600 mg. In some embodiments, the anti-CD38 antibody or antigen binding fragments thereof is administered by subcutaneous administration once every two weeks in a dosage of about 100 mg to about 600 mg. In some embodiments, the anti-CD38 antibody or antigen binding fragments thereof is administered by subcutaneous administration once every three weeks in a dosage of about 100 mg to about 600 mg. In some embodiments, the anti-CD38 antibody or antigen binding fragments thereof is administered by subcutaneous administration once every four weeks in a dosage of about 100 mg to about 600 mg.

[0397] Suitably, the weekly dosage may be about 100 mg. Suitably, the weekly dosage may be about 125 mg. Suitably, the weekly dosage may be about 150 mg. Suitably, the weekly dosage may be about 175 mg. Suitably, the weekly dosage may be about 200 mg. Suitably, the weekly dosage may be about 225 mg. Suitably, the weekly dosage may be about 250 mg. Suitably, the weekly dosage may be about 275 mg. Suitably, the weekly dosage may be about 300 mg. Suitably, the weekly dosage may be about 325 mg. Suitably, the weekly dosage may be about

350 mg. Suitably, the weekly dosage may be about 375 mg. Suitably, the weekly dosage may be about 400 mg. Suitably, the weekly dosage may be about 425 mg. Suitably, the weekly dosage may be about 450 mg. Suitably, the weekly dosage may be about 475 mg. Suitably, the weekly dosage may be about 500 mg. Suitably, the weekly dosage may be about 525 mg. Suitably, the weekly dosage may be about 550 mg. Suitably, the weekly dosage may be about 575 mg. Suitably, the weekly dosage may be about 600 mg. Such administration as disclosed herein may be repeated, *e.g.*, 4 to 12 times. In some embodiments, such administration as disclosed herein may be repeated 4 times, *e.g.*, weekly for a total of 4 weeks. In some embodiments, such administration as disclosed herein may be repeated 5 times, *e.g.*, weekly for a total of 5 weeks. In some embodiments, such administration as disclosed herein may be repeated 6 times, *e.g.*, weekly for a total of 6 weeks. In some embodiments, such administration as disclosed herein may be repeated 7 times, *e.g.*, weekly for a total of 7 weeks. In some embodiments, such administration as disclosed herein may be repeated 8 times, *e.g.*, weekly for a total of 8 weeks. In some embodiments, such administration as disclosed herein may be repeated 9 times, *e.g.*, weekly for a total of 9 weeks. In some embodiments, such administration as disclosed herein may be repeated 10 times, *e.g.*, weekly for a total of 10 weeks. In some embodiments, such administration as disclosed herein may be repeated 11 times, *e.g.*, weekly for a total of 11 weeks. In some embodiments, such administration as disclosed herein may be repeated 12 times, *e.g.*, weekly for a total of 12 weeks.

[0398] In one embodiment, the anti-CD38 antibody or antigen binding fragment thereof is administered in weekly dosage of about 100 mg to about 600 mg.

[0399] Suitably, the weekly dosage may be from about 100 mg to about 600 mg. Suitably, the weekly dosage may be from about 100 mg to about 575 mg. Suitably, the weekly dosage may be from about 100 mg to about 550 mg. Suitably, the weekly dosage may be from about 100 mg to about 525 mg. Suitably, the weekly dosage may be from about 100 mg to about 500 mg. Suitably, the weekly dosage may be from about 100 mg to about 475 mg. Suitably, the weekly dosage may be from about 100 mg to about 450 mg. Suitably, the weekly dosage may be from about 100 mg to about 425 mg. Suitably, the weekly dosage may be from about 100 mg to about 400 mg. Suitably, the weekly dosage may be from about 100 mg to about 375 mg. Suitably, the weekly dosage may be from about 100 mg to about 350 mg. Suitably, the weekly dosage may be

from about 100 mg to about 325 mg. Suitably, the weekly dosage may be from about 300 mg to about 600 mg. Suitably, the weekly dosage may be from about 300 mg to about 575 mg. Suitably, the weekly dosage may be from about 300 mg to about 550 mg. Suitably, the weekly dosage may be from about 300 mg to about 525 mg. Suitably, the weekly dosage may be from about 300 mg to about 500 mg. Suitably, the weekly dosage may be from about 300 mg to about 475 mg. Suitably, the weekly dosage may be from about 300 mg to about 450 mg. Suitably, the weekly dosage may be from about 300 mg to about 425 mg. Suitably, the weekly dosage may be from about 300 mg to about 400 mg. Suitably, the weekly dosage may be from about 300 mg to about 375 mg. Suitably, the weekly dosage may be from about 300 mg to about 350 mg. Suitably, the weekly dosage may be from about 300 mg to about 325 mg. Suitably, the weekly dosage may be from about 125 mg to about 600 mg. Suitably, the weekly dosage may be from about 150 mg to about 600 mg. Suitably, the weekly dosage may be from about 175 mg to about 600 mg. Suitably, the weekly dosage may be from about 200 mg to about 600 mg. Suitably, the weekly dosage may be from about 225 mg to about 600 mg. Suitably, the weekly dosage may be from about 250 mg to about 600 mg. Suitably, the weekly dosage may be from about 275 mg to about 600 mg. Suitably, the weekly dosage may be from about 300 mg to about 600 mg. Suitably, the weekly dosage may be from about 325 mg to about 600 mg. Suitably, the weekly dosage may be from about 350 mg to about 600 mg. Suitably, the weekly dosage may be from about 375 mg to about 600 mg. Suitably, the weekly dosage may be from about 400 mg to about 600 mg. Suitably, the weekly dosage may be from about 425 mg to about 600 mg. Suitably, the weekly dosage may be from about 450 mg to about 600 mg. Suitably, the weekly dosage may be from about 475 mg to about 600 mg. Suitably, the weekly dosage may be from about 500 mg to about 600 mg. Suitably, the weekly dosage may be from about 525 mg to about 600 mg. Suitably, the weekly dosage may be from about 550 mg to about 600 mg. Suitably, the weekly dosage may be from about 575 mg to about 600 mg. The dosage may be determined or adjusted by measuring the amount of compound of the present disclosure in the blood upon administration, for instance, by taking a biological sample and using anti-idiotypic antibodies that target the antigen binding region of the anti-CD38 antibody.

[0400] In one embodiment, the therapeutic antibody is formulated at about 5 mg/mL concentration. In another embodiment, the therapeutic antibody is formulated at about 20

mg/mL concentration. In another embodiment, the therapeutic antibody is formulated at about 50 mg/mL concentration. In another embodiment, the therapeutic antibody is formulated at about 100 mg/mL concentration. In another embodiment, the therapeutic antibody is formulated at about 120 mg/mL concentration. In another embodiment, the therapeutic antibody is formulated at about 150 mg/mL concentration. In some embodiments, 0.8 mL, 0.9 mL, 1.8 mL, 2.7 mL, or 2.8 mL volume is injected in the thigh, abdomen, or arm. In another embodiment, the therapeutic antibody is formulated at about 75 mg/mL concentration. In some embodiments, 0.53 mL, 0.6 mL, 1.2 mL, 1.8 mL, or 1.87 mL volume is injected in the thigh, abdomen, or arm. In another embodiment, the therapeutic antibody is formulated at about 90 mg/mL concentration. In some embodiments, 0.44 mL, 0.5 mL, 1.0 mL, 1.5 mL, or 1.56 mL volume is injected in the thigh, abdomen, or arm. In another embodiment, the therapeutic antibody is formulated at about 100 mg/mL concentration. In some embodiments, 0.4 mL, 0.45 mL, 0.9 mL, 1.35 mL, or 1.4 mL volume is injected in the thigh, abdomen, or arm. In some embodiments, the dose is administered over a 1-, 2-, 4-, 6-, 8-, or 10- hour period of time. In some embodiments, the doses are administered every week. In some embodiments, the doses are administered every 2 weeks. In some embodiments, the doses are administered every 3 weeks. In some embodiments, the doses are administered every 4 weeks.

[0401] In some embodiments, the disclosure provides a unit dosage form comprising an isolated antibody or antigen binding fragment thereof that comprises a VH region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a VL region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; wherein the isolated antibody or antigen binding fragment thereof binds to human CD38 (SEQ ID NO: 1), and the unit dosage form is formulated for subcutaneous administration of the antibody or antigen binding fragment thereof at a dosage of from about 100 mg to about 600 mg in the treatment of ITP.

[0402] In some embodiments, the disclosure provides unit dosage forms for administration in the treatment of ITP. In some embodiments, ITP is primary ITP. In some embodiments, the ITP is secondary ITP. In some embodiments, the ITP is treating newly diagnosed ITP, acute ITP,

persistent ITP, chronic ITP, and/or refractory ITP. In some embodiments, the ITP is newly diagnosed primary ITP, acute primary ITP, persistent primary ITP, chronic primary ITP, and/or refractory primary ITP. In some embodiments, the ITP is persistent or chronic primary ITP.

[0403] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the primary ITP has persisted for at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, or at least about 12 months. In some embodiments, the primary ITP has persisted for at least about 3 months.

[0404] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the unit dosage form is administered to a subject, wherein a subject has had an insufficient response or intolerance to other therapy. In some embodiments, the other therapy comprises one or more of a corticosteroid, immunoglobulins, splenectomy, a thrombopoietin receptor agonist (TPO-RA) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag), rituximab, fostamatinib, and/or background ITP medication(s). In some embodiments, the other therapy comprises one or more of immunoglobulins, splenectomy, romiplostim, eltrombopag, avatrombopag, hetrombopag, methotrexate, azathioprine, leflunomide, cyclosporine, fostamatinib, mycophenolate, danazol, dapsone, methylprednisolone, hydrocortisone, cortisone, prednisolone, prednisone, and/or dexamethasone. In some embodiments, the insufficient response to other treatment is defined as failure to achieve a sustained platelet count of at least 50,000/μL or doubling of baseline platelet count after an appropriate course of the other therapy. In some embodiments, the intolerance to other therapy is defined as a documented side effect causing discontinuation of the therapy.

[0405] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the unit dosage form is administered to a subject, wherein the subject has had a prior response to other therapy. In some embodiments, the subject has had a prior response to other therapy excluding a thrombopoietin receptor agonist (TPO-RA). In some embodiments, the prior response is defined as achieving a platelet count of ≥10,000/mL, ≥20,000/mL, ≥30,000/mL, ≥40,000/mL, or ≥50,000/mL. In some embodiments, the prior response is defined as achieving a platelet count of ≥50,000/mL.

[0406] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the unit dosage form is administered to a subject, wherein the subject has a baseline mean platelet count of <10,000/μL, <20,000/μL, <30,000/μL, <40,000/μL, or <50,000/μL from at least 2 consecutive measurements taken at least about 1 day apart, at least about 3 days apart, at least about 5 days apart, or at least about 10 days apart. In some embodiments, the subject has a baseline mean platelet count of <30,000/μL from at least 2 consecutive measurements taken at least about 5 day apart. In some embodiments, the baseline mean platelet count comprises individual values ≤35,000/μL.

[0407] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the antibody or antigen binding fragment thereof further comprises one or more engineered glycoforms. In some embodiments, the engineered glycoform comprises glycosylation of one or more polypeptides, and the glycosylation is N-linked glycosylation or O-linked glycosylation. In some embodiments, the glycosylation is N-linked glycosylation. In some embodiments, the glycosylation is O-linked glycosylation.

[0408] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the VH region of the antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 90% to SEQ ID NO: 9, and/or the VL region of the antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 90% to SEQ ID NO: 10.

[0409] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the VH region comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 9.

[0410] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the VL region comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 10.

[0411] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the VH region comprises an amino acid sequence having an identity of at least 99% to SEQ ID NO: 9.

[0412] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the VL region comprises an amino acid sequence having an identity of at least 99% to SEQ ID NO: 10.

[0413] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the HC of the antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 11.

[0414] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the HC of the antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 14.

[0415] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the LC of the antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 12.

[0416] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the isolated antibody or antigen binding fragment thereof interacts with at least K121, F135, Q139, D141, E239, W241, C275, K276, F284, P291 and E292 of SEQ ID NO: 1 and SEQ ID NO: 2, based on human sequence numbering.

[0417] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the isolated antibody or antigen binding fragment thereof binds to human CD38 (SEQ ID NO: 1) with a KD of 10^{-8} M or a greater affinity, and wherein the affinity is measured by a standard Biacore assay.

[0418] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the VH region comprises SEQ ID NO: 9 and the VL region comprises SEQ ID NO: 10.

[0419] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the isolated antibody or antigen binding fragment thereof comprises an HC as set forth in SEQ ID NO: 11 and a LC as set forth in SEQ ID NO: 12.

[0420] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the isolated antibody or antigen binding fragment thereof comprises an HC as set forth in SEQ ID NO: 14 and a LC as set forth in SEQ ID NO: 12.

[0421] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the isolated antibody or antigen binding fragment thereof further comprises an Fc domain. In some embodiments, the Fc domain is a human Fc domain. In some embodiments, the Fc domain is a variant Fc domain.

[0422] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the isolated antibody or antigen binding fragment is a human IgG antibody. In some embodiments, the human IgG antibody is a human IgG1 antibody.

[0423] In some embodiments, the disclosure provides the unit dosage form as disclosed herein further comprising background ITP medication(s). In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the isolated antibody or antigen binding fragment thereof is used in combination with one or more background ITP medication(s).

[0424] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the background ITP medication(s) is one or more selected from the group consisting of a thrombopoietin receptor agonist (TPO-RA), a corticosteroid, an immunosuppressant, and/or an inhibitor. In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the background ITP medication(s) is one or more selected from the group consisting of romiplostim, eltrombopag, avatrombopag, hetrombopag, methotrexate, azathioprine, leflunomide, cyclosporine, fostamatinib, mycophenolate, danazol, dapsone, methylprednisolone, hydrocortisone, cortisone, prednisolone, prednisone, and dexamethasone. In some embodiments, the unit dosage form as disclosed herein comprises the one or more background ITP medications.

[0425] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the antibody or antigen binding fragment thereof is administered in a dosage of about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, or about 600 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of 100 mg. In some embodiments, the antibody or antigen

binding fragment thereof is administered in a dosage of 125 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of 150 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of 175 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of 200 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of 225 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of 250 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of 275 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of 300 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of 325 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of 350 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of 375 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of 400 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of 450 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of 475 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of 500 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of 525 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of 550 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of 575 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of 600 mg.

[0426] In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 100 mg to about 600 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 100 mg to about 575 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 100 mg to about 550 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 100 mg to about 525 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 100 mg to about 500 mg. In some embodiments, the antibody or antigen binding

fragment thereof is administered in a dosage of from about 100 mg to about 475 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 100 mg to about 450 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 100 mg to about 425 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 100 mg to about 400 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 100 mg to about 375 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 100 mg to about 350 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 100 mg to about 325 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 100 mg to about 300 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 300 mg to about 600 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 300 mg to about 575 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 300 mg to about 550 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 300 mg to about 525 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 300 mg to about 500 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 300 mg to about 475 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 300 mg to about 450 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 300 mg to about 425 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 300 mg to about 400 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 300 mg to about 375 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 300 mg to about 350 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 300 mg to about 325 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 125 mg to about 600 mg. In some

embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 150 mg to about 600 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 175 mg to about 600 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 200 mg to about 600 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 225 mg to about 600 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 250 mg to about 600 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 275 mg to about 600 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 325 mg to about 600 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 350 mg to about 600 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 375 mg to about 600 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 400 mg to about 600 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 425 mg to about 600 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 450 mg to about 600 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 475 mg to about 600 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 500 mg to about 600 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 525 mg to about 600 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 550 mg to about 600 mg. In some embodiments, the antibody or antigen binding fragment thereof is administered in a dosage of from about 575 mg to about 600 mg. In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the dosage is a dosage administered once every week, once every two weeks, once every three weeks or once every four weeks.

[0427] In some embodiments, the disclosure provides the unit dosage form as disclosed herein further comprising at least one pharmaceutically acceptable carrier, excipient, and/or stabilizer.

[0428] In some embodiments, the disclosure provides the unit dosage forms as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in a length of platelet response of at least about 1 week, at least about 5 weeks, at least about 10 weeks, at least about 15 weeks, at least about 20 weeks, at least about 25 weeks, at least about 30 weeks, at least about 35 weeks, at least about 40 weeks, at least about 45 weeks, or at least about 50 weeks, wherein the length of the platelet response is defined as the sum of all weeks in which the subject achieves a platelet response, and wherein the platelet response is defined as a platelet count of ≥50,000/μL, ≥60,000/μL, ≥70,000/μL, ≥80,000/μL, ≥90,000/μL, ≥100,000/μL, ≥110,000/μL, ≥120,000/μL, ≥130,000/μL, ≥140,000/μL, or ≥150,000/μL. In some embodiments, the length of platelet response is at least about 1 week, at least about 5 weeks, at least about 10 weeks, at least about 15 weeks, at least about 20 weeks, at least about 25 weeks, at least about 30 weeks, at least about 35 weeks, at least about 40 weeks, at least about 45 weeks, or at least about 50 weeks, wherein the length of the platelet response is defined as the sum of all weeks in which the subject achieves a platelet response, and wherein the platelet response is defined as a platelet count of ≥50,000/μL.

[0429] In some embodiments, the disclosure provides the unit dosage forms as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in a platelet response, wherein the platelet response is defined as a platelet count of ≥10,000/μL, ≥20,000/μL, ≥30,000/μL, ≥40,000/μL, ≥50,000/μL, ≥60,000/μL, ≥70,000/μL, ≥80,000/μL, ≥90,000/μL, ≥100,000/μL, ≥110,000/μL, ≥120,000/μL, ≥130,000/μL, ≥140,000/μL, or ≥150,000/μL. In some embodiments, the platelet response is defined as a platelet count of ≥20,000/μL above baseline, for example, ≥30,000/μL, ≥40,000/μL, ≥50,000/μL, ≥60,000/μL, ≥70,000/μL, ≥80,000/μL, ≥90,000/μL, or ≥100,000/μL above baseline. In some embodiments, the platelet response is defined as a platelet count of ≥50,000/μL and ≥20,000/μL above baseline. In some embodiments, the platelet response is defined as a platelet count of ≥50,000/μL and/or the platelet response is defined as a platelet count of ≥30,000/μL and at least doubled from baseline. In some embodiments, the platelet response is defined as a platelet count of ≥50,000/μL. In some embodiments, the platelet response is defined as a platelet count of ≥30,000/μL and at least doubled from baseline. In some embodiments, the platelet response is defined as a platelet count of ≥10,000/μL, ≥20,000/μL, ≥30,000/μL, ≥40,000/μL, or ≥50,000/μL

at about 2 weeks after the administering, about 4 weeks after the administering, about 6 weeks after the administering, about 8 weeks after the administering, about 10 weeks after the administering, about 12 weeks after the administering, about 14 weeks after the administering, about 16 weeks after the administering, about 18 weeks after the administering, or about 20 weeks after the administering. In some embodiments, the platelet response is defined as a platelet count of $\geq$50,000/μL at about 16 weeks after the administering. In some embodiments, the platelet response is achieved in about six weeks or less, about five weeks or less, about four weeks or less, about three weeks or less, about two weeks or less, or about one week or less. In some embodiments, the platelet response is achieved in about one week or less. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet response for at least about 2 cumulative number of weeks, at least about 4 cumulative number of weeks, at least about 8 cumulative number of weeks, at least about 10 cumulative number of weeks, at least about 12 cumulative number of weeks, at least about 14 cumulative number of weeks, at least about 16 cumulative number of weeks, at least about 18 cumulative number of weeks, or at least about 20 cumulative number of weeks from baseline to about 24 weeks after the administering.

[0430] In some embodiments, the disclosure provides the unit dosage forms as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in a durable platelet response, wherein the durable platelet response is defined as a durable platelet response for at least 1 of 6 biweekly measurements, at least 2 of 6 biweekly measurements, at least 3 of 6 biweekly measurements, at least 4 of 6 biweekly measurements, or at least 5 of 6 biweekly measurements from about 10 weeks to about 24 weeks after the administering, optionally wherein the subject has not received a rescue therapy. In some embodiments, the durable platelet response is defined as a durable platelet response for at least 1 of 6 weekly measurements, at least 2 of 6 weekly measurements, at least 3 of 6 weekly measurements, at least 4 of 6 weekly measurements, or at least 5 of 6 weekly platelet measurements from baseline to about 24 weeks after the administering. In some embodiments, the durable platelet response is defined as a durable platelet response for at least 4 of 6 biweekly measurements from about 10 weeks to about 24 weeks after the administering, wherein the subject has not received a rescue therapy. In some embodiments, the platelet response is defined at a platelet count of

≥10,000/μL, ≥20,000/μL, ≥30,000/μL, ≥40,000/μL, ≥50,000/μL, ≥60,000/μL, ≥70,000/μL, ≥80,000/μL, ≥90,000/μL, ≥100,000/μL, ≥110,000/μL, ≥120,000/μL, ≥130,000/μL, ≥140,000/μL, or ≥150,000/μL. In some embodiments, the platelet response is defined at a platelet count of ≥50,000/μL. In some embodiments, the durable platelet response is defined as a platelet count of ≥10,000/μL, ≥20,000/μL, ≥30,000/μL, ≥40,000/μL, or ≥50,000/μL on at least 1 of 6, at least 2 of 6, or at least 3 of 6 weekly platelet measurements from baseline to about 24 weeks after the administering, from about 5 weeks to about 24 weeks after the administering, from about 10 weeks to about 24 weeks after the administering, from about 15 weeks to about 24 weeks after the administering, or from about 19 weeks to about 24 weeks after the administering. In some embodiments, the durable platelet response is defined as a platelet count of ≥50,000/μL on at least 2 of 6 weekly platelet measurements from about 10 weeks to about 24 weeks after the administering. In some embodiments, the durable platelet response is defined as a platelet count of ≥50,000/μL on at least 4 of 6 weekly platelet measurements from about 19 weeks to about 24 weeks after the administering. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a durable platelet response, wherein the durable platelet response is measured as the cumulative number of weeks in which platelet count is sustained (e.g., ≥30,000/μL or ≥50,000/μL). In some embodiments, the platelet response is sustained for at least about 2 weeks, at least about 4 weeks, at least about 6 weeks, at least about 8 weeks, at least about 10 weeks, at least about 12 weeks, at least about 14 weeks, at least about 16 weeks, at least about 18 weeks, at least about 20 weeks, at least about 25 weeks, at least about 30 weeks, at least about 35 weeks, at least about 40 weeks, at least about 45 weeks, or at least about 50 weeks after the administration of the isolated human anti-CD38 antibody or antigen binding fragment thereof. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a durable platelet response, wherein the durable platelet response is defined as a durable platelet response for at least 4 of 6 biweekly measurements from about 10 weeks to about 24 weeks after the administering, wherein the subject has not received a rescue therapy, and wherein the platelet response is defined at a platelet count of ≥50,000/μL.

[0431] In some embodiments, the disclosure provides the unit dosage forms as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in a complete platelet response, wherein the complete platelet response is defined as a platelet count

of ≥50,000/μL, ≥60,000/μL, ≥70,000/μL, ≥80,000/μL, ≥90,000/μL, ≥100,000/μL, ≥110,000/μL, ≥120,000/μL, ≥130,000/μL, ≥140,000/μL, ≥150,000/μL, ≥175,000/μL, or ≥200,000/μL. In some embodiments, the complete platelet response is defined as a platelet count of ≥100,000/μL. In some embodiments, the complete platelet response is measured on at least one visit, at least two visits, at least three visits, at least four visits, or at least five visits from baseline to about 10 weeks after the administering, from baseline to about 12 weeks after the administering, from baseline to about 14 weeks after the administering, from baseline to about 16 weeks after the administering, from baseline to about 18 weeks after the administering, from baseline to about 20 weeks after the administering, from baseline to about 22 weeks after the administering, or from baseline to about 24 weeks after the administering, optionally wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the complete platelet response is measured in at least one measurement, at least two measurements, at least three measurements, at least four measurements, or at least five measurements from baseline to about 10 weeks after the administering, from baseline to about 12 weeks after the administering, from baseline to about 14 weeks after the administering, from baseline to about 16 weeks after the administering, from baseline to about 18 weeks after the administering, from baseline to about 20 weeks after the administering, from baseline to about 22 weeks after the administering, or from baseline to about 24 weeks after the administering. In some embodiments, the complete platelet response is measured on at least two visits from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the complete platelet response is defined as a platelet count of ≥100,000/μL on at least two visits from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the complete platelet response is defined as a platelet count of ≥100,000/μL in at least one measurement from baseline to about 24 weeks after the administering. In some embodiments, the complete platelet response is defined as a platelet count of ≥100,000/μL in at least two measurements from baseline to about 24 weeks after the administering.

[0432] In some embodiments, the disclosure provides the unit dosage forms as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in a clinically meaningful platelet response, wherein the clinically meaningful platelet response is

defined as a platelet count ≥20,000/μL, ≥30,000/μL, ≥40,000/μL, ≥50,000/μL, ≥60,000/μL, ≥70,000/μL, ≥80,000/μL, ≥90,000/μL, or ≥100,000/μL above baseline. In some embodiments, the clinically meaningful platelet response is defined as a platelet count ≥20,000/μL above baseline. In some embodiments, the clinically meaningful platelet response is measured on at least one visit, at least two visits, at least three visits, at least four visits, or at least five visits from baseline to about 10 weeks after the administering, from baseline to about 12 weeks after the administering, from baseline to about 14 weeks after the administering, from baseline to about 16 weeks after the administering, from baseline to about 18 weeks after the administering, from baseline to about 20 weeks after the administering, from baseline to about 22 weeks after the administering, from baseline to about 24 weeks after the administering, or from baseline to about 32 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the clinically meaningful platelet response is measured on at least two visits from baseline to about 16 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the clinically meaningful platelet response is measured on at least two visits from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a clinically meaningful platelet response, wherein the clinically meaningful platelet response is defined as a platelet count of ≥20,000/μL above baseline on at least two visits from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the clinically meaningful platelet response is measured in at least one measurement, at least two measurements, at least three measurements, at least four measurements, or at least five measurements from baseline to about 10 weeks after the administering, from baseline to about 12 weeks after the administering, from baseline to about 14 weeks after the administering, from baseline to about 16 weeks after the administering, from baseline to about 18 weeks after the administering, from baseline to about 20 weeks after the administering, from baseline to about 22 weeks after the administering, from baseline to about 24 weeks after the administering, or from baseline to about 32 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the clinically meaningful platelet response is measured in at least two measurements from baseline to about 16 weeks after the

administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, the clinically meaningful platelet response is measured in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a clinically meaningful platelet response, wherein the clinically meaningful platelet response is defined as a platelet count of ≥20,000/μL above baseline in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks.

[0433] In some embodiments, the disclosure provides the unit dosage forms as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in a hemostatic platelet response, wherein the hemostatic platelet response is defined as a platelet count of ≥30,000/μL, ≥40,000/μL, ≥50,000/μL, ≥60,000/μL, ≥70,000/μL, ≥80,000/μL, ≥90,000/μL, or ≥100,000/μL. In some embodiments, the hemostatic platelet response is defined as a platelet count of ≥20,000/μL, ≥30,000/μL, ≥40,000/μL, ≥50,000/μL, ≥60,000/μL, ≥70,000/μL, ≥80,000/μL, ≥90,000/μL, or ≥100,000/μL above baseline. In some embodiments, the hemostatic platelet response is defined as a platelet count of ≥30,000/μL and ≥20,000/μL above baseline. In some embodiments, the hemostatic platelet response is measured on at least one visit, at least two visits, at least three visits, at least four visits, or at least five visits from baseline to about 10 weeks after the administering, from baseline to about 12 weeks after the administering, from baseline to about 14 weeks after the administering, from baseline to about 16 weeks after the administering, from baseline to about 18 weeks after the administering, from baseline to about 20 weeks after the administering, from baseline to about 22 weeks after the administering, from baseline to about 24 weeks after the administering, or from baseline to about 32 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks and the subject has a baseline platelet count of <15,000/μL. In some embodiments, the hemostatic platelet response is measured on at least two visits from baseline to about 18 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks and the subject has a baseline platelet count of <15,000/μL. In some embodiments, the hemostatic platelet response is measured on at least two visits from baseline to

about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks and the subject has a baseline platelet count of <15,000/μL. In some embodiments, the baseline platelet count is <12,000/μL, <10,000/μL, <8,000/μL, <5,000/μL, or <1,000/μL. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a hemostatic platelet response, wherein the hemostatic platelet response is defined as a platelet count of ≥30,000/μL and ≥20,000/μL above baseline on at least two visits from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks and the subject has a baseline platelet count of <15,000/μL. In some embodiments, the hemostatic platelet response is measured in at least one measurement, at least two measurements, at least three measurements, at least four measurements, or at least five measurements from baseline to about 10 weeks after the administering, from baseline to about 12 weeks after the administering, from baseline to about 14 weeks after the administering, from baseline to about 16 weeks after the administering, from baseline to about 18 weeks after the administering, from baseline to about 20 weeks after the administering, from baseline to about 22 weeks after the administering, from baseline to about 24 weeks after the administering, or from baseline to about 32 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks and the subject has a baseline platelet count of <15,000/μL. In some embodiments, the hemostatic platelet response is measured in at least two measurements from baseline to about 18 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks and the subject has a baseline platelet count of <15,000/μL. In some embodiments, the hemostatic platelet response is measured in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks and the subject has a baseline platelet count of <15,000/μL. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a hemostatic platelet response, wherein the hemostatic platelet response is defined as a platelet count of ≥30,000/μL and ≥20,000/μL above baseline in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks and the subject has a baseline platelet count of <15,000/μL.

[0434] In some embodiments, the disclosure provides the unit dosage forms as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in a platelet count of >10,000/μL, >20,000/μL, >30,000/μL, >40,000/μL, >50,000/μL, >60,000/μL, >70,000/μL, >80,000/μL, >90,000/μL, or >100,000/μL. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet count of >50,000/μL. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in a platelet count of >100,000/μL.

[0435] In some embodiments, the disclosure provides the unit dosage forms as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in a reduction in immunoglobulin(s). In some embodiments, the immunoglobulin is one or more selected from the group consisting of IgA, IgG, and IgM. In some embodiments, the immunoglobulin(s) (*e.g.*, IgA, IgG, and/or IgM) are reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 90%, or at least about 95% relative to baseline levels of the immunoglobulin(s). In some embodiments, IgA is reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 90%, or at least about 95% relative to baseline levels of the IgA. In some embodiments, IgG is reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 90%, or at least about 95% relative to baseline levels of the IgG. In some embodiments, IgM is reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 90%, or at least about 95% relative to baseline levels of IgM. In some embodiments, IgA is reduced by at least about 50% relative to baseline levels of IgA. In

some embodiments, IgG is reduced by at least about 30% relative to baseline levels of IgG. In some embodiments, IgM is reduced by at least about 40% relative to baseline levels of IgM. In some embodiments, the reduction in immunoglobulin(s) (*e.g.*, IgA, IgG, and/or IgM) is achieved in six weeks or less, five weeks or less, four weeks or less, three weeks or less, two weeks or less, or one week or less. In some embodiments, the reduction in immunoglobulin(s) is achieved in one week or less.

[0436] In some embodiments, the disclosure provides the unit dosage forms as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in less than about 75%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, or less than about 5% incidence of use of a rescue therapy. In some embodiments, the unit dosage form is not used in combination with a rescue therapy.

[0437] In some embodiments, the disclosure provides the unit dosage forms as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in a reduction in ITP disease activity and/or progression in a subject diagnosed with ITP. In some embodiments, the ITP disease activity and/or progression is measured one or more assessments selected from the group consisting of World Health Organization (WHO) Bleeding Scale, Immune Thrombocytopenic Purpura Subject Assessment Questionnaire (ITP-PAQ), and/or 5-Level EuroQol Five Dimensions (EQ-5D-5L). In some embodiments, the ITP disease activity and/or progression is measured by World Health Organization (WHO) Bleeding Scale. In some embodiments, the ITP disease activity and/or progression is measured by Immune Thrombocytopenic Purpura Subject Assessment Questionnaire (ITP-PAQ). In some embodiments, the ITP disease activity and/or progression is measured by 5-Level EuroQol Five Dimensions (EQ-5D-5L). In some embodiments, the ITP disease activity and/or progression is measured by a change from baseline in Symptoms, Fatigue/Sleep, Physical Health-Activity, Physical Health-Bother, Psychological Health, Overall Quality of Life, Social Activity, and/or Work scales scores of the ITP-PAQ from baseline to about 24 weeks after the administering. In some embodiments, the ITP disease activity and/or progression is measured by a change from baseline in the Menstrual Symptoms subscale scores of the ITP-PAQ from baseline to about 24 weeks after the administering in a female subject who had at least one menstrual period within

12 months before the receiving the isolated antibody. In some embodiments, the ITP disease activity and/or progression is measured by a change from baseline in the Fertility subscale scores of the ITP-PAQ in a female subject from baseline to about 24 weeks after the administering. In some embodiments, the ITP disease activity and/or progression is measured by a change from baseline in the EQ-5D-5L utility index score and/or VAS score from baseline to about 24 weeks after the administering. In some embodiments, the ITP disease activity and/or progression is measured by a change in a Symptoms Scale Score of ITP-PAQ from baseline to about 24 weeks after the administering.

[0438] In some embodiments, the disclosure provides the unit dosage forms as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in in a reduction in bleeding events in the subject. In some embodiments, bleed events are measured by Immune Thrombocytopenia-specific Bleeding Assessment Tool (ITP-BAT). In some embodiments, the bleeding events comprise Grade $\geq$2 in the Skin domain, Grade $\geq$1 in the Mucosal domain, and/or Grade $\geq$1 in the Organ domain.

[0439] In some embodiments, the disclosure provides the unit dosage forms as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in ITP remission. In some embodiments, ITP remission is defined as all platelet counts $\geq$50,000/μL for at least about 12 or at least about 24 weeks after any treatment cycle with the isolated antibody or antigen binding fragment thereof in the absence of other therapy for ITP.

[0440] In some embodiments, the disclosure provides the unit dosage forms as disclosed herein, wherein the isolated antibody or antigen binding fragment thereof is from about 2 times to about 4 times more efficacious than fostamatinib and/or efgartigimod. In some embodiments, the isolated antibody or antigen binding fragment thereof results in from about 2 times to about 4 times more durable or sustained platelet response as compared to fostamatinib and/or efgartigimod.

[0441] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein administering the antibody or antigen binding fragment thereof results in less than 10% incidence of grade 3 or 4 of one or more treatment-related adverse events (TRAEs) or treatment-emergent adverse events (TEAEs). In some embodiments, the TRAEs or TEAEs are selected

from the group consisting of gingival bleeding, heavy menstrual bleeding, haematochezia, mouth haemorrhage, haematoma, traumatic haematoma, epistaxis, petechiae, ecchymosis, conjunctival haemorrhage, blood urine, and haemorrhagic ovarian cyst.

[0442] In some embodiments, a TRAE or TEAE resulting from the administration of the antibody or antigen binding fragment thereof has a maximum intensity of Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or Grade 2.

[0443] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in a reduction in dose and/or frequency of use of background ITP medication(s).

[0444] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein administering the isolated antibody or antigen binding fragment thereof results in a reduction in ITP-associated bleeding adverse events (AEs) relative to placebo. In some embodiments, administering the isolated antibody or antigen binding fragment thereof results in at least about 5%, at least about 10%, at least about 15%, at least about 20%, or at least about 25% reduction in ITP-associated bleeding adverse events (AEs) relative to placebo.

[0445] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the unit dosage form is administered to a subject having has a baseline mean platelet count of less than or equal to about 100×10^9/L, less than or equal to about 50×10^9/L, less than or equal to about 45×10^9/L, less than or equal to about 40×10^9/L, less than or equal to about 35×10^9/L, less than or equal to about 30×10^9/L, less than or equal to about 25×10^9/L, less than or equal to about 20×10^9/L, less than or equal to about 15×10^9/L, or less than or equal to about 10×10^9/L.

[0446] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, the unit dosage form is administered to a subject having an ITP disease duration (*e.g.*, mean ITP disease duration) of at least about 0.1 years, at least about 0.2 years, at least about 0.3 years, at least about 0.4 years, at least about 0.5 years, at least about 0.6 years, at least about 0.7 years, at least about 0.8 years, at least about 0.9 years, at least about 1 year, at least about 2 years, at least about 3 years, at least about 4 years, at least about 5 years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, at least about 10 years, at least about 11 years,

at least about 12 years, at least about 13 years, at least about 14 years, at least about 15 years, at least about 20 years, at least about 25 years, at least about 30 years, or at least about 35 years.

[0447] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the unit dosage form is administered to a subject having received a mean of about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, or about 13 prior ITP treatments.

[0448] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the isolated antibody or antigen binding fragment thereof comprises an HC as set forth in SEQ ID NO: 11 and an LC as set forth in SEQ ID NO: 12; and wherein the antibody or antigen binding fragment thereof is subcutaneously administered once weekly for 8 weeks. In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the isolated antibody or antigen binding fragment thereof further comprises one or more engineered glycoforms, wherein the engineered glycoform comprises glycosylation of one or more polypeptides and the glycosylation is N-linked glycosylation.

[0449] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the isolated antibody or antigen binding fragment thereof comprises an HC as set forth in SEQ ID NO: 14 and an LC as set forth in SEQ ID NO: 12; and wherein the antibody or antigen binding fragment thereof is subcutaneously administered once weekly for 8 weeks. In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the isolated antibody or antigen binding fragment thereof further comprises one or more engineered glycoforms, wherein the engineered glycoform comprises glycosylation of one or more polypeptides and the glycosylation is N-linked glycosylation.

[0450] In some embodiments, the disclosure provides the unit dosage form as disclosed herein, wherein the isolated antibody or antigen binding fragment thereof is administered to a subject once a week for 8 weeks, the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of about 600 mg, the isolated antibody or antigen binding fragment thereof is mezagitamab, the ITP is persistent or chronic ITP, the subject is an adult, and the subject has had an insufficient response or intolerance to other therapy. In some embodiments, the subject has had an insufficient response or intolerance to other therapy. In

some embodiments, the other therapy comprises one or more of a corticosteroid, immunoglobulins, splenectomy, a thrombopoietin receptor agonist (TPO-RA), and background ITP medication(s) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag, methotrexate, azathioprine, leflunomide, cyclosporine, fostamatinib, mycophenolate, danazol, dapsone, methylprednisolone, hydrocortisone, cortisone, prednisolone, prednisone, and/or dexamethasone).

Treatment Modalities

[0451] In the methods of the disclosure, therapy is used to provide a positive therapeutic response with respect to a disease or condition. The term "positive therapeutic response" refers to an improvement in a disease or condition, and/or an improvement in the symptoms associated with the disease or condition.

[0452] Positive therapeutic responses in any given disease or condition can be determined by standardized response criteria specific to that disease or condition. In addition to the positive therapeutic responses, the subject undergoing therapy may experience the beneficial effect of an improvement in the symptoms associated with the disease.

[0453] Measurements of efficacy in treating ITP can be assessed based on of World Health Organization (WHO) Bleeding Scale, Immune Thrombocytopenic Purpura Subject Assessment Questionnaire (ITP-PAQ), and/or 5-Level EuroQol Five Dimensions (EQ-5D-5L) as disclosed in Example 1.

[0454] Treatment according to the present disclosure includes a "therapeutically effective amount" of the medicaments used. The terms "therapeutically effective amount" and "therapeutically effective dosage" refer to an amount of a therapy that is sufficient to reduce or ameliorate the severity and/or duration of a disorder or one or more symptoms thereof; prevent the advancement of a disorder; cause regression of a disorder; prevent the recurrence, development, onset, or progression of one or more symptoms associated with a disorder; or enhance or improve the prophylactic or therapeutic effect(s) of another therapy (*e.g.*, prophylactic or therapeutic agent), at dosages and for periods of time necessary to achieve a desired therapeutic result. A therapeutically effective amount may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the medicaments to

elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the antibody or antibody portion are outweighed by the therapeutically beneficial effects.

Anti-CD38 Antibody Kits

[0455] In another aspect, kits are provided for the treatment of ITP. In one embodiment, the kit comprises a dose of an anti-CD38 antibody described herein, such as TAK-079. In one embodiment, the kit comprises a dose of an anti-CD38 antibody described herein, such as mezagitamab. In some embodiments, the kits provided herein may contain one or more doses of a liquid or lyophilized formulation as provided herein. When the kits comprise a lyophilized formulation of an anti-CD38 antibody described herein such as mezagitamab, generally the kits will also contain a suitable liquid for reconstitution of the liquid formulation, for example, sterile water or a pharmaceutically acceptable buffer. In some embodiments, the kits may comprise an anti-CD38 antibody formulation described herein prepackaged in a syringe for subcutaneous administration by a health care professional or for home use.

[0456] In certain embodiments, the kit will be for a single administration or dose of an anti-CD38 antibody described herein such as mezagitamab. In other embodiments, the kit may contain multiple doses of an anti-CD38 antibody described herein such as mezagitamab for subcutaneous administration. In one embodiment, the kit may comprise an anti-CD38 antibody formulation described herein prepackaged in a syringe for subcutaneous administration by a health care professional or for home use.

Articles Of Manufacture

[0457] In other embodiments, an article of manufacture containing materials useful for the treatment of the disorders described above is provided. The article of manufacture comprises a container and a label. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is effective for treating the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The active agent in the composition is the antibody. The label on, or associated with, the container indicates that the composition is used

for treating the condition of choice. The article of manufacture may further comprise a second container comprising a pharmaceutically acceptable buffer, such as phosphate-buffered saline, Ringer's solution, or dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, syringes, and package inserts with instructions for use.

EXAMPLES

EXAMPLE 1: A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE SAFETY, TOLERABILITY, AND EFFICACY OF TAK-079 IN SUBJECTS WITH PERSISTENT/CHRONIC PRIMARY IMMUNE THROMBOCYTOPENIA

Summary

[0458] In Part B of the Phase 2 study of subjects with chronic/persistent ITP, results from an interim analysis of an ongoing Phase 2 study demonstrated mezagitamab (600 mg) administered once weekly for 8 weeks was superior to placebo in achieving platelet response (PLR) by study week 16 (91% vs. 23% respectively). The onset of action of mezagitamab was rapid, platelet counts were restored to near normal, and the beneficial effect was maintained up to 8 weeks post-therapy. In an ad hoc analysis evaluating durability of platelet response between weeks 10-24, 64% of mezagitamab treated subjects achieved durable platelet response (PLR) versus 8% in placebo. In this study, mezagitamab was well tolerated without any dose dependent increase in adverse events or new safety signals compared to previous studies.

[0459] The main clinical evidence supporting mezagitamab for the treatment of chronic/persistent ITP is from Part A of the Phase 2 study. In Part A, based on the pre-specified Go/No Go evaluations at week 16, a robust dose-exposure-platelet response relationship was observed in ITP subjects treated with mezagitamab.

[0460] The results outperformed the efficacy attributes of mezagitamab and matched the upper level of the safety target.

Objectives

Primary Objective

[0461] The primary objective was to evaluate the safety and tolerability of mezagitamab in participants with persistent/chronic primary immune thrombocytopenia (ITP).

Secondary Objective

[0462] The secondary objective was to assess the effects of mezagitamab administration on platelet counts in participants with persistent/chronic primary ITP.

Additional Objectives

[0463] The exploratory objectives were as follows:

- To determine the pharmacokinetics (PK) of mezagitamab.
- To determine the pharmacodynamic (PD) profile of mezagitamab.
- To explore the durability of the platelet response.
- To determine the effects of mezagitamab on platelet-associated antibody levels and subtypes.
- To determine frequency and proportion of participants requiring rescue therapy.
- To explore bleeding assessment using the ITP bleeding score.
- To determine the impact of treatment on health-related quality of life.
- To explore vaccine-inducted protective antibodies.
- To explore the effects of repeated administration of mezagitamab on antidrug antibodies (ADA) and exploratory biomarkers of disease activity.

Outcome Measures

Primary Outcome Measures

[0464] Percentage of Subjects with at least one grade 3 or higher treatment emergent adverse event (TEAE), serious adverse event (SAE), and adverse event (AE) leading to TAK-079 discontinuation (time frame: from the first dose of study drug up to week 32).

Secondary Outcome Measures

[0465] Percentage of subjects with platelet response (time frame: up to week 32). Platelet response is defined as a platelet count ≥50,000/microliter (μL) and ≥20,000/μL above baseline on at least 2 visits without a dosing period-permitted rescue treatment in the previous 4 weeks and without any other previous rescue therapy.

[0466] Percentage of subjects with complete platelet response (time frame: up to week 32). Complete platelet response is defined as a platelet count ≥100,000/μL on at least 2 visits without a dosing period-permitted rescue treatment in the previous 4 weeks and without any other previous rescue therapy.

[0467] Percentage of subjects with clinically meaningful platelet response (time frame: up to week 32). A clinically meaningful platelet response is defined as a platelet count ≥20,000/μL above baseline on at least 2 visits without a dosing period-permitted rescue treatment in the previous 4 weeks and without any other previous rescue therapy.

[0468] Percentage of subjects with hemostatic platelet response (time frame: up to week 32). A hemostatic platelet response is defined for subjects with a baseline platelet count of <15,000/μL who achieve a platelet count of ≥30,000/μL and ≥20,000/μL above baseline on at least 2 visits without a dosing period-permitted rescue treatment in the previous 4 weeks and without any other previous rescue therapy.

[0469] Samples for hematology testing were collected at weeks 1, 1 day 3, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, and 16.

Exploratory Endpoints

[0470] The exploratory endpoints were assessed through the following parameters:

- Serum concentration-time profile of mezagitamab. PK parameters included, but were not limited to, C_{trough} over time.
- PD analysis of the presence and changes of immune cells in peripheral blood before and during therapy.
- Cumulative number of weeks of platelet response in the absence of any concomitant rescue therapy.
- Change from baseline in platelet-associated autoantibody level and the number of platelet associated autoantibody subtypes.
- Change in serum immunoglobulin levels.
- Frequency and proportion of participants requiring rescue therapy.
- Change from baseline in the ITP Bleeding Score.
- Change from baseline in the Symptoms, Physical Activity, and Women's Reproductive Health domains of the ITP Patient Assessment Questionnaire (ITP-PAQ) to assess impact of treatment on health-related quality of life.
    - Clinically meaningful change was defined as mean change exceeding the minimal important difference threshold of 8 or 10 points.
- Change in levels of the following vaccine-protective antibodies: measles, mumps, rubella, diphtheria, and tetanus.
- Immunogenicity assessment to include ADA and other relevant biomarkers in peripheral blood associated with disease activity, such as specific markers of CD38 pathway modulation.

[0471] Bloods samples for PK evaluation were collected weekly during the dosing period and at weeks 12 and 16 in the follow-up period. Samples for IgG evaluation were collected weekly during the dosing period and at weeks 10, 12, 14, and 16 in the follow-up period. Samples for PD evaluation were taken at weeks 1, 2, 4, 8, and 16.

[0472] Prevalidation characterization and technical validation were completed for flow cytometric assays to evaluate levels of CD45+ lymphocytes, T cells, B cells (CD45+, CD19+, CD3-), NK cells, monocytes, granulocytes, plasmablasts, and plasma (CD45+, CD19+, CD27+, CD138+, CD3-, CD38+) cells in whole blood, and to analyze CD38 expression and monitor changes in immune cells .

[0473] NK cells were identified through CD45+, CD16+, CD56+, CD19-, CD3- staining. Plasmablasts were identified through CD45+, CD19+, CD27+, CD3-, and CD38+ staining.

[0474] Impact of treatment on health-related quality of life was assessed using the ITP-PAQ which was completed by participants at weeks 1, 5, 10 and 16 before other assessments.

Statistical Methods

[0475] This study is exploratory and is not powered to address a prespecified hypothesis. Sample size calculations were not performed, but part A would comprise 24–36 participants and part B 12–18 participants.

[0476] All participants who received at least one study dose were included in the safety analysis. Only participants with a baseline and at least one valid postbaseline result were included in the efficacy, PK or PD analyses.

[0477] Descriptive statistics were used to summarize baseline characteristics, frequency to summarize adverse events, and change from baseline to assess other participant characteristics and clinical laboratory results.

[0478] Efficacy endpoints were summarized by descriptive statistics and are presented by treatment group and/or by the number and percentage attaining a response. Efficacy data were analyzed using observed case data only based on a "missing at random" assumption.

[0479] Barnard's test was used to analyze binary responder endpoints.

[0480] Change from baseline was analyzed using a mixed-model repeated-measures analysis including treatment, visit, and (treatment × visit) interaction terms as factors, with baseline values as covariates.

[0481] All tests of treatment effects were conducted at a 2-sided α level of 0.05, with 95% CIs for the differences in proportions and least squares means; CIs and p-values were not adjusted for multiplicity.

Safety

[0482] Safety was evaluated by the frequency of TEAEs, severity and types of TEAEs, and by changes from baseline in vital signs, weight, and clinical laboratory results using the safety analysis set. Exposure to investigational medicinal product (IMP) was tabulated.

Efficacy

[0483] The full analysis set was used for analyses of efficacy endpoints. For each type of efficacy endpoint, response was to be attained on at least 2 visits where none of the following occurred: (1) the participant received rescue therapy at any time prior to the visit; (2) the participant received a dosing-period permitted rescue treatment within 4 weeks prior to the visit; (3) the participant prematurely discontinued from study drug prior to the visit; and (4) the platelet count was missing at the visit.

[0484] The number and percentage of participants attaining each type of efficacy response by Week 16 in the main study was summarized by treatment group. CIs for percentages were presented. Differences in percentages between each mezagitamab arm and placebo were presented along with CIs for the main study. In addition, for mezagitamab participants in the main study, the number and percentage of participants attaining each type of response by Week 32 were presented along with CIs for the percentages. For participants in the OLE, the number and percentage of participants attaining each type of response by Week 16 and Week 32 were presented along with CIs for the percentages.

PK

[0485] The PK analysis set was used for presentations of PK data. Analysis of PK data was performed separately for the main study and the OLE phase and based on pooled data from the main study and the OLE phase.

[0486] Due to sparse PK sampling, no noncompartmental analysis was conducted. Individual mezagitamab concentration-time data were summarized using descriptive statistics (including n,

mean, SD, minimum, maximum, median, geometric mean, and geometric percent coefficient of variation by treatment group and nominal time point. Individual and mean concentration-time profiles were plotted by treatment group using box plots and line plots.

PD and Biomarker

[0487] The PD analysis set was used for all presentations of PD and biomarker data. Analysis of PD data was performed separately for the main study and the OLE phase and based on pooled data from the main study and the OLE phase.

[0488] For PD measures and biomarker measures, if not otherwise specified, observed values, change from baseline and percent change from baseline values at different timepoints were summarized by treatment group.

Immunogenicity

[0489] Immunogenicity results were analyzed descriptively using the immunogenicity analysis set, and all results were listed. Analysis of immunogenicity data was performed separately for the main study and the OLE phase and based on pooled data from the main study and the OLE phase. For the OLE phase, baseline was defined as the lats evaluable immunogenicity sample before the first dose in the OLE at extension week 1.

[0490] The numbers and percentages of participants with a positive ADA result were summarized by treatment group and nominal time point. The number and percentage of participants were also summarized by immunogenicity status and treatment group. The relationship between immunogenicity and PK, PD, efficacy, and safety was explored.

Eligibility Criteria

[0491] Key eligibility criteria of prior studies of other agents in this indication were evaluated to accurately contextualize the results of the Phase 2 study (**Table 5**). In general, the ITP subject population studied in this study was comparable to the study population in the prior trials.

Table 5. Eligibility criteria.

Agent	Eligibility Criteria
Rituximab	Corticosteroid unresponsive subjects with ITP and platelet count of $<30\times10^9$/L

TPO-RA *(Eltrombopag Ph3)**	Primary ITP with ≥ 6 mos duration, baseline platelet counts <30x10^9/L; insufficient response to at least 1 previous ITP treatment
Anti-FcRn *(Efgartigimod Ph2)*	Confirmed primary ITP (with an average of two platelet count measurements during the screening <30×10^9/L)
Anti-FcRn *(Efgartigimod Ph3)*	Subjects were heavily pretreated and 67% of subjects had received three or more prior ITP therapies, including 59% who had prior thrombopoietin receptor agonist (TPO-RAs) experience
BTK Inhibitor *(Rilzabrutinib Ph1/2)*	Relapsed or refractory primary or secondary ITP (subjects were heavily pretreated with average of 6 prior LoT)
Syk Inhibitor *(Fostamatinib)*	Primary ITP with ≥ 3 month duration, average platelet counts <30x10^9/L
Anti-CD38 *(Daratumumab)*	Primary ITP w/ platelet count ≤30x10^9/L tx with CS therapy, and at least one 2L including rituximab and/or TPO-RA

Inclusion Criteria

[0492] Each subject must have met all the following inclusion criteria to be randomized to treatment: (a) diagnosed with ITP that has persisted for ≥3 months, diagnosed in accordance to The American Society of Hematology 2011 Evidence-based Practice Guideline for Immune Thrombocytopenia (Neunert *et al.*, Blood (2011), 117 (16); 4190-4207, incorporated herein by reference in its entirety) or the International Consensus Report on The Investigation and Management of Primary Immune Thrombocytopenia (Provan *et al.* Blood (2010) 115 (2): 168–186, herein incorporated by reference in its entirety) as locally applicable; (b) has a mean platelet count of <30,000/μL (and individually ≤35,000/μL) on at least 2 measurements at least 1 week apart during screening; (c) diagnosis of ITP supported by a prior response to an ITP therapy (other than a TPO-RA) that achieved a platelet count of ≥50,000/μL; and (d) if receiving standard background treatment for ITP, treatment should be stable in dose and frequency for at least 4 weeks before dosing.

[0493] Permitted standard background treatments may include: 1 oral corticosteroid; ±1 immunosuppressant from the following list: azathioprine, danazol, dapsone, cyclosporine, mycophenolate mofetil, mycophenolate sodium; ±1 TPO-RA (romiplostim, eltrombopag, avatrombopag); ±fostamatinib. Corticosteroids, including dexamethasone, must be given as oral, daily, or every-other-day therapy as opposed to pulse therapy. The dose of any permitted standard background therapy must be expected to remain stable through the study unless dose reduction is required because of toxicities.

Exclusion Criteria

[0494] Subjects meeting any of the following exclusion criteria were not randomized to treatment: (a) use of anticoagulants or any drug with antiplatelet effect (such as aspirin) within 3 weeks before screening; (b) has a history of any thrombotic or embolic event within 12 months before screening; (c) has a history of splenectomy within 3 months before screening; (d) use of intravenous immunoglobulin (IVIg), subcutaneous immunoglobulin or anti-D immunoglobulin treatment within 4 weeks of screening, or an expectation that any therapy besides the subject's standard background therapies may be used for treatment of thrombocytopenia (*e.g.*, a rescue therapy) between screening and dosing; (e) diagnosed with chronic obstructive pulmonary disease (COPD) or asthma, and a prebronchodilatory forced expiratory volume in 1 second (FEV1) <50% of predicted normal; (f) use of rituximab or any monoclonal antibody (mAb) for immunomodulation within 4 months before first dosing. Note: Subjects with prior exposure to rituximab must have cluster of differentiation (CD) 19 counts within the normal range at screening; (g) use of immunosuppressants (such as cyclophosphamide, vincristine) other than permitted oral immunosuppressants within 6 months before first dosing; (h) has been diagnosed with myelodysplastic syndrome; (i) has received a live vaccine within 4 weeks before screening or has any live vaccine planned during the study; and (j) has had an opportunistic infection ≤12 weeks before initial study dosing or is currently undergoing treatment for a chronic opportunistic infection, such as tuberculosis (TB), pneumocystis pneumonia, cytomegalovirus, herpes simplex virus, herpes zoster, or atypical mycobacteria.

Phase 2 Study Results (Part A and Part B)

Study Design

[0495] The Phase 2 study was a 32-week randomized, double-blind, placebo-controlled study evaluating the safety, tolerability, efficacy, PK, and PD of mezagitamab with or without stable background therapy in subjects with primary persistent/chronic ITP. The study is divided into 2 parts: Part A and B (**Figures 2A**, **2B**, and **2C**).

[0496] In Part A, subjects were randomized in a double-blind 1:1:1 ratio to receive either mezagitamab (100 mg or 300 mg) or matching placebo QW for a maximum of 8 doses. After the dosing period, subjects entered an 8-week safety follow-up period, after which they are

unblinded. Subjects who received placebo in Part A, without a durable platelet response, had the option to enroll in an open-label extension in which they received either 100 mg or 300 mg mezagitamab. Subjects who received mezagitamab in Part A continued to be followed, off treatment, until week 32.

[0497] In Part B of the study, subjects were randomized in a 2:1 ratio to either 600 mg of mezagitamab or standard of care (placebo). The design was similar to Part A: 600 mg of mezagitamab was administered once weekly for 8 weeks, followed by an 8-week safety period, unblinding and an optional open label extension where non-responders in the placebo arm could receive mezagitamab. Part B was designed to validate the signal from Part A by evaluating the efficacy (platelet response) and safety of the 600 mg dose of mezagitamab. The primary endpoint was safety, while the efficacy (secondary) endpoint was platelet response, which is an objective, lab-based validated measure of clinical benefit that has been accepted by regulators as a valid primary efficacy endpoint for ITP registrational trials. Exploratory endpoints included the cumulative duration (sum of weeks) of platelet response.

[0498] Following the 8-week dosing period, a 6-month follow-up period (*i.e.*, Safety follow-up (SFP) and Long-term follow-up (LFP)) allowed for the continued monitoring of safety laboratory test results and for evaluating the durability of any clinical benefit. An open-label extension (OLE) phase was available for all placebo participants in either study part (Part A and B) who wished to obtain access to mezagitamab following the completion of the main study doing period and a 2-month SFP.

[0499] To prevent hypersensitivity reactions, methylprednisolone 40 mg orally was given 1–3 hours before the first dose of study drug. In addition, acetaminophen 500–1000 mg orally and cetirizine 10 mg orally or IV were given on study days 1, 2, and 3, and famotidine 20 mg orally or IV on study days 2 and 3. For subsequent doses, acetaminophen 500–1000 mg orally and cetirizine 10 mg orally or IV were administered. Acetaminophen 500–1000 mg orally and cetirizine 10 mg orally or IV could be given as postdose medication if indicated. Equivalents to the doses given were administered as appropriate.

[0500] Permitted rescue medications included, but were not limited to, high-dose corticosteroids, IVIg, and increasing or adding background therapies and use generally resulted in

discontinuation of study dosing and advancement to the follow-up period. However, platelet transfusion, a single dose of IVIg up to 1 g/kg, or an additional 20 mg prednisone (or equivalent) per day for up to 7 days were allowed as a bridge therapy (especially at the beginning of the study), and did not lead to discontinuation from the dosing period.

[0501] Stable background treatment for ITP was permitted throughout the study and could include: 1 oral corticosteroid; ±1 immunosuppressant (azathioprine, danazol, dapsone, cyclosporine, mycophenolate mofetil, mycophenolate sodium); ±1 TPO-RA (romiplostim, eltrombopag, avatrombopag); ± fostamatinib. Oral corticosteroids (dexamethasone) were permitted but not as pulse therapy.

[0502] The study comprised adult participants (≥18 years) diagnosed with ITP in accordance with The American Society of Hematology 2011 Evidence-based Practice Guideline for Immune Thrombocytopenia (Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011;117:4190-207, incorporated herein by reference in its entirety) or the International Consensus Report on The Investigation and Management of Primary Immune Thrombocytopenia (Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010;115:168-86, incorporated herein by reference in its entirety) and persisting for ≥3 months. The inclusion criteria also required a mean platelet count of <30,000/μL (and individually ≤35,000/μL) on at least 2 measurements at least 1 week apart during screening and a prior response to an ITP therapy (other than a thrombopoietin receptor agonists) that achieved a platelet count of ≥50,000/μL.

[0503] An unblinded safety review of data from Part A was conducted after at least 24 subjects had received a minimum of 4 study doses. The purpose of this safety review was to determine the appropriateness of proceeding to Part B at the 600 mg dose of mezagitamab. Results from Part A of this study showed promising durable platelet responses for both the 100 and 300 mg doses of mezagitamab compared to placebo. Fifty percent of subjects treated with mezagitamab versus none in the placebo arm achieved a complete platelet response. In the mezagitamab treatment arms, the observed increase in platelet count was rapid, occurring within a week of therapy initiation. In most subjects that responded, the platelet counts were restored to near normal values. Uniquely for mezagitamab in this indication, the platelet response was durable

for up to 8 weeks post-treatment without any new safety signals. Based on these results, the study progressed to Part B.

Disposition of Participants

[0504] In total, 85 participants were screened; however, 44 did not enter the study. Forty-one participants were randomized at 24 study sites in 9 countries: Bulgaria, China, Croatia, Greece, Italy, Japan, Slovenia, Spain, and Ukraine.

[0505] Of the 41 participants in Part A or Part B of the main study, 37 participants (13 in the placebo combined group and 24 in the mezagitamab combined group) completed dosing with the IMP. Four participants (2 in mezagitamab 100 mg, 0 in mezagitamab 300 mg, and 2 in mezagitamab 600 mg) discontinued the IMP during the main study, and the reason for discontinuation was an AE, and five discontinued the study for reasons of participant withdrawal or other (war in Ukraine).

[0506] Sixteen subjects were randomized in Part B, 11 to 600 mg mezagitamab and 5 to standard of care (placebo). For the placebo arm, treatment emergent adverse events (TEAE) and efficacy data from the 5 placebo subjects enrolled in part B and 8 placebo subjects from part A (total placebo N=13) were combined to enable a robust comparison against mezagitamab.

[0507] A total of 36 participants completed the study, and 5 participants discontinued from the study (all during the main study: 1 who received placebo, 2 who received mezagitamab 100 mg, 0 who received mezagitamab 300 mg, and 2 who received mezagitamab 600 mg). Only 1 participant in this group discontinued treatment early; the remaining 4 participants completed dosing per protocol and then discontinued from the study. The most common reason for discontinuation from the study was withdrawal by participant, reported for 4 participants. Of the 4 participants who discontinued for the reason of withdrawal by participant, 1 participant had had an AE that led to discontinuation of IMP (Grade 4 thrombocytopenia); the other 3 participants did not have a concurrent AE before they discontinued from the study. One participant in the mezagitamab 100 mg group discontinued from the study for a reason of "other" (war crisis in Ukraine).

[0508] Of the 13 participants who received placebo in the main study, 12 enrolled in the OLE period of the study. One participant discontinued after completion of the main study but before

the first dosing in the OLE period. All 12 participants in the OLE completed dosing with IMP during the OLE period.

Subject Demographics and Baseline Characteristics

[0509] In summary, baseline and demographic data were generally comparable between placebo and the 600 mg arm without any imbalances that could have impacted the outcome. Subjects (N=41) had a mean age of 46.2 years, 68.3% of the subjects were female, and 90.2% of the subjects were white. Subjects (N=41) had a mean disease duration of 10.98 (range: 0.3–35.2) years and received a mean of 3.9 (range: 1–13) prior ITP treatments. A summary of the subject disposition (main study, enrolled set) is summarized in **Figure 3A** and a participant flow diagram is summarized in **Figure 3B**, demographic and baseline characteristics are provided in **Table 6**, and baseline ITP characteristics are provided in **Table 7**.

Table 6. Demographics and baseline characteristics (safety analysis set).

	TAK-079 100 mg (N=9)	**TAK-079 300 mg (N=8)**	**TAK-079 600 mg (N=11)**	**TAK-079 Combined (N=28)**	**Placebo Combined (N=13)**
Age (years), Mean ± SD Range	49.0 ± 14.45 32-80	52.3 ± 16.59 24-79	48.4 ± 19.68 24-88	49.7 ± 16.7 24-88	38.8 ± 15.86 20-65
Sex, n (%) Females	5 (55.6)	5 (62.5)	9 (81.8)	19 (67.9)	9 (69.2)
Race, n (%) Asian (Chinese) White Not reported	 0 9 (100) 0	 0 8 (100) 0	 2 (18.2) 9 (81.8) 0	 2 (7.1) 26 (92.9) 0	 1 (7.7) 11 (84.6) 1 (7.7)
Ethnicity, n (%) Not Hispanic or Latino Not reported	 9 (100) 0	 8 (100) 0	 9 (81.8) 2 (18.2)	 26 (92.9) 2 (7.1)	 12 (92.3) 0
Height (cm), Mean ± SD	166.4 ± 7.54	167.5 ± 6.95	163.1 ± 8.53		166.5 ± 8.00
Weight (kg), Mean ± SD	86.9 ± 16.45	79.5 ± 18.07	70.11 ± 14.20		78.15 ± 18.92
BMI (kg/m^2), Mean ± SD	31.3 ± 5.21	28.4 ± 6.45	26.3 ± 4.80		28.3 ± 7.13

Table 7. Baseline ITP characteristics (safety analysis set).

Mean ± SD or n (%)	TAK-079 100 mg (N=9)	TAK-079 300 mg (N=8)	TAK-079 600 mg (N=11)	TAK-079 Combined (N=28)	Placebo Combined (N=13)
Years Since ITP Diagnosis	13.4 ± 12.07	15.4 ± 13.12	5.5 ± 5.01	10.8 ± 10.8	11.3 ± 10.90
Mean Platelet Count at Screening (10^9/L)	17.9 ± 14.51	19.6 ± 14.39	19.8 ± 11.41	19.1 ± 12.8	17.3 ± 10.41
Number of Prior ITP Treatments (range)	4.2 ± 3.3 1–9	3.6 ± 1.9 1–6	3.7 ± 2.2 2–9	3.9 ± 2.4 1-9	4.2 ± 3.4 1–13
Number of Prior ITP Treatments (by category) (min, max)	2.9 ± 1.96 (1, 6)	2.6 ± 1.30 (1, 4)	2.6 ± 1.13 (1, 5)	2.7 ± 1.4	2.8 ± 1.68 (1, 6)
Participants previously treated with TPO-Ras	5 (55.6)	5 (62.5)	8 (72.7)	18 (64.3)	8 (61.5)
On ITP Treatment at the Time of Enrollment	3 (33.3)	5 (62.5)	9 (81.8)	17 (60.7)	7 (53.8)
Prior Splenectomy	3 (33.3)	2 (25.0)	1 (9.1)	6 (21.4)	3 (23.1)

[0510] Demographic characteristics were generally comparable among the treatment groups. Overall, most of the participants were white (90.2%) and of European origin (87.8%). The median age in the total population was 46.0 years with a maximum age of 88 years. The median age in the mezagitamab combined group was 16.5 years older than that of the placebo combined group.

[0511] In the total study population, there were more female participants (28 of 41, 68.3%) than male participants (13 of 41, 31.7%). Sex distribution within each study group ranged from 55.6% females in the mezagitamab 100 mg group to 81.8% female in the mezagitamab 600 mg group; however, the placebo combined and mezagitamab combined groups had similar proportions of female participants (69.2% and 67.9%, respectively).

[0512] The mean time since ITP diagnosis was 10.98 years (range: 0.3-35.2 years) in the total population. Time since ITP diagnosis was comparable between the placebo combined and mezagitamab combined groups overall but with a shorter mean time since diagnosis (5.45 years) in the 600 mg mezagitamab group. Overall, 34 of 41 (82.9%) of participants had chronic ITP (disease duration > 1 year).

[0513] Easy or excessive bleeding was reported for 17 of 41 participants (41.5%) of the total population. Superficial bleeding into the skin was the most common type of bleeding, experienced by 28 of 41 participants (68.3%), followed by bleeding from the gums in 18 of 41

participants (43.9%), and bleeding from the nose in 9 of 41 participants (22.0%). Heavy menstrual flow was reported for 7 of 17 (17.1%) of applicable female participants.

[0514] Bleeding history was generally balanced between mezagitamab and placebo, although bleeding from the nose was more common in the mezagitamab group (8 of 28, 28.6%) compared to the placebo group (1 of 13, 7.7%). Overall, the profile of bleeding history was generally comparable between placebo and mezagitamab groups.

[0515] Most participants had not experienced another autoimmune disorder. Systemic lupus erythematosus and ulcerative colitis were each experienced by 2 of 41 participants (4.9%), antiphospholipid syndrome was experienced by 1 of 41 participants (2.4%), and other autoimmune diseases were experienced by 4 of 41 participants (9.8%). No participants in the study had experienced rheumatoid arthritis, Crohn's disease, or autoimmune hemolytic anemia.

[0516] Nearly half of the participants (20 of 41, 48.8%) had been hospitalized for any ITP complication since diagnosis of ITP. The percentage of participants who had been hospitalized for any ITP complication since diagnosis of ITP was higher in the mezagitamab combined group (15 of 28, 53.6%) compared to the placebo combined group (5 of 13, 38.5%).

[0517] Most participants had not had any blood transfusion therapy within the last year was (median: 0; range: 0-4). A total of 9 of 41 participants (22.0%) had had a splenectomy, and no participants had undergone a hematopoietic stem cell transplant.

[0518] Among the 41 participants, 34 participants (82.9%) reported some medical history (*i.e.*, any significant condition or disease that, at the time of informed consent, had stopped in the past or was still ongoing).

[0519] All 41 participants (100%) had received treatment with a prior ITP medication. The most common category of prior ITP medication was corticosteroids (95.1% in the total population), followed by TPO-RAs (63.4%) and IVIG (39.0%). Prior use of each medication category was generally balanced between the placebo combined and the mezagitamab combined groups.

[0520] Most participants (58.5%) in the study received ongoing ITP medication, *i.e.*, medication that was ongoing at the participant's enrollment and either ended during the study or were administered throughout the study. These included corticosteroids (primarily

methylprednisolone and prednisone), given to 15 participants (36.6%), and TPO-RAs (primarily eltrombopag and romiplostim), given to 14 participants (34.1%).

[0521] The background ITP therapies administered to participants during the study were consistent with the study inclusion criteria and standard background treatment for patients with ITP. The proportions of participants with ongoing background ITP medications were generally comparable across treatment groups.

[0522] Any rescue therapy that was not a dosing-period-permitted rescue therapy resulted in the discontinuation from study dosing and advancement to the SFP. In the placebo combined group through Week 16, 2 of 13 (15.4%) participants received a rescue therapy that was not a dosing-period-permitted rescue therapy, compared to 4 of 9 participants (44.4%) in the mezagitamab 100 mg group, 0 of 8 participants (0%) in the mezagitamab 300 mg group, and 1 of 11 participants (9.1%) in the mezagitamab 600 mg group. The differences among treatment groups were not statistically significant.

[0523] By Week 32, 1 additional participant required rescue therapy, a participant in the mezagitamab 600 mg group, for a cumulative total of 2 of 11 participants (18.2%) who required rescue therapy by Week 32.

[0524] During the main study, 1 participant in total (a participant in the mezagitamab 600 mg group) required dosing period–permitted rescue therapy. No participants required dosing period–permitted rescue therapy during the OLE.

[0525] All 41 participants (100%) received at least one coadministered prophylactic medication on the day of dosing in the main study. In accordance with the protocol-specified prophylactic coadministration regimen, the most commonly administered (>10%) pre- and post-dose medications in the total population were paracetamol in 41 participants (100%), glucocorticoid steroids in 40 of 41 participants (97.6%), anti-histamines in 41 of 41 participants (100%), and famotidine in 14 of 41 participants (34.1%).

[0526] All 12 participants (100%) in the OLE received at least one coadministered prophylactic medication. Categories of medications were generally consistent with those administered in the main study.

[0527] There were no apparent imbalances between placebo and mezagitamab treatment groups in premedications.

Summary of Study Results

[0528] The primary endpoint of the Phase 2 study was safety. All doses of mezagitamab (100, 300, and 600 mg) in adult subjects with persistent or chronic ITP in this study were well tolerated. This favorable safety profile is consistent with accumulated safety data from other mezagitamab autoimmune clinical trials in adults with systemic lupus erythematosus and myasthenia gravis, where a favorable safety profile was demonstrated at doses ranging from 45 to 600 mg. The favorable safety profile of mezagitamab represents a potentially important therapeutic advantage over existing therapies, such as corticosteroids, whose considerable side effects limit their use in subjects with ITP.

[0529] Regarding efficacy, the secondary endpoint, 600 mg of mezagitamab was superior to placebo (and better than both the 100 and 300 mg doses) in terms of platelet response across all four domains of platelet response evaluated, *i.e.*, platelet response (PLR), complete PLR, clinically meaningful PLR, and hemostatic PLR. The onset of action of mezagitamab was rapid, within a week of the first dose platelets were restored to near normal levels, and the beneficial effect sustained for up to 8 weeks following cessation of therapy.

Safety

[0530] Overall, mezagitamab was well tolerated in participants with ITP in this study. There were no substantial imbalances in AEs between the treatment groups, and no dose-dependent AEs or new safety concerns were identified.

[0531] During the main study, 28 participants received at least 1 dose of mezagitamab, and 13 participants received at least 1 dose of placebo. During the OLE, 12 participants received at least 1 dose of mezagitamab. In total, 40 participants received at least 1 dose of mezagitamab during the study.

[0532] The mean (SD) number of doses taken was 8.0 (0.0) in the placebo combined group, 6.8 (2.4) in the mezagitamab 100 mg group, 7.9 (0.4) in the 300 mg group, and 7.3 (1.5) in the 600 mg group.

[0533] There were 41 subjects in the safety population analyzed, including 13 subjects who received placebo in Parts A and B of the study (the combined placebo group) and 28 subjects in the combined mezagitamab group, comprising 9 in the 100 mg group, 8 in the 300 mg group, and 11 in the 600 mg group.

[0534] The proportion of participants with any TEAE was comparable between participants receiving placebo (9 of 13, 69.2%) and mezagitamab (19 of 28, 67.9%) during the main study. There was no evidence of a dose-dependent trend in the incidence of TEAEs.

[0535] The proportion of participants with TEAEs considered related to study drug by the investigators was comparable between participants receiving placebo (5 of 13, 38.5%) and mezagitamab (9 of 28, 32.1%) during the main study. There was no dose-dependent trend in incidence of TEAEs related to study drug.

[0536] The only TEAE reported in >10% of the total population, and the most common TEAE considered related to study drug by investigators, was injection site haematoma, reported in a comparable proportion of participants receiving placebo (3 of 13, 23.1%) and mezagitamab (2 of 28, 7.1%) receiving mezagitamab. All TEAEs of injection site haematoma were considered related to study drug.

[0537] Most TEAEs were Grade 1 or Grade 2 in severity. The proportion of participants with Grade 3 or higher TEAEs was comparable between those receiving placebo (3 of 13, 23.1%) and those receiving mezagitamab (5 of 28, 17.9%) in the main study.

[0538] The proportion of participants experiencing a treatment-emergent SAE was comparable between those receiving placebo (1 of 13, 7.1%) and those receiving mezagitamab (4 of 28, 14.3%) given the longer time of observation for mezagitamab. There was no dose-dependent trend in incidence of SAEs.

[0539] Seven serious AEs were reported in five participants: hemorrhagic ovarian cyst (placebo); ITP, staphylococcal bacteremia, and conjunctivitis allergic (mezagitamab 100 mg); thrombocytopenia, pyelonephritis chronic, and acute kidney injury (mezagitamab 600 mg). Among them, two were considered related to study drug including allergic conjunctivitis (in 100 mg arm on Study Day 2) and thrombocytopenia (in 600 mg arm on Study Day 146 (approximately 90 days after end of treatment). A summary of the AEs is provided in **Table 8**,

which shows that there were similar rates of TEAEs across all four cohorts. A summary of the serious adverse events is provided in **Table 9**, which shows only a few events were reported with only one event being related to the study drug during the treatment phase.

Table 8. Adverse events (main study).

n (%) m*	TAK-079 100 mg (N=9)	TAK-079 300 mg (N=8)	TAK-079 600 mg (N=11)	TAK-079 Combined (N=28)	Placebo Combined (N=13)
Length of Observation Period, Weeks Mean (SD)				29.2 (5.8)	18.3 (2.3)
Any TEAE	7 (77.8) 21	5 (62.5) 24	7 (63.6) 19	19 (67.9) 64	9 (69.2) 46
TEAE Related to Study Drug	2 (22.2) 3	4 (50.0) 7	3 (27.3) 3	9 (32.1) 13	5 (38.5) 10
Serious TEAE	2 (22.2) 3	0	2 (18.2) 3	4 (14.3) 6	1 (7.7) 1
Serious TEAE Related to Study Drug	1 (11.1) 1	0	1 (9.1) 1	2 (7.1) 2	0
TEAE Leading to Death	0	0	0	0	0
TEAE Leading to Hospitalization	2 (22.2) 3	0	2 (18.2) 3	4 (14.3) 6	1 (7.7) 1
TEAE Leading to Discontinuation	2 (22.2) 3	0	2 (18.2) 3	4 (14.3) 5	0
≥ Grade 3 TEAE	2 (22.2) 3	0	3 (27.3) 5	5 (17.9) 8	3 (23.1) 3
≥ Grade 3 TEAE Related to Study Drug	1 (11.1) 1	0	1 (9.1) 1	2 (7.1) 2	0
AEs Reported in ≥10% of Participants, n (%)					
Injection site hematoma				2 (7.1)	3 (23.1)
COVID-19				3 (10.7)	1 (7.7)
Conjunctival hemorrhage				1 (3.6)	2 (15.4)
Asthenia				0	2 (15.4)
Contusion				0	2 (15.4)
Petechiae				0	2 (15.4)

* Number (n) and percentage of subjects with TEAEs, with overall number of events (m).
Study drug: mezagitamab or placebo.

Table 9. Serious adverse events (treatment phase).

Subject	Study Arm	Sex	Reported Term	Duration	Toxicity Grade/ Causality	Action Taken with Study Drug	Hospitalized	Outcome
6	Placebo (Part B)	F	Haemorrhagic Ovarian Follicle	6	Gr 3/ Not Related	N/A	Yes	Recovered/ Resolved
2	TAK-079 100 mg	F	ITP Worsening	*	Gr 3/ Not Related	Dose Not Changed	Yes	Recovering/ Resolved
			Bacteriemia *Staphylococcus aureus*	26	Gr 3/ Not Related	Study Drug Withdrawn	Yes	Recovered/ Resolved
4	TAK-079 100 mg	F	Allergic Conjunctivitis	8	Gr 3/ Related	Study Drug Withdrawn 2	Yes	Recovered/ Resolved w/ Sequelae
1	OLE TAK-079 100 mg	M	COVID-19 Infection	13	Gr 2/ Not Related	N/A	Yes	Recovered/ Resolved
3	TAK-079 600 mg	M	Acute Renal Failure	1	Gr 1/ Not Related	Study Drug Withdrawn (Day 17)	Yes	Recovered/ Resolved
			Chronic Aggravated Pyelonephritis	8	Gr 3/ Not Related		Yes	Recovered/ Resolved
5	TAK-079 600 mg	F	Thrombocytopenia	4	Gr 4/ Related	N/A	Yes	Recovered/ Resolved

Gr = Grade; *End date of AE was not reported.

[0540] TEAEs leading to discontinuation of study drug were reported in 4 participants (4 of 28, 14.3%) who received mezagitamab during the main study (2 with 100 mg, 0 with 300 mg, and 2 with 600 mg). Specifically, AEs leading to study drug discontinuation were conjunctivitis allergic in a participant in the mezagitamab 100 mg group, ITP and staphylococcal bacteremia in a participant in the mezagitamab 100 mg group, grade 1 acute kidney injury and grade 3 pyelonephritis chronic in a participant in the mezagitamab 600 mg group, and grade 4 worsening of thrombocytopenia in a participant in the mezagitamab 600 mg group. Only one of these, allergic conjunctivitis occurring in the 100 mg arm, was considered related to study drug. There was no dose-dependent trend in incidence of TEAEs leading to study drug discontinuation.

[0541] There were no deaths during the study.

[0542] Rates of infection-related TEAEs were generally comparable for placebo and mezagitamab groups. TEAEs were reported for 2 participants (15.4%) in the placebo group over 18.31 weeks and 6 participants (21.4%) in the mezagitamab combined group over 29.21 weeks during the main study. COVID-19 was the most commonly reported infection; all other infections were reported for 1 participant each. The cases of pyelonephritis chronic and staphylococcal bacteremia were categorized as serious and Grade 3 in severity, and therefore resulted in study drug discontinuation. Apart from injection site cellulitis, infection-related AEs were considered not related to study drug.

[0543] Injection site reactions were reported for 4 of 13 of participants (30.8%) receiving placebo and 5 of 28 of participants (17.9%) receiving mezagitamab in the main study. All injection site reactions were Grade 1 or Grade 2 in severity, were not serious, and were recovered/resolved by the end of the study.

[0544] With regard to ITP-specific TEAEs, mouth hemorrhage occurred in 1 subject in the 100 mg group, one episode each of gingival bleeding, traumatic hematoma, and epistaxis were observed in 3 subjects in the mezagitamab 300 mg group (**Table 10**). In the combined placebo group (n=13), there were multiple reports of bleeding adverse events including one each of gingival bleeding, heavy menstrual bleeding, hematochezia, hematoma, epistaxis, hematuria, and hemorrhagic ovarian cyst. In addition, there were 5 episodes of petechiae in 2 subjects and 2 episodes of conjunctival hemorrhage in 2 subjects. There were no bleeding events in the 600 mg

cohort and there were no deaths in the study. In general, ITP-associated bleeding adverse events were infrequent. Furthermore, there were fewer subjects with ≥1 ITP-associated bleeding AEs in the mezagitamab groups (17.9%) versus placebo (46.2%).

Table 10. ITP-associated bleeding adverse events.

n (%) m*	TAK-079 100 mg (N=8)	TAK-079 300 mg (N=9)	TAK-079 600 mg (N=11)	TAK-079 Combined (N=28)	Placebo Combined (N=13)
Any Bleeding TEAE	3 (33.3) 4	2 (25.0) 3	0	5 (17.9) 7	6 (46.2) 14
Gingival bleeding	0	1 (12.5) 1	0	1 (3.6) 1	1 (7.7) 1
Heavy menstrual bleeding	0	0	0	0	1 (7.7) 1
Haematochezia	0	0	0	0	1 (7.7) 1
Mouth haemorrhage	1 (11.1) 2	0	0	1 (3.6) 1	
Haematoma	0	0	0	0	1 (7.7) 1
Traumatic Haematoma	0	1 (12.5) 1	0	1 (3.6) 1	0
Epistaxis	0	1 (12.5) 1	0	1 (3.6) 1	1 (7.7) 1
Petechiae	0	0	0	0	2 (15.4) 5
Ecchymosis	1 (11.1) 1	0	0	1 (3.6) 1	0
Conjunctival Haemorrhage	1 (11.1) 1	0	0	1 (3.6) 1	2 (15.4) 2
Blood urine present	0	0	0	0	1 (7.7) 1
Haemorrhagic ovarian cyst	0	0	0	0	1 (7.7) 1
* Number (n) and percentage of subjects with TEAEs, with overall number of events (m).					

[0545] Mezagitamab is administrated subcutaneously and so it is not unusual for subjects to report injection site adverse events. However, in this study, reports of systemic administration reactions or hypersensitivity reactions following drug administration were infrequent (**Table 11**, based on hypersensitivity/anaphylaxis/anaphylactoid SMQ and terms flagged as IRR). In the few reported cases, adverse events were observed immediately following the injection and were generally mild in severity. Three events were reported in the 300 mg arm, 2 events in the 600 mg, 1 event in a placebo subject from Part B. All events resolved within a few days.

[0546] Four participants had AEs of hypersensitivity reactions that were considered related to study drug by investigators (1 with 100 mg mezagitamab, 2 with 300 mg mezagitamab, and none with 600 mg mezagitamab) in the main study. None were consistent with cytokine release syndrome. In the OLE, one participant had a grade 1 AE of pyrexia on the day of the first dose that was consistent with cytokine release syndrome. Clinical review of the available information indicated that the hypersensitivity reactions were generally mild, self-limiting, and recovered without any additional intervention.

Table 11. Systemic administration/hypersensitivity reactions.

Subject	Part	Treatment Arm	Event Term	Study Start Day	Study End Day	Duration	Grade/ Causality	Outcome
5	A	TAK-079 300 mg	Hypotension	9	10	2	Gr 1/ related	Recovered/ Resolved
3	A	TAK-079 300 mg	Chills	1	1	1	Gr 1/ related	Recovered/ Resolved
1	A	OLE: TAK-079 300 mg	Chills	120 (Day 1 OLE)	121	2	Gr 1/ not related	Recovered/ Resolved
3	B	Placebo	Pruritus	21	22	2	Gr 1/ not related	Recovered/ Resolved
		OLE: TAK-079 600 mg	Dyspnoea	155 (Day 35 OLE)	156	2	Gr 1/ not related	Recovered/ Resolved
2*	B	TAK-079 600 mg	Urticaria	184	204	21	Gr 1/ not related	Recovered/ Resolved

*Occurred during long-term follow-up phase.

[0547] No doses were held due to anemia, leukopenia, or neutropenia.

[0548] There were no adverse trends related to mezagitamab in abnormal laboratory evaluations, vital signs, or electrocardiograms.

[0549] Proportions of participants with undetectable titers of vaccine-induced antibodies were generally unchanged from baseline throughout the study in all of the mezagitamab treatment groups.

[0550] No dose dependent AEs or new safety concerns were identified.

Efficacy

[0551] Efficacy was the secondary endpoint in this study. Four secondary efficacy endpoints related to platelet response were analyzed and showed higher efficacy in the mezagitamab groups than in the placebo group in a generally dose-dependent manner, with highest efficacy observed at 600 mg mezagitamab. The difference between the combined placebo and mezagitamab groups was statistically significant and this was consistent across all 4 platelet-response-related endpoints. Specifically, the efficacy analyses were conducted by week 16, with platelet response assessed using 4 different response definitions: the proportion of responders with a platelet response rate (PLR), complete PLR, clinically meaningful PLR, and hemostatic PLR. In all four metrics of platelet response, the response rate in the 600 mg arm was consistently higher than the 100 and 300 mg doses groups and statistically significantly higher than combined placebo treatment arm.

[0552] As shown in **Figure 4A**, all doses of mezagitamab outperformed standard of care, especially with respect to "normalizing" the platelet count (complete PLR). There was a dose dependent response with the 600 mg dose doing better than both the 100 and 300 mg dose groups. Finally, in subjects with low platelet counts at baseline, an identified high-risk factor and predictor of a poor outcome in ITP, the 600 mg dose reliably achieved a durable PLR in this population. Of note, the response definitions required meeting the platelet count threshold specified on at least 2 visits within the reference period of measurement. There were fewer participants with bleeding-related TEAEs in the mezagitamab groups (18%) versus placebo (46%).

[0553] The percentage of participants with a platelet response by Week 16 was higher overall in mezagitamab compared to placebo and the difference was statistically significant. The platelet response ranged from 3 of 13 (23.08%) in the placebo group to 10 of 11 (90.91%) in the 600 mg mezagitamab group. Specifically, at Week 16, the percentage (95% CI) of participants with a platelet response was 23% (5–54) for placebo compared to 67% (30–93), 63% (25–92), and 91% (59–100) for 100, 300, and 600 mg mezagitamab, respectively.

[0554] The percentage of participants with a complete platelet response by Week 16 was higher overall in mezagitamab compared to placebo and the difference was highly statistically significant. The complete platelet response ranged from 0 of 13 (0%) in the placebo group to 9 of 11 (81.82%) in the 600 mg mezagitamab group. Specifically, a complete platelet response was observed in 0% (0–25) of placebo participants compared to 56% (21–86), 50% (16–84), and 82% (48–98) of participants receiving 100, 300, and 600 mg mezagitamab, respectively.

[0555] Clinically meaningful and hemostatic platelet responses showed similar trends. The percentage of participants with a clinically meaningful platelet response by Week 16 was higher overall in mezagitamab compared to placebo and the difference was statistically significant. Specifically, the clinically meaningful platelet response ranged from 4 of 13 (30.77%) in the placebo group to 10 of 11 (90.91%) in the 600 mg mezagitamab group.

[0556] In participants with a baseline platelet count under 15,000/µl, the percentage of participants with a hemostatic platelet response by Week 16 was higher overall in mezagitamab compared to placebo and the difference was statistically significant. The clinically meaningful

platelet response ranged from 0 of 5 (0%) in the placebo group to 4 of 4 (100%) in the 600 mg mezagitamab group.

[0557] **Figure 5** shows the least squares (LS) mean change from baseline in platelet count at all postbaseline visits up to week 16. While this graph depicts the mean response across all subjects, individual subject changes from baseline profiles that we reviewed are consistent with the LS mean changes presented above. It also illustrates the rapid onset of action of mezagitamab in all treatment arms, following the first dose, the restoration of the platelet towards near normal (>/=100,000/μL) in all mezagitamab arms but most profound in the 600 mg arm, and the preservation of this effect above the 50k platelet threshold up to week 16, about 8 weeks after stopping mezagitamab therapy. Estimated mean change from baseline in platelet count was higher for all mezagitamab dose groups than placebo at all visits, starting from two days after the first dose and continuing beyond the end of the 8-week dosing period through Week 16. This response occurred as early as the first timepoint at ~2 days post first dose. There was also a trend for a dose response at most timepoints. A sensitivity analysis that excluded any assessments obtained within 4 weeks of administration of systemic corticosteroids >20 mg prednisone or equivalent showed consistent results. This approach allowed estimation of the treatment effect under the hypothetical situation in which the dosing schedule was adhered to without use of rescue therapy.

[0558] The placebo response, which is distinct from and lower than all 3 dose arms of mezagitamab, clearly illustrates the unmet need for a new agent with good efficacy, rapid onset, restoration of platelet count and durability of response (**Figure 6**).

[0559] The mean cumulative duration of platelet response in the absence of rescue therapy by Week 16 was higher for mezagitamab compared to placebo in a dose-dependent manner, ranging from a mean of 1.1 weeks in the placebo group to 10.6 weeks in the mezagitamab 600 mg group. Specifically, the mean ± SD cumulative duration of platelet response at Week 16 was 1 ± 2.3 week for placebo compared to 6 ± 5.2, 8 ± 7.2, and 11 ± 5.5 weeks for 100, 300, and 600 mg mezagitamab, respectively.

[0560] Mezagitamab concentrations were measurable postdose in all participants up to at least Weeks 8, 12, and 16 in the 100 mg, 300 mg, and 600 mg dose groups, respectively.

[0561] A post-hoc mixed-effects model analysis of change from baseline in platelet count over time showed a higher estimated mean change in platelet count for all mezagitamab-treated groups compared to placebo at all time points in a dose-dependent manner. Platelet counts were higher for mezagitamab-treated groups at the first measured time point 2 days after the first dose and remained higher than baseline after the last dose of mezagitamab compared to placebo.

[0562] Overall, few participants required rescue therapies that were not dosing-period-permitted: 2 of 13 (15.4%) in the combined placebo group compared to 5 of 28 (17.9%) in the combined mezagitamab group.

[0563] Skin and oral bleeding, identified through physical examinations, were the most common types of bleeding observed with the ITP Bleeding Score. Among participants with any bleeding (Grade >0) at baseline, improvements to no bleeding (Grade 0) at Week 16 were observed in both placebo and mezagitamab groups.

[0564] In the Symptoms scale of the ITP-PAQ, participants in all mezagitamab groups had group-level change from baseline scores at Week 16 that exceeded the established MID, suggesting clinically meaningful improvement. In contrast, no clinically meaningful improvement was observed in the placebo group. Clinically meaningful improvements were also observed in the Fatigue/Sleep, Physical Activity, and Women's Reproductive Health (including Menstrual Symptoms and Fertility subscales), Bother-Physical Health, Psychological Health, Overall Quality of Life, and Social Activity scales in mezagitamab groups but not in the placebo group.

[0565] The Phase 2 study protocol specified endpoint assessed platelet response on at least 2 visits through week 16 which corresponds to 8 weeks after the last dose of mezagitamab. Because of mezagitamab's mechanism of action in ITP disease, which results in a rapid increase in the platelet count within a week after commencing therapy, evaluating platelet response up to week 16 is considered an appropriate measure of durable platelet response. The fact that the drug works virtually immediately means 16 weeks is sufficient time to establish and demonstrate that the drug-induced platelet response is durable.

[0566] In comparison, recent clinical trials of the anti-FcRn (efgartigimod; Vyvgart®), which has a substantially slower onset of action (up to 12 weeks), and the Syk inhibitor (fostamatinib;

Tavalisse®), were evaluated for durable platelet response by measuring the proportion of subjects with platelet count exceeding $50x10^9$/L at any 4 out of 6 visits ranging between weeks 14 to 24 across the studies of both drugs (**Table 12**). It is important to note here that for both fostamatinib and efgartigimod, subjects remained on therapy throughout the total study duration, including during the assessment period for platelet response.

Table 12. Definitions of durable platelet response across mezagitamab Phase 2, Fostamatinib Phase 3, and Efgartigimod IV Phase 3.

Drug (Phase)	Dosing Regimen	Platelet Visit Schedules	Sustained/Durable Platelet Response Definition
Mezagitamab (Phase 2) SC	8 x Q1W SC (100 mg, 300 mg, 600 mg)	Weekly 1-8; Biweekly 10-16; Monthly 20-32	A platelet count of at least $50x10^9$/L on at least 4 of the 6 visits over Weeks 10-24.
Fostamatinib (Phase 3) Oral	100 mg BID; Could be increased to 150 mg BID after 4 weeks or later, depending on platelet count	Biweekly 1-24	A platelet count of at least $50x10^9$/L on at least 4 of the 6 visits over Weeks 14-24.
Efgartigimod (Phase 3) IV	10mg/kg weekly x 4 weeks, followed by either once a week or qow depending on response up to 24 weeks	Weekly 1-24	The primary endpoint, evaluated in the chronic population, was sustained A platelet count of at least 50×10^9/L for at least 4 of the last 6 weeks over Week 18 –24.

[0567] To enable a lateral comparison of results from the Phase 2 Study and previous trials in this indication, an ad hoc analysis of the Phase 2 study data was performed using a durable platelet response definition analogous to that of the previous trials. Durable platelet response was defined in this ad hoc analysis as the proportion of subjects with a platelet count $>50x10^9$/L at any 4 out of 6 visits between weeks 10 and 24. Of note, the entry window was expanded to week 10 (instead of week 14 or 18 as in fostamatinib and efgartigimod) because the Phase 2 study design did not have enough scheduled platelet measurements between weeks 18 and 24 to evaluate 6 visits with a platelet response. Unlike the other agents, all time points in which the platelet count was evaluated in our study between weeks 10-24 were off therapy.

[0568] The results of the ad hoc analysis of the various doses of mezagitamab, placebo, and prior studies are shown in **Figure 7**. Noteworthy is that the 600 mg dose of mezagitamab outperformed the 100 and 300 mg doses, placebo, and as well both trials of efgartigimod and fostamatinib (even though the assessments for platelet response in the mezagitamab arm(s) were taken between 2-16 weeks after the cessation of therapy). These results are very encouraging and highlight the potential of mezagitamab to transform the management of subjects with ITP.

Pharmacokinetic (PK)/Pharmacodynamic (PD) Analysis

[0569] The clinical pharmacology attributes of mezagitamab in subjects with ITP were also evaluated in this Phase 2 study. Pharmacokinetic (PK) analysis included sparse measurement of serum concentrations of mezagitamab, and Pharmacodynamics (PD) analysis included measurement of key biomarkers, such as immunoglobulins (IgA, IgG, and IgM). Overall, both PK and PD were adequately assessed and characterized. The results of key clinical pharmacology findings are summarized below:

PK

[0570] Following multiple dose subcutaneous administration of mezagitamab (100 mg, 300 mg, and 600 mg dose levels), serum concentrations of mezagitamab were detectable in all subjects for the active dosing period (**Figure 8**). Moreover, following multiple dose subcutaneous administration of mezagitamab, mezagitamab concentrations were measurable post-dose in all participants up to at least Week 8, Week 12, and Week 16 in the 100, 300, and 600 mg dose groups, respectively. The serum C_{trough} values were below measurable in all participants by Week 24 in the 100 mg dose group and Week 32 in the 300 mg dose groups. In the 600 mg dose group, the serum C_{trough} values were below measurable in 89% of participants by Week 32.

[0571] The increase in serum C_{trough} of mezagitamab was greater than dose proportional in the 100 to 300 mg dose range and dose proportional in the 300 to 600 mg dose range. The observed non-linear PK profile indicates saturable elimination for mezagitamab due to target-mediated drug disposition. An increase in dose from 100 mg to 300 mg increased the geometric mean mezagitamab C_{trough} at week 8 from 5953.6 to 104071.39 ng/mL (17-fold); the corresponding increase for 300 mg to 600 mg was from 104071.4 to 195036.1 ng/mL (1.9-fold).

[0572] During mezagitamab treatment, slight accumulation of mezagitamab PK trough exposures occurred following each weekly dosing. After 8 consequent weekly SC administrations at 600 mg, the geometric mean C_{trough} was was 195036.1 vs. 37536.5 ng/mL (approximately 5-fold higher) than following the first weekly dosing.

[0573] PK profiles of mezagitamab were nonlinear due to target-mediated drug elimination following CD38 binding, consistent with that observed in previously conducted studies (multiple myeloma, myasthenia gravis, and SLE). Greater than dose-proportional increase in mezagitamab

PK exposures was observed in the tested dose range, with nonlinear elimination saturated at 600 mg. More variability in 100 mg dose group versus 300 mg and 600 mg cohorts. Based on the current data available, the PK of mezagitamab is not expected to be substantially different across age, race, sex, and ethnicity.

PD

[0574] In general, the mean number of plasmablasts, CD38+ B cells, NK cells, and CD38+ NK cells reduced from baseline for all mezagitamab dose groups during the dosing period, with no trend of reduction observed with placebo (**Figures 16A**, **16B**, **16C**, **16D**, and **16E**). There were no trends in change in total numbers of granulocytes, lymphocytes, monocytes, B cells, and T cells over time.

[0575] Concentrations of the total IgA, IgG, and IgM from subjects with ITP were evaluated as surrogate biomarkers to demonstrate potential reduction in antiplatelet antibodies pertinent to the pathophysiology of ITP. Thus, reductions in these immunoglobulins can directly be associated with improved ITP disease activity in ITP subjects.

[0576] Binding of mezagitamab to immune cells led to 60-99% receptor occupancy during the 8-week treatment period and was associated with a decrease of 80-90% in CD38+ immune cells, including plasmablasts and natural killer (NK) cells.

[0577] The mean number of plasmablasts was reduced from baseline for all mezagitamab dose groups during dosing, while no trend of reduction from baseline was observed for the placebo group. A maximum percent decrease from baseline of 87.5% was observed for 600 mg mezagitamab 1week after the first dose.

[0578] The mean number of NK cells was reduced from baseline for all mezagitamab dose groups during dosing, while no trend of reduction from baseline was observed for the placebo group. A maximum percent decrease from baseline of 71.9% was observed for 300 mg mezagitamab 3 weeks after the first dose.

[0579] Serum circulating immunoglobulin levels were reduced by mezagitamab, with maximum reductions observed at the 600 mg dose. Maximum mean percent reduction from baseline was 62.5% for IgA, 38.4% for IgG, and 45.5% for IgM. Following the end of the dosing period,

immune cell counts, and immunoglobulin levels had generally recovered towards baseline levels by 32 weeks.

[0580] **Figure 9** provides key mechanistic evidence of mezagitamab dose-dependent decrease in serum immunoglobulins for the investigational use mezagitamab in ITP subject population. At the highest dose of 600 mg, the maximum mean decrease from baseline of IgA, IgG, and IgM was ~60%, ~40%, and ~45%, respectively. These reductions in immunoglobulins were consistent with other studies, closely associated with cumulative mezagitamab PK exposures and in expectation with overall drug pharmacology. In comparison, subjects treated with placebo exhibited substantially lower (only ~9% maximum reduction from baseline) serum immunoglobulin reduction. Similar to the platelet clinical response, pharmacodynamic response with mezagitamab was generally maintained for ≥ 8 weeks after the completion of treatment.

Immunogenicity Results

[0581] Treatment-induced ADA was reported in 66.7%, 37.5%, and 45.5% of participants in the 100, 300, and 600 mg dose groups, respectively. Most ADA-positive participants were transiently ADA-positive; a total of 2 mezagitamab-treated participants (7.1%) reported persistently positive ADA (1 participant each in the mezagitamab 100 mg and mezagitamab 600 mg group).

[0582] The presence of ADA had no apparent effect on the mezagitamab PK profile in this study.

Inference-Driven Selective Key Clinical Pharmacology Points from Phase 2 Study Results

[0583] Mezagitamab demonstrated target-mediated drug disposition with non-linear kinetics. Mezagitamab PK exposures were more than dose-proportional (up to 300 mg) and exhibited moderate inter-individual variability (at the highest dose of 600 mg).

[0584] From a PK perspective, no additional dose adjustment is recommended for Phase 3 to account for key intrinsic factors (*i.e.*, age, sex, race).

[0585] Following multiple mezagitamab weekly administrations, rapid, substantial, durable, and dose and exposure-dependent reductions in serum immunoglobulins (IgG, IgM, and IgA) were

observed. In particular, reduction in IgG from baseline in part is pertinent to ITP disease pathogenesis and was moderately associated with sustained PLT response.

[0586] Mezagitamab improved platelet count and elicited durable platelet response in cumulative mezagitamab PK exposures (*i.e.*, C_{ave} and AUC) dependent manner (**Figure 10**).

[0587] The selected Phase 3 dose of TAK-079 600 mg SC is supported by (a) favorable safety, tolerability, and efficacy data from the Phase 2 study; and (b) robust clinical pharmacology data from the Phase 2 study. Exposure-response analysis provided supplemental evidence on the overall clinical effectiveness of mezagitamab in ITP subjects.

Application of Proof of Concept (POC) Criteria

[0588] POC criteria were: at least 50% of subjects in the dosing group having a positive platelet response (≥50,000/μL on at least two occasions) by week 16, with a rate at least double that of placebo, to safeguard against the confounding effect of an extraordinarily high placebo rate (with a placebo rate of ~10%). This Go criterion was evaluated at two Go/No-Go (GnG) time points in this trial. GnG-1 occurred after all subjects in Part A advanced through week 16 (8 weeks of dosing and 8 weeks of follow-up), while GnG-2 occurred after all subjects in Part B advance through week 16.

[0589] As demonstrated in **Figure 4A**, the platelet response for the combined placebo group was 23.1% and the platelet response rate is more than double the placebo rate at all doses of mezagitamab. Therefore, the GnG-2 criteria were satisfied to enable advancement to Phase 3. In fact, the platelet response rate is almost 3x the placebo response rate for the 100 and 300 mg dose groups and almost 4x greater than the placebo response rate for the 600 mg cohort.

Results Summary

[0590] ITP is a rare autoimmune bleeding disorder characterized by a reduction in platelet numbers and consequent hemorrhagic risk. Mezagitamab, a fully human anti-CD38 IgG1 monoclonal antibody, depletes CD38-expressing cells targeting cell- and antibody-mediated platelet destruction underlying ITP etiology. The aims of this study were to evaluate the safety/tolerability and efficacy of mezagitamab in individuals with chronic/persistent ITP.

[0591] This Phase 2 study had two parts: 25 participants were randomized (1:1:1) to mezagitamab 100 mg or 300 mg, or placebo in Part A; 16 participants were randomized (2:1) to mezagitamab 600 mg or placebo in Part B. Participants received once weekly subcutaneous mezagitamab or placebo for 8 doses, followed by ≥8 weeks of safety follow-up. At week 16, participants were unblinded and placebo participants could receive mezagitamab in an open-label extension. Those in mezagitamab groups continued for additional 16-week follow-up. Stable background ITP treatment was continued during the study. Primary endpoint was percentage of participants with treatment-emergent adverse events (TEAEs). Secondary endpoints included platelet response (PR), complete platelet response (CPR), clinically meaningful platelet response (CMPR), and hemostatic platelet response (HPR). Exploratory endpoints included durability of platelet response (number of weeks with platelet count ≥50,000/μL) and change from baseline in ITP patient assessment questionnaire (ITP-PAQ). Clinically meaningful change was defined as mean change exceeding the minimal important difference threshold of 8 or 10 points.

[0592] Overall, data from this Phase 2 study demonstrated that mezagitamab was tolerable at all doses tested with few injection-related events, showing a favorable safety profile with no dose dependent increase in safety events. Mezagitamab also demonstrated a rapid and sustained improvement in platelet response compared with placebo, with sustained effect after the end of the 8-week treatment period through week 16. All secondary endpoint changes were greatest for the mezagitamab 600 mg dose. Furthermore, clinically meaningful improvements in health-related quality of life were observed with mezagitamab.

[0593] Safety analyses, the primary endpoint, found a similar incidence of AEs among participants treated with mezagitamab and those treated with placebo. The most common infection was COVID 19, which was consistent with the general population given the timing of the study and highlights the importance of a treatment shift from general immunosuppression to more targeted therapy.5 Overall, infection occurred on 21.4% of the mezagitamab combined group compared with 15.4% of the placebo combined group. However, there were no opportunistic infections, and apart from COVID 19, other infections each occurred in one participant only.

[0594] Subjects (N=41) had a mean disease duration of 11 (range: 0.3–35.2) years and received a mean of 4.0 (range: 1–13) prior ITP treatments. In the prespecified interim analysis, TEAE

incidence was similar between mezagitamab-treated (19/28, 68%) and placebo-treated (9/13, 69%) subjects. In mezagitamab-treated versus placebo groups, 14.3% versus 0%, 17.9% versus 23.1%, and 14.3% versus 7.7% of subjects had TEAEs leading to discontinuation, Grade ≥3 TEAEs, and serious adverse events, respectively. All three mezagitamab groups showed rapid/sustained improvement in platelet counts that persisted after the last dose through Week 16. By Week 16, PR, CPR, CMPR, and HPR were higher in all mezagitamab dose groups versus placebo; highest responses were observed with mezagitamab 600 mg. Estimated mean change from baseline in platelet count was higher for all mezagitamab groups than placebo at all visits, starting from two days after the first dose through week 16. For participants in 100 mg mezagitamab group, clinically meaningful changes in patient-reported outcomes including symptoms, physical activity, women's reproductive health, and menstrual symptoms were observed. For fatigue/sleep, participants in 300 mg mezagitamab group showed clinically meaningful changes. There were fewer subjects with ≥1 ITP-associated bleeding AEs in the mezagitamab groups (17.9%) versus placebo (46.2%).

[0595] All three mezagitamab groups showed higher durability of platelet response at week 16 compared with placebo. The duration of platelet response through week 16 was increased in all mezagitamab groups in a dose-dependent manner (**Figure 13**). The mean ±SE (95% CI) increase in duration of platelet response with mezagitamab over placebo was 4.9±1.6 (1.5–8.3) weeks for 100 mg, 6.9±2.1 (2.5–11.4) for 300 mg, and 9.6±1.7 (6.1–13.0) for 600 mg. Clinically meaningful increases in ITP-PAQ scores were observed in the mezagitamab groups. Mean change from baseline ITP-PAQ scale scores showed clinically meaningful improvement in mezagitamab groups but not in placebo (**Figures 14** and **15**).

[0596] Mezagitamab provided a greater increase in platelets over baseline through week 16 at all doses compared with placebo with a trend for greater improvement in platelet counts with the higher dose at most time points. The efficacy analysis showed that 91% (10/11) of mezagitamab treated subjects achieved the secondary efficacy endpoint of platelet response (defined as ≥50,000/μL and ≥20,000/μL above baseline on at least two visits without a dosing period rescue treatment in the previous 4 weeks and without other previous rescue therapy) versus 23% (3/13) of subjects randomized to standard of care (placebo). The characteristics of the efficacy response, including the rapidity of observed platelet count increase and early signal of durable

platelet response post-treatment, were consistent with data from Part A. All four metrics of platelet response are greatest for the 600 mg dose of mezagitamab with statistically significant improvement in all response over placebo by week 16. Greater durability (>16 weeks) of platelet response was observed at 600 mg dose. The impact of immunogenicity on efficacy, safety, and PK was not apparent; the rate of immunogenicity was relatively lower at the highest dose of 600 mg. PK exposures were generally consistent with other studies and fell within the expected range. For key pharmacodynamic biomarkers (*i.e.*, serum immunoglobulin reductions as a surrogate to antiplatelet antibodies), mezagitamab demonstrated rapid dose-dependent reductions in IgG, explaining in part the observed improvement in overall ITP disease activity. At the highest dose of 600 mg, maximum mean reductions of ~60% were observed for IgA and ~40% for both IgM and IgG, in agreement with prior results in other studies. Immunoglobulins showed rapid reductions after treatment, with gradual return to baseline starting from week 20. In terms of the demographics and baseline characteristics of the subjects, the cohorts were generally well balanced, though the placebo cohort had a younger age range and the mezagitamab 600 mg cohort had a shorter duration of ITP.

[0597] The Part B results were a strong validation of the Part A data and suggest that the multi-modal mechanism of action of mezagitamab is well-suited to address the pathology of ITP.

[0598] In contrast, the most recently approved ITP treatment, fostamatinib, was licensed with only an 18% durable platelet response rate, while a recent Phase 3 study of IV efgartigimod, a leading anti-FcRn IV achieved a 21.8% durable platelet response rate, despite measuring the primary endpoint while subjects were still on therapy. In the latter study, unlike mezagitamab, platelet counts over 50,000 were only achieved after about 12 weeks on therapy. Moreover, a second Phase 3 study of efgartigimod in ITP, which employed a subcutaneous formulation, recently failed.

Conclusions

[0599] Mezagitamab weekly treatment (for a total of 8 weeks duration) across 3 dose levels (100 mg, 300 mg, and 600 mg) was generally well tolerated and safe in participants with persistent/chronic primary ITP. No new safety concerns were identified, and no dose dependencies in TEAEs of clinical interest were observed.

[0600] Efficacy was evaluated as a secondary endpoint by measuring 4 different endpoints related to platelet response, which investigated the magnitude and durability of effect of mezagitamab. All doses of mezagitamab had higher rates of response than the placebo group, which began rapidly after the first dose and were sustained after the last dose. Results for the other pre-specified efficacy endpoints were directionally similar.

[0601] Mezagitamab induced a sustained reduction in CD38+ immune cell populations and immunoglobulin isotypes and these recovered to baseline or were trending toward baseline after drug withdrawal.

[0602] This study established that mezagitamab had favorable safety and provided a clinical proof of concept for mezagitamab in participants with persistent/chronic primary ITP.

[0603] In conclusion, mezagitamab had a favorable safety/tolerability profile and demonstrated improvement in platelet response by Week 16 versus placebo in subjects with chronic/persistent ITP.

EXAMPLE 2: A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE EFFICACY AND SAFETY OF MEZAGITAMAB SUBCUTANEOUS INJECTION IN SUBJECTS WITH PERSISTENT OR CHRONIC PRIMARY IMMUNE THROMBOCYTOPENIA

[0604] Phase 3 comprises a single Phase 3 double blind randomized controlled trial (RCT) to evaluate efficacy and safety of mezagitamab in subjects with persistent or chronic primary ITP who have not responded to one or more prior treatments for ITP including 1st and 2nd line. This mirrors the Phase 2 population upon which the rationale to proceed to Phase 3 was based. As demonstrated by the Phase 2 study, mezagitamab overcomes safety limitations of other agents for ITP, with very high efficacy, offering subjects treatment-free periods of remission.

[0605] The Phase 3 study is a multi-center study which includes 171 subjects randomized across 95 clinical trial sites in 16 countries (US 30%, EU 30%, JP 10%, CN 15%, and RoW 15%), ensuring the diversity of subjects and minimizing the potential for a single center effect on the outcomes.

[0606] The study achieves comparability of the investigational and standard of care arms via randomization (with the relatively robust sample size), as well as by stratifying subjects at baseline by their: splenectomy status, baseline platelet count (< or >/= 15,000), and concomitant ITP medications, all of which are established predictors of outcome.

[0607] The primary endpoint is objective and the same as used in the Phase 2 study, *i.e.*, durable platelet response. The timing of the endpoint varies slightly, reflecting the current regulatory precedence and the mechanism of action of mezagitamab. Platelet response is evaluated at 4 out of 6 study visits within a defined period up to week 18. The primary endpoint statistical methodology has been designed to show a significant degree of statistical significance ($p<0.05$), and clinical relevance is deemed to have been achieved if the difference between the mezagitamab and placebo response rate at the primary endpoint is at least 35%.

Endpoints

Primary Objective and Associated Endpoint and Estimands

[0608] The primary objective of the study is to assess the efficacy of mezagitamab 600 mg QW for 8 weeks compared with placebo in achieving durable platelet response following therapy (week 8) up to week 18 in adults with persistent or chronic ITP.

[0609] The primary endpoint of durable platelet response is assessed by evaluating the proportion of subjects in each arm that achieve a platelet count of 50,000/μL or higher for at least 4 out of 6 biweekly visits between weeks 8 to 18 without receipt of rescue therapy. **Table 13** shows the primary objective and associated endpoint and estimands.

Table 13. Primary objective and associated endpoint and estimand.

Primary Objective	**Primary Endpoint**
To assess the efficacy of mezagitamab 600 mg QW for 8 weeks compared with placebo in achieving durable platelet response in adults with persistent or chronic ITP	Durable platelet response is defined as a sustained platelet response at least 4 of 6 biweekly visits between Weeks 14-24 without receipt of rescue therapy, where platelet response is defined as a platelet count of ≥50,000/μL on the scheduled visit.
Objective	**Estimand**
To assess the efficacy of mezagitamab 600 mg QW for 8 weeks compared with placebo in achieving durable platelet response in adults with persistent or chronic ITP	The primary estimand is the comparison of the effect of mezagitamab with placebo on platelet counts. Population: FAS. Variable or endpoint: Durable platelet response is defined as a sustained platelet response at least 4 of 6 biweekly visits between Weeks 14-24 without receipt of rescue therapy, where platelet response is defined as a platelet count of ≥50,000/μL on the scheduled visit Intercurrent events (ICEs): • Use of rescue therapy. • Premature treatment discontinuation due to 1) met dose discontinuation criteria; 2) use of prohibited concomitant therapy; or 3) AEs or lack of efficacy. • Premature discontinuation from the study. • Missing platelet count measurement. Strategy for addressing ICEs: The subject will be considered as not having durable platelet response in the follow cases (composite strategy): • Subject received rescue therapy or prematurely discontinued from the treatment due the reasons as specified in above ICEs at any time prior to Week 14. • Subject received rescue therapy or prematurely discontinued from the study at any time during Weeks 14-24 and had fewer than 4 visits with platelet response. • Subject missed platelet count measurement during Weeks 14-24 and had fewer than 4 visits with platelet response. Population-level summary: Difference in proportions of subjects with durable platelet response in the mezagitamab group compared to the placebo group.
ICE: intercurrent event; ITP: immune thrombocytopenia; FAS: full analysis set; QW: once weekly.	

[0610] This timing of the primary endpoint is such that the evaluations of efficacy are conducted between 0-8 weeks after the cessation of mezagitamab therapy, which differentiates it from existing and pipeline therapies. The sustained effect off treatment would represent a major

treatment advance in ITP, with changing the treatment paradigm with a year-long sustained effect with successful re-treatment.

[0611] The timing of the primary endpoint in the Phase 3 study has been modified from that of the Phase 2 study (a) consistent with the observed onset of and durable effect of mezagitamab therapy and (b) to more closely align with recent regulatory precedents. The rationale for assessing the durable PLR of mezagitamab off therapy is due to its unique mechanism of action, where its depletion of plasma cells and plasmablasts leads to long term decreases in levels of IgG (up to week 32). This persistently lowered IgG level is thought to correlate with the PLR observed post-therapy. In addition to the ad hoc analysis of the Phase 2 Part B results showing good efficacy up to 24 weeks following a single course of mezagitamab (though lower than at week 16), long term follow-up of Part A data up to week 32, *i.e.*, 24 weeks after cessation of mezagitamab, showed that 3 of out of the 4 responders at week 16 in the 300 mg arm of mezagitamab maintained a platelet count >/=50k up to week 32. By measuring the endpoint between weeks 8-18, it is possible to demonstrate both excellent efficacy in terms of durable PLR as well as differentiation due to post therapy effect (without the potential lowering of the effect magnitude by week 24).

Secondary Endpoints and Associated Endpoints and Estimands

[0612] In alignment with available treatment guidelines, the secondary efficacy objective is to assess the efficacy of mezagitamab 600 mg QW for 8 weeks compared with placebo in achieving platelet response (including complete, clinically meaningful, or hemostatic platelet response). This is done by measuring the following endpoints (**Table 14**):

> the length of platelet response, which is measured by the sum of all the weeks which a platelet response is attained, where platelet response is defined as a platelet count of ≥50,000/μL on the scheduled visit without rescue therapy;
>
> extended platelet response, defined as platelet count ≥50,000/μL on at least 4 of 6 biweekly visits from weeks 14 through 24 without having received rescue therapy; platelet response is defined as a platelet count ≥50,000/μL on at least 2 visits without rescue therapy;
>
> complete platelet response, defined as a platelet count ≥100,000/μL on at least 2 visits without rescue therapy. A clinically meaningful platelet response is defined as a platelet count ≥20,000/μL on at least 2 visits without rescue therapy; and.

hemostatic platelet response, defined for subjects with a baseline platelet count of <15,000/μL who achieve a platelet count of ≥30,000/μL and ≥20,000/μL above baseline on at least 2 visits without rescue therapy.

Furthermore, the use of rescue therapy in subjects receiving mezagitamab 600 mg SC QW for 8 weeks compared with those receiving placebo is assessed as a secondary endpoint.

[0613] Lastly, the secondary endpoints include assessments of the safety and tolerability of mezagitamab such as the occurrence of TEAEs, SAEs, drug discontinuations, *etc*.

Table 14. Secondary objectives and associated endpoints and estimands.

Secondary Objective	Secondary Endpoint
To assess the efficacy of mezagitamab 600 mg QW for 8 weeks compared with placebo in achieving platelet response (including complete, clinically meaningful, or hemostatic platelet response) in adults with persistent or chronic ITP	• Duration of platelet response is measured by the sum of all the weeks on which a platelet response is attained, where platelet response is defined as a platelet count of ≥50,000/μL on the scheduled visit in the absence of any rescue therapy. • Platelet response is defined as a platelet count ≥50,000/μL on at least 2 visits without a bridging therapy in the previous 4 weeks and without any previous rescue therapy. • Complete platelet response is defined as a platelet count ≥100,000/μL on at least 2 visits without bridging therapy in the previous 4 weeks and without any previous rescue therapy. • A clinically meaningful platelet response is defined as a platelet count ≥20,000/μL above baseline on at least 2 visits without bridging therapy in the previous 4 weeks and without any previous rescue therapy. • Hemostatic platelet response is defined for subjects with a baseline platelet count of <15,000/μL who achieve a platelet count of ≥30,000/μL and ≥20,000/μL above baseline on at least 2 visits without a bridging therapy in the previous 4 weeks and without any previous rescue therapy.
To assess the use of rescue therapy in subjects receiving mezagitamab 600 mg QW for 8 weeks compared with those receiving placebo	• The occurrence of receiving rescue therapy. • The time to first rescue therapy.

Secondary Objective	Estimands
To assess the efficacy of mezagitamab 600 mg QW for 8 weeks compared with placebo in achieving platelet response (including complete, clinically meaningful, or hemostatic platelet response) in adults with persistent or chronic ITP	**First secondary estimand**: Definition: Comparison of the effect of mezagitamab with placebo on platelet counts. Population: FAS. Variable or endpoint: Duration of platelet response is measured by the sum of all the weeks which a platelet response is attained, where platelet response is defined as a platelet count of ≥50,000/μL on the scheduled visit at least 4 weeks after the last dose of bridging therapy and in the absence of any previous rescue therapy. Intercurrent events (ICEs): • Use of rescue therapy. • Use of bridging therapy. • Premature treatment discontinuation due to 1) meeting dose discontinuation criteria; 2) use of prohibited concomitant therapy; or 3) AE or lack of efficacy. • Missing platelet count measurements. Strategy for addressing ICEs: The subject will be not considered as having platelet response at the scheduled visit in the following cases (composite strategy): • Subject who received any rescue therapy or prematurely discontinued study treatment due to the reasons as specified in above ICEs at any time prior the visit. • Subject who received bridging therapy <4 weeks prior the visit. • Subject who missed platelet count measurement at the visit. Population-level summary: Difference of the cumulative number of weeks with platelet response during Weeks 1-24 between subjects in the mezagitamab group compared with placebo group.
To assess the efficacy of mezagitamab 600 mg QW for 8 weeks compared with placebo in achieving platelet response (including complete, clinically meaningful, or hemostatic platelet response) in adults with persistent or chronic ITP	**Second secondary estimand** Definition: Comparison of the effect of mezagitamab with placebo on platelet counts. Population: FAS. Variable or endpoint: Platelet response is defined as a platelet count ≥50,000/μL on at least 2 visits without a bridging therapy in the previous 4 weeks and without any other previous rescue therapy.

	Intercurrent events (ICEs): • Use of rescue therapy. • Use of bridging therapy. • Premature treatment discontinuation due to 1) met dose discontinuation criteria; 2) use of prohibited concomitant therapy; or 3) AE or lack of efficacy. • Missing platelet count measurements. Strategy for addressing ICEs: The subject will be not considered as having platelet response in the following cases (composite strategy): • Subject received prohibited rescue therapy or prematurely discontinued from the treatment due to the reasons specified in above ICEs before having 2 visits with platelet count ≥50,000/μL. • Subject did not have 2 visits with platelet count ≥50,000/μL after exclusion of the 4 weeks period following the use of bridging therapy. • Subject who missed platelet count measurement and did not have 2 visits with platelet count ≥50,000/μL. Population-level summary: Difference in proportions of subjects with platelet response between subjects in the mezagitamab compared to placebo group.
To assess the efficacy of mezagitamab 600 mg QW for 8 weeks compared with placebo in achieving platelet response (including complete, clinically meaningful, or hemostatic platelet response) in adults with persistent or chronic ITP	**Third secondary estimand** Definition: Comparison of the effect of mezagitamab with placebo on platelet counts. Population: FAS. Variable or endpoint: Complete platelet response is defined as a platelet count ≥100,000/μL on at least 2 visits without a bridging therapy in the previous 4 weeks and without any other previous rescue therapy. Intercurrent events (ICEs): • Use of rescue therapy. • Use of bridging therapy. • Premature treatment discontinuation due to 1) met dose discontinuation criteria; 2) use of prohibited concomitant therapy; or 3) AE or lack of efficacy. • Missing platelet count measurements. Strategy for addressing ICEs: The subject will be not considered as having complete platelet response in the following cases (composite strategy): • Subject received rescue therapy or prematurely discontinued from treatment due to the reasons specified in above ICE before having platelet

	count ≥100,000/μL on at least 2 visits. • Subject did not have 2 visits with platelet count ≥100,000/μL on at least 2 visits after exclusion of the 4-week period following the use of bridging therapy. • Subject who missed platelet count measurement and did not have 2 visits with platelet count ≥100,000/μL. Population-level summary: Difference in proportions of subjects with complete platelet response between mezagitamab compared to placebo group.
To assess the efficacy of mezagitamab 600 mg QW for 8 weeks compared with placebo in achieving platelet response (including complete, clinically meaningful, or hemostatic platelet response) in adults with persistent or chronic ITP	**Fourth secondary estimand** Definition: Comparison of the effect of mezagitamab with placebo on platelet counts. Population: FAS. Variable or endpoint: A clinically meaningful platelet response is defined as a platelet count ≥20,000/μL above baseline on at least 2 visits without bridging therapy in the previous 4 weeks and without any other previous rescue therapy. Intercurrent events (ICEs): • Use of rescue therapy. • Use of bridging therapy. • Premature treatment discontinuation due to 1) met dose discontinuation criteria; 2) use of prohibited concomitant therapy; or 3) AE or lack of efficacy. • Missing platelet count measurements. Strategy for addressing ICEs: The subject will be not considered as having a clinically meaningful platelet response in the following cases (composite strategy): • Subject received rescue therapy or prematurely discontinued from treatment due to the reasons specified in above ICE before having platelet count ≥20,000/μL on at least 2 visits. • Subject did not have platelet count ≥20,000/μL on at least 2 visits after exclusion of the 4-week period following the use of bridging therapy. • Subject who missed platelet count measurement and did not have 2 visits with platelet count ≥20,000/μL. Population-level summary: Difference in proportions of subjects with clinically meaningful platelet response between mezagitamab compared to placebo

	group.
To assess the efficacy of mezagitamab 600 mg QW for 8 weeks compared with placebo in achieving platelet response (including complete, clinically meaningful, or hemostatic platelet response) in adults with persistent or chronic ITP	**Fifth secondary estimand** Definition: Comparison of the effect of mezagitamab with placebo on platelet counts. Population: FAS. Variable or endpoint: Hemostatic platelet response is defined for subjects with a baseline platelet count of <15,000/μL who achieve a platelet count of ≥30,000/μL and ≥20,000/μL above baseline on at least 2 visits without bridging therapy in the previous 4 weeks and without any other previous rescue therapy. Intercurrent events (ICEs): • Use of rescue therapy. • Use of bridging therapy. • Premature treatment discontinuation due to 1) met dose discontinuation criteria; 2) use of prohibited concomitant therapy; or 3) AE or lack of efficacy. • Missing platelet count measurements. Strategy for addressing ICEs: The subject will be not considered as having a clinically meaningful platelet response in the following cases (composite strategy): • The subject with baseline platelet count of <15,000/μL who received rescue therapy or prematurely discontinued from treatment due to the reasons specified in above ICE before having platelet count of ≥30,000/μL and ≥20,000/μL above baseline on at least 2 visits. • The subject who did not have a baseline platelet count of <15,000/μL and achieve a platelet count of ≥30,000/μL and ≥20,000/μL above baseline on at least 2 visits after exclusion of the 4-week period following the use of bridging therapy. • Subject who missed platelet count measurement and did not have 2 visits with platelet count of <15,000/μL and achieve a platelet count of ≥30,000/μL and ≥20,000/μL above baseline. Population-level summary: Difference in proportions of subjects with a hemostatic platelet response between mezagitamab compared to placebo group
To assess the use of rescue therapy in subjects receiving mezagitamab 600 mg QW for 8 weeks compared with	**Sixth secondary estimand** Definition: The effect of mezagitamab on the use of rescue therapy compared to placebo

those receiving placebo	Population: FAS. Variable or endpoint: The occurrence of rescue therapy. Intercurrent events (ICEs): The subject who prematurely discontinued from study. Strategy for addressing ICEs: Data analyzed as collected (treatment policy strategy). The subject who discontinued the study without receiving rescue therapy will not be considered as received rescue therapy. Population-level summary: Difference in proportions of subjects who received rescue therapy between mezagitamab compared to placebo group.
To assess the use of rescue therapy in subjects receiving mezagitamab 600 mg QW for 8 weeks compared with those receiving placebo	**Seventh secondary estimand** Definition: The effect of mezagitamab on the use of rescue therapy compared to placebo. Population: FAS. Variable or endpoint: The time to first use of rescue therapy. Intercurrent events (ICEs): The subject who prematurely discontinued. Strategy for addressing ICEs: The subject who discontinued the study without receiving rescue therapy will be censored at the end of follow-up (composite strategy). Data analyzed as collected (treatment policy strategy). Population-level summary: Hazard ratio between mezagitamab and placebo group.
ICE: intercurrent event; ITP: immune thrombocytopenia; FAS: full analysis set; QW: once weekly.	

Safety Objectives and Associated Endpoints

[0614] The safety objectives and associated safety endpoints are shown in **Table 15**.

Table 15. Safety objectives and associated endpoints.

Safety Objective	Safety Endpoint
To evaluate the safety and tolerability of mezagitamab 600 mg QW in adults with persistent or chronic ITP compared with those receiving placebo.	• Incidence of treatment-emergent adverse events (TEAEs) by MedDRA PT occurring in ≥5% of the safety population during the intervention period. • Incidence of treatment-related adverse events (TRAEs) by MedDRA PT occurring in ≥5% of the safety population during the intervention period • Incidence of Grade ≥3 TEAEs by MedDRA PT during the intervention period. • Observed values and change from baseline in clinical laboratory test results and vital signs.
MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; TEAE: treatment-emergent adverse event; TRAE: treatment-related adverse event.	

Exploratory Objectives and Associated Endpoints

[0615] The exploratory objectives and endpoints are shown in **Table 16**.

Table 16. Exploratory objectives and associated endpoints.

Exploratory Objective	Exploratory Endpoint
To determine the PK profile of mezagitamab	The PK concentration and PK parameters for mezagitamab (*e.g.*, C_{trough}) during and after intervention
To determine the PD profile of mezagitamab	Presence of and changes in PD biomarkers during and after intervention
To evaluate the immunogenicity of mezagitamab and its effect on efficacy, safety, and PK	Incidence of and change in ADA and other relevant biomarkers
To assess the incidence of bleeding events in adults with persistent or chronic ITP	Frequency of bleeding based on the grades in the WHO Bleeding Scale
To explore the effects of ITP on health-related quality of life	Change from baseline in the Symptoms, Physical Health-Activity, Women's Reproductive Health (including Menstrual Symptoms and Fertility subscales), Physical Health-Bother, Psychological Health, Overall Quality of Life, and Social Activity scales scores of the ITP-PAQ Change from baseline in EQ-5D-5L scores, including the mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and overall health status in the EQ-VAS

ADA: antidrug antibodies; EQ-5D-5L: EuroQol Five Dimensions questionnaire 5-level version; EQ-VAS: EuroQol visual analogue scale ITP: immune thrombocytopenia; ITP-PAQ: ITP Subject Assessment Questionnaire; PD: pharmacodynamic; PK: pharmacokinetic; WHO: World Health Organization.

Study Design

[0616] The Phase 3 study has been designed in alignment with current international treatment guidelines, available regulatory guidance (EMA 2014), and is almost identical in design to the Phase 2 study. A schematic diagram of the study is provided in **Figure 11**.

[0617] The objective of this trial is to demonstrate the efficacy and safety of mezagitamab both as add-on to standard of care treatment or stand-alone treatment in subjects who do not have an adequate standard of care option (due to intolerance or lack of response).

[0618] The trial has 3 periods: (1) up to a 4-week screening period; (2) 8-week dosing period; and (3) 16-week follow-up period. The maximum overall duration for an individual subject is 28 weeks, including screening, intervention, and safety follow-up periods. After the pivotal study, subjects could enroll in the 36-week continuation study.

[0619] The intervention model for this trial is parallel groups with 2 arms: experimental treatment arm and placebo comparator arm.

[0620] The screening period is a maximum of 4 weeks. Eligible subjects then receive treatment intervention for a maximum of 8 weeks and will participate in a safety follow up period for a maximum of 16 weeks. The maximum overall duration for an individual subject is 28 weeks, including screening, intervention, and safety follow-up periods. When a subject has completed all required screening procedures and all eligibility criteria are met, the subject is randomly assigned to 1 of the 2 trial arms on the basis of the randomization schedule. To minimize the potential for bias, treatment assignment remains double blinded throughout the duration of the trial.

[0621] A schedule of activity is provided in **Table 17**.

Table 17. Schedule of activities.

Trial Procedures [a]	Intervention Period 1: 8 Weeks								Dosing-Free Period (biweekly visits)				Intervention Period 2: 8 Weeks								
									↓ Week 8 Assessments												EOT
Week	**0** [b]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**14**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Day [c]	1	8	15	22	29	36	43	50	57	71	85	99	113	120	127	134	141	148	155	162	169
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Visit Window	±2 days																				
Administrative Procedures																					
Randomization	X																				
Concomitant medications (including standard-of-care ITP therapy) and procedures review	*Throughout the trial from the signing of the ICF*																				
Clinical Procedures																					
AE assessment (including SAEs) c	*Throughout the trial from the signing of the ICF*																				
Body weight (kg)	X								X				X								X
Vital signs [d, e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [e]	X								X				X								X
ECG (minimum 12 leads) [e]									X				X								X
Trial Dosing and Predosing Assessments and Administration																					
Predosing criteria assessment [e, f]	X	X	X	X	X	X	X	X					X	X	X	X	X	X	X	X	
Prophylactic coadministration premedication [g]	X	X	X	X	X	X	X	X					X	X	X	X	X	X	X	X	
Mezagitamab/placebo dosing [h]	X	X	X	X	X	X	X	X					X	X	X	X	X	X	X	X	
Pregnancy Tests																					
Pregnancy test (local lab) [e, i, j]	X				X				X		X		X				X				X
Laboratory Assessments																					
Clinical chemistry panel (serum) (central lab) [e, i, k, l]	X				X				X		X		X				X				X
Central laboratory hematology (blood) [e, l]	X		X		X		X		X	X	X	X	X		X	X	X	X	X	X	X
Local laboratory hematology (blood) [e, k, l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quantitative IgA/IgM/IgG (serum) (central lab) [e, i, m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity (serum) (central lab) [e, i]	X				X						X	X	X	X	X		X		X		X

Vaccine-induced protective antibodies (serum) [e, i]	X								X				X							X
TBNK assay (blood) (central lab) [e]	X								X				X							X
Direct/indirect Coombs test (local lab) [e]	X				X				X				X							
Mezagitamab PK (serum) (central lab) [e, i]	X	X			X						X	X	X	X	X		X		X		X
Patient-reported Outcomes																				
ITP-PAQ [e, n]	X				X				X		X		X				X				X
EQ-5D-5L [e, n]	X								X				X								X
PGI-S: ITP Symptoms [e, n]	X				X				X		X		X				X				X
PGI-S: ITP Fatigue [e, n]	X				X				X		X		X				X				X
PGI-C: ITP Symptoms [e, n]					X				X		X		X				X				X
PGI-C: ITP Fatigue [e, n]					X				X		X		X				X				X
Clinician-reported Outcomes																				
ITP-BAT [e, o]	X		X		X		X		X	X	X	X	X		X		X		X		X

AE: adverse event; ANC: absolute neutrophil count; CRS: cytokine release syndrome; ECG: electrocardiogram; EOT: end of trial; EQ-5D-5L: EuroQoL 5-Dimension 5-Level; FSH: follicle-stimulating hormone; hCG: human chorionic gonadotropin; HBV: hepatitis B virus; HCV: hepatitis C virus; ICF: informed consent form; IEC: independent ethics committee; Ig: immunoglobulin; IMP: investigational medicinal product; IRB: institutional review board; ITP: immune thrombocytopenia; ITP-BAT: ITP-specific Bleeding Assessment Tool; ITP-PAQ: ITP Patient Assessment Questionnaire; IVIg: intravenous immunoglobulin; PGI-C: Patient Global Impression of Change; PGI-S: Patient Global Impression of Severity; PK: pharmacokinetic(s); SAE: serious adverse event; TBNK: T cells, B cells, and natural killer cells; WBC: white blood cells.

If the date of a participant visit does not conform to the schedule, the timing of subsequent visits should be planned so that the visit schedule relative to randomization is maintained.

Early termination visit consists of the end-of-trial (Week 24) assessments.

[a] Participants undergo additional unscheduled laboratory assessments and observations as necessary based on the investigator's best medical judgment, and as warranted by exhibited clinical signs or symptoms at each trial visit. Clinical laboratory values that are not resulted, not explained, or are otherwise of concern to the investigator or a subinvestigator may be repeated until resulted, explained or resolved.

[b] On Days 2 and 3 (first intervention period) and Days 114 and 115 (second intervention period), postdose prophylactic medications are self-administered (*i.e.*, participants do not need to report to the clinic) if clinically indicated, and in consultation with and approval from the medical monitor or medical director. Site staff verify self-administration of postdose prophylactic medications at Week 1 (Day 8) and Week 17 (Day 120).

[c] If the date of a participant visit does not conform to the schedule, the timing of subsequent visits is planned so that the visit schedule relative to randomization is maintained.

[d] On dosing days, vital signs (body temperature, blood pressure, respiratory rate, and pulse) are assessed before the dose; vital signs are also assessed 2 hours (+15 minutes) after the second injection at the Week 0 and Week 1 doses and the Week 16 and Week 17 doses). In addition, vital signs are assessed whenever clinically warranted. When vital signs are scheduled at the same time as blood sample collection, the blood sample collection takes priority, and vital signs are obtained within 0.5 hours after the blood sample collection.

[e] On dosing days, this procedure is performed before dosing.

[f] For the Day 1 dose, predosing criteria laboratory assessments (ANC and absolute lymphocyte count) are evaluated using results obtained within 7 days before Day 1; for all other doses, laboratory results are obtained on the day before or the day of dosing.

[g] The prophylactic coadministration regimen is followed as discussed below. Prophylactic premedications given on day of dosing are administered approximately 1 to 3 hours before IMP injection.

[h] Time and anatomical site are recorded for each injection. After the first and second IMP dosing events of each intervention period, *i.e.*, the Week 0 and 1 doses and the Week 16 and 17 doses, participants are closely monitored in the clinic until at least 2 hours after the second injection. Before discharge, the possible signs and symptoms of anaphylactic reactions and CRS are reviewed with participants.

[i] The assessment is performed on the day before the day of the indicated visit.

[j] Women of childbearing potential must have a negative serum pregnancy (hCG) test result at screening and a negative pregnancy test result (serum or urine) before receiving the first dose of trial intervention (either before dosing on Day 1 or within 1 day before the Day 1 dose). During the trial, women of childbearing potential must have a negative pregnancy test result (serum or urine) at the specified visits to continue in the trial. If a participant reports delayed menses, a serum pregnancy test is completed and a negative result obtained before subsequent dosing of trial intervention. Additional pregnancy tests are conducted during the trial as requested by the IRB and/or as required by local regulations.

[k] Details of clinical chemistry and hematology tests are provided below.

[l] Platelet count is evaluated at both local and central laboratories. The local laboratory results are used to determine predosing assessment and decisions regarding participant care. Central laboratory platelet results are used for analysis of endpoints related to platelet counts. To have been eligible for randomization, participants must have a mean platelet count of <30,000/μL (with individual values ≤35,000/μL) from at least 2 measurements at least 5 days apart between signing of the ICF and Day 1, including at least 1 of those measurements within 14 days before Day 1. If samples for screening hematology laboratory testing were drawn ≥7 days before Day 1, new hematology samples for ANC and absolute lymphocyte count must be drawn for the Day 1 predosing criteria assessment within 7 days before first dose.

[m] Quantitative immunoglobulins are tested at a central laboratory and sites are blinded to the results. Sites are notified if the dose hold criterion is met.

[n] Participants complete all the patient-reported outcome assessments on an electronic device on site, preferably before site personnel perform any clinical and laboratory assessments. On visits in which multiple outcome assessments are completed, the order of assessments is as follows: ITP-PAQ, EQ-5D-5L, PGI-S: ITP Symptoms, PGI-S: ITP Fatigue, PGI-C: ITP Symptoms, and finally PGI-C: ITP Fatigue.

[o] ITP-BAT grading is based on physical examination at the time of the visit by the ITP-BAT certified rater .

[0622] The 2-arm parallel-group design was selected for this trial to facilitate the simultaneous collection of data from subjects receiving mezagitamab or receiving placebo without introducing unplanned cross-over between treatments. Subjects may also be receiving stable SOC ITP therapy throughout the trial. The random assignment to 1 of the 2 groups with stratification factors ensures that baseline characteristics that may affect study outcomes are similar between groups.

[0623] The duration of trial intervention and dosing schedule for this study were based on data from the Phase 2 study of mezagitamab in subjects with ITP. The reductions in IgG from the Phase 2 study were consistent with the results of a previously conducted trial in subjects with relapsed/refractory multiple myeloma, in which an approximate 50% reduction in IgG was observed after 8 QW doses of mezagitamab 300 or 600 mg.

[0624] The 24-week duration of the entire study (intervention plus safety follow-up period) was determined based on the established time period for evaluation of durable platelet response in subjects with ITP.

[0625] The primary endpoint was selected based on available treatment guidelines and regulatory guidance (*e.g.*, 2014 EMA Guideline on the Clinical Development of Medicinal Products Intended for the Treatment of Chronic Primary Immune Thrombocytopenia); additionally, the platelet count level of ≥50,000/μL was selected based on the accepted treatment goal for subjects with ITP (*i.e.*, providing sufficient platelet count to prevent or stop bleeding) (Provan *et al.* 2019; Rodeghiero *et al.* 2009). The secondary endpoints were selected to further inform the clinical efficacy profile of treatment with mezagitamab for increasing platelet counts and preventing the need for rescue therapy. The safety endpoints were selected to provide comprehensive analysis of adverse events and other data relevant to evaluate the benefit-risk profile of treatment with mezagitamab for subjects with persistent or chronic ITP. The exploratory endpoints were selected to further characterize the PK, PD, and immunogenicity of mezagitamab and the effects of treatment on health-related quality of life.

[0626] At the time of protocol development, first-line treatments for ITP include corticosteroids and, in the case of severe or life-threatening bleeding, intravenous immunoglobulin (IVIg) and anti-D immunoglobulin (anti-D) (Matzdorff *et al.* 2018; Provan *et al.* 2019; Rodeghiero 2023).

While corticosteroids are effective in the short term, long term use is not recommended, as up to 70% of subjects experience relapse in the long term and require additional treatment for prevention of bleeding (Lozano *et al.* 2021; Mingot-Castellano *et al.* 2022; Neunert *et al.* 2019; Provan *et al.* 2019).

[0627] Second-line nonsurgical treatment options include thrombopoietin receptor agonists (TPO-RAs) such as romiplostim, eltrombopag, and avatrombopag; the mAb rituximab (which is widely used but not approved for treatment of ITP); and the kinase inhibitor fostamatinib (Neunert *et al.* 2019; Provan *et al.* 2019). These treatments have shown varying levels of efficacy in the short and long term but are associated with adverse safety outcomes such as hepatotoxicity (Promacta (eltrombopag) Tablets for Oral Use; for Oral Suspension 2015), increased reticulin and collagen fibrosis (Nplate (romiplostim) for Injection for Subcutaneous Use 2022), and progressive multifocal leukoencephalopathy (Mingot-Castellano *et al.* 2022; Rituxan (rituximab) Injection for Intravenous Use 2021). Other immunomodulatory and corticosteroid-sparing agents (*e.g.*, azathioprine, cyclosporine A, cyclophosphamide, danazol, dapsone, hydroxychloroquine, and mycophenolate mofetil) have been used to treat ITP in subjects for whom other therapies have failed; however, these are limited by variable efficacy, toxicities, and transient responses (Mingot-Castellano *et al.* 2022; Provan et al. 2019; Rodeghiero 2023). Presently, only fostamatinib has been approved for subjects who have had insufficient response to a prior treatment (with reported response rate of 43% and stable response rate of 18%) (Bussel *et al.* 2018).

[0628] Given the varying long-term efficacy of currently available second-line treatments and modest efficacy of fostamatinib, potential serious risks associated with available treatments, and lack of accepted treatment paradigm after loss of response or intolerance to prior therapy, placebo was selected as the comparator for this trial. The use of placebo as comparator will facilitate optimal evaluation of mezagitamab efficacy as a potential therapy for subjects with ITP who have insufficient response or intolerance to other therapies and reduces the risk of bias by providing a comparison group that receives treatment that is identical to the mezagitamab in both appearance and administration.

[0629] Although one-third of subjects in this trial receive placebo, these subjects are not without access to treatment if required. All study subjects—including those receiving placebo—are

allowed to continue use of stable SOC ITP therapy throughout the study. In addition, bridging or rescue therapy is not withheld from any subject who requires use during the study; subjects who require rescue therapy during the intervention period are prematurely discontinued from trial intervention and their condition is managed according to local standard of care.

[0630] At any point in the study, subjects may receive rescue therapy to control and manage ITP. However, if rescue therapy is given within 4 weeks of an efficacy endpoint assessment, the subject is considered a non-responder at that timepoint.

Continuation Study

[0631] All subjects who complete the 16-week follow-up period of the pivotal trial are eligible to enter a continuation study, a separate open-label continuation trial in which all subjects receive mezagitamab 600 mg QW for 8 weeks if platelet counts reach the treatment/retreatment threshold as defined in the continuation trial protocol and if all dosing eligibility criteria are met. Subjects are eligible to enter the continuation trial regardless of whether they received mezagitamab or placebo in this trial. If the subject meets the criteria for posttrial access, it is provided per local regulations. A 36-week continuation study immediately following the pivotal trial is to assess long term safety and provide mezagitamab to qualifying placebo subjects from the pivotal study. In addition, the continuation study allows redosing for qualifying previously treated mezagitamab study subjects. Treatment with mezagitamab for subjects randomized to placebo or re-treatment with mezagitamab in subjects who received mezagitamab during the pivotal trial occurs if eligibility criteria for treatment/re-treatment are met and the first dose is received between Trial Week 0 and Week 13. This allows for at least 16 weeks of follow up after an 8-week intervention period for subject who were enrolled in the pivotal study, with a total trial duration no longer than 36 weeks. Trial visits occur every 2 weeks until eligibility for treatment/retreatment is met (up to Week 13), at which time subjects enter the intervention period for 8 weekly visits, followed by a follow-up period with biweekly visits until Week 36. For subjects who do not meet eligibility criteria to receive intervention, trial visits occur every 2 weeks until Week 14, then every four weeks from Week 14 to Week 36.

Subject Population and Eligibility Criteria

[0632] The study seeks to demonstrate mezagitamab for the treatment of persistent or chronic primary immune thrombocytopenia (ITP) in adult subjects who have had insufficient response to other ITP treatments (including insufficient response due to treatment failure or contraindication to other agents).

[0633] The sample size for the Phase 3 study is 171 subjects. The population is adult subjects with a diagnosis of primary ITP for at least 3 months, who were previously treated for ITP, and have had an inadequate or unsustained response (including non-response because of intolerance to prior ITP therapy). Persistent ITP is defined as ITP lasting 3-12 months while ITP lasting beyond 12 months is chronic. The study population is randomized 2:1 to either mezagitamab or placebo.

[0634] To reflect the broad range of therapies that subjects may use in clinical practice, subjects are allowed to enter having received varying numbers of prior ITP therapies. Subjects are allowed to enter the study regardless of whether they are currently on standard background therapy. The permitted background treatments may include up to 3 concurrent medications, with 1 medication from each of the following 3 drug categories: thrombopoietin receptor agonist (TPO-RA) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag); and/or oral corticosteroid: given daily or every other day (not to exceed prednisone 20 mg daily or equivalent dose); and/or one of the following other medications: methotrexate, azathioprine, leflunomide, cyclosporine, and/or fostamatinib.

[0635] The selection criteria for this trial were designed to facilitate enrollment of subjects who reflect the general population of subjects with persistent or chronic primary ITP who have had insufficient response or intolerance (including contraindication) to other ITP treatments. To reflect the broad range of therapies that subjects may use in clinical practice, subjects are allowed to enter having received varying numbers of prior ITP therapies or types of therapy, and will be allowed to enter regardless of whether they are currently on a standard-of-care ITP treatment.

[0636] This study is targeted at primary ITP, thought to be due to autoantibodies. Consistent with the 2014 EMA Guideline on the Clinical Development of Medicinal Products Intended for the Treatment of Chronic Primary Immune Thrombocytopenia, which states that treatment for

secondary ITP (*i.e.*, caused by underlying disease or induced by medication) is targeted toward the underlying medical condition, subjects with evidence of causes of secondary ITP will be excluded. Also excluded are subjects with the following conditions: (i) active infection with hepatitis B virus, hepatitis C virus or HIV; (ii) active TB infection; and (iii) anti-CD20 treatment, including rituximab (anti-CD20 treatment within 6 months of screening is exclusionary and for anti-CD20 treatment between 24 and 48 weeks prior to screening, a CD19+count less than lower limit of normal is exclusionary).

Inclusion Criteria

[0637] To be eligible to participate in this trial, an individual must meet all of the following criteria: (i) the subject is aged ≥18 years at the time of signing the informed consent form (ICF); (ii) the subject (and the subject's legally acceptable representative, if applicable per local regulations or determination) has provided informed consent (that is, in writing, documented via a signed and dated ICF and/or eConsent) and any required privacy authorization before the initiation of any study procedures; (iii) the subject has been diagnosed with primary ITP that has persisted for at least 3 months—diagnosis is in accordance with The American Society of Hematology 2019 Guidelines for ITP (Neunert *et al.* Blood Adv (2019) 3 (23): 3829–3866) or the Updated International Consensus Report on The Investigation and Management of Primary ITP (Provan *et al.* Blood Adv (2019) 3 (22): 3780–3817), as locally applicable; (iv) the subject's diagnosis of ITP is supported by a prior response to ITP therapy, defined as having achieved a platelet count ≥50,000/μL; (v) the subject has documented insufficient response, intolerance, and/or contraindication to current or other treatment for ITP; (vi) the subject has a mean platelet count of <30,000/μL (with individual values ≤35,000/μL) from at least 2 measurements at least 5 days apart during the screening period, including 1 measurement within 7 days prior to the first dose of mezagitamab or placebo (Day 1); (vii) if the subject is receiving allowed standard-of-care (SOC) treatment for ITP at screening and continued use is intended, treatment may continue during the study if the dose and frequency have been stable for at least 4 weeks before receiving the first dose of mezagitamab or placebo (*i.e.*, Day 1) and are expected to remain stable throughout the study; (viii) women of childbearing potential are not pregnant during screening (confirmed by negative serum hCG) and on Day 1 prior to first dose of trial intervention (confirmed by negative urine pregnancy test); and (ix) if enrolled at a site in Japan, the subject

has documented negative H pylori test result at or after diagnosis of ITP or has documented history of successful H pylori eradication therapy at least 12 weeks prior to Day 1.

Exclusion Criteria

[0638] An individual who meets any of the following criteria will be excluded from participation in this trial: (i) in the investigator's opinion, the subject (and the subject's legally acceptable representative, if applicable per local regulations or determination) is unwilling and/or unable to understand and fully comply with study procedures and requirements (including digital tools and applications); (ii) the subject has evidence of secondary ITP (drug-induced or associated with another medical condition such as autoimmune thyroid disease, systemic lupus erythematosus, *H. pylori* infection, lymphoma, chronic lymphocytic leukemia, viral infection, *etc.*); (iii) the subject has had any thrombotic or embolic event within 12 months before screening; (iv) the subject has had a splenectomy within 3 months before screening; (v) the subject has active infection with hepatitis B and/or hepatitis C virus; (vi) the subject has active tuberculosis infection; (vii) the subject has had an opportunistic infection ≤12 weeks before Day 1 or is currently undergoing treatment for a chronic opportunistic infection (*e.g.*, TB, pneumocystis pneumonia, cytomegalovirus, herpes simplex virus, herpes zoster, or atypical mycobacteria). A mild, localized herpes simplex infection within 12 weeks before first dose of mezagitamab or placebo is allowed, as long as the lesion has resolved without systemic therapy before Day 1; (viii) the subject has been diagnosed with myelodysplastic syndrome; (ix) the subject has (1) been diagnosed with or has suspected chronic obstructive pulmonary disease (COPD) or asthma and (2) has a prebronchodilatory forced expiratory volume in 1 second (FEV_1) <50% of predicted normal at screening; (x) in the opinion of the investigator, the subject is currently experiencing any medical condition that might interfere with participation in the study (*e.g.*, significant ocular, cardiovascular, pulmonary, hematologic, gastrointestinal, endocrinologic, hepatic, renal, neurologic, malignancy, or infectious disease), that poses an added risk for the subject, or could confound the assessment of trial results; (xi) in the opinion of the investigator, the subject has a serious medical or psychiatric illness that could potentially interfere with the completion of treatment according to this protocol; (xii) if the subject has received anti-CD20 treatment, the subject is excluded if either of the following apply: the last dose was received within 6 months prior to screening, or the last dose was received between 6 and 12 months prior

to screening and the subject has a CD19+ count below the lower limit of normal (subjects who have received the last dose of anti-CD20 treatment >12 months prior to screening are not excluded from study participation based on this criterion and are not required to undergo CD19+ testing); (xiii) the subject has received any monoclonal/polyclonal antibody for immunomodulation within 6 months prior to Day 1; (xiv) participation in any other investigational drug trial (including vaccine trial) or has been exposed to another investigational agent within 4 weeks or 5 half-lives, whichever is longer, before Day 1; (xv) the subject has used anticoagulants (*e.g.*, vitamin K agonists, direct oral anticoagulants) within 3 weeks before screening; (xvi) the subject has received a live vaccine within 4 weeks before screening or has any live vaccine planned during the study; (xvii) the subject has used immunosuppressants (*e.g.*, cyclophosphamide, vincristine) other than permitted oral immunosuppressants within 6 months before Day 1; (xviii) the subject has used IVIg, subcutaneous immunoglobulin, recombinant human thrombopoietin (rhTPO), or anti-D immunoglobulin treatment within 4 weeks before screening or it is expected that any treatment for thrombocytopenia other than the subject's SOC ITP therapy (*e.g.*, rescue therapy) may be used between screening and Day 1; (xix) the subject has a history of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in the mezagitamab/placebo formulation; (xx) the subject has any of the following clinically significant laboratory abnormalities at screening: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN), total bilirubin >1.5 × ULN (subjects with a diagnosis of Gilbert syndrome are not excluded based on this criterion), absolute neutrophil count <1500/mm^3, hemoglobin <8 g/dL, IgG <500 mg/dL, lymphocyte count <500/mm^3, creatinine clearance, CrCl, <30 mL/min (*i.e.*, CrCl ≥30 mL/min is allowed); (xxi) is capable of breastfeeding but does not agree to forego breastfeeding from first dose of mezagitamab or placebo through a certain number of days after the last dose of mezagitamab/placebo; (xxii) the subject is a woman of childbearing potential (WOCBP) but does not agree to use at least 1 form of highly effective contraception and 1 barrier method of contraception (preferably male condom) until at least a certain amount of days after the last dose of mezagitamab/placebo; (xxiii) the subject is a fertile man but does not agree to use a condom, preferably combined with at least 1 form of acceptable contraception for any WOCBP partner(s), until at least a certain number of days after the last dose of mezagitamab/placebo; and (xxiv) the

subject has used a recombinant human thrombopoietin (rhTPO) within 3 weeks prior to screening.

[0639] Screening failures: an individual who has provided informed consent to participate in the trial may be categorized as a screen failure for any of the following reasons: did not meet entrance criteria; adverse event; lost to follow-up; pregnancy; withdrawal by subject; met eligibility criteria but not needed; trial terminated by sponsor; other.

[0640] Subjects are not considered screen failures if they were randomized but not treated.

[0641] An individual who has been designated a screen failure may be rescreened. Subjects whose screening laboratory results (*e.g.*, platelets, hematology, CrCL) do not meet eligibility criteria may have these evaluations repeated within the 28-day screening period at the investigator's discretion when other eligibility criteria have been fulfilled. Subjects who do not meet all eligibility criteria may be rescreened in the future (in a new screening period and after completing new informed consent) if their clinical course results in a change that enables them to be eligible for the trial.

Trial Intervention and Concomitant Therapy

[0642] This trial has the following investigational medicinal products: mezagitamab and placebo, as shown in **Tables 18** and **19**.

Table 18. Trial Interventions.

Product Name	**Mezagitamab**	**Placebo**
Designation	Investigational product	placebo
Identification in the Protocol	Mezagitamab	Placebo
European/European Economic Area (EEA) Marketing Authorization (MA)	No	No
Used Within MA	Not Applicable	Not Applicable
Active Substance	Mezagitamab	None
Dose Formulation	Solution for injection	Solution for injection (to match mezagitamab solution for injection)
Dose Strength(s)	150 mg/mL	N/A
Route of Administration [a]	SC injection	SC injection
Dosage Level(s)	600 mg	Placebo volume to match mezagitamab 600 mg
Dose Regimen	QW	QW
Duration	8 weeks	8 weeks
Arm (subjects receiving the medicinal product)	Random assignment for all subjects	Random assignment for all subjects
Sourcing	Provided centrally by the Sponsor or designee	Provided centrally by the Sponsor or designee
Packaging	1 vial per carton	1 vial per carton
Labeling	Supplies of mezagitamab are labeled according to the current ICH guidelines on GCP and Good Manufacturing Practices and include any locally required statements.	Supplies of mezagitamab are labeled according to the current ICH guidelines on GCP and Good Manufacturing Practices and include any locally required statements.
Storage Conditions	2-8 °C	2-8 °C

IB: Investigator's Brochure; N/A: not applicable; SC: subcutaneous; QW: once weekly.
[a] The device components (*i.e.*, needle and syringe) that are recommended in the pharmacy manual will be similar in size and manufacturer to those are used in the pre-filled syringe in development for the continuation trial and for commercial supply.

Table 19. Trial Interventions.

Group of Medicines	**Corticosteroids**
Product name	Methylprednisolone, hydrocortisone, cortisone, prednisolone, prednisone, or dexamethasone PO
Designation	Pre-dose medications
Active substance	Methylprednisolone sodium succinate; hydrocortisone sodium succinate; dexamethasone sodium phosphate

Dose formulation	Tablets: Methylprednisolone, Prednisone, Prednisilone, Hydrocortisone, Cortisone, Dexamethasone
Dose strength(s)	Methylprednisolone: 40 mg; Prednisone: 50 mg; Prednisilone: 50 mg; Hydrocortisone: 200 mg; Cortisone: 250 mg; Dexamethasone: 7.5 mg
Route of administration	Methylprednisolone: PO Prednisilone: PO Prednisone: PO Hydrocortisone: PO Dexamethasone: PO
Dosage level(s)	Methylprednisolone: 40 mg; Prednisone: 50 mg; Prednisilone: 50 mg; Hydrocortisone: 200 mg; Cortisone: 250 mg; Dexamethasone: 7.5 mg
Dose regimen	Per local SmPC guidance.
Duration	Per local SmPC guidance.
Arm (subjects receiving the medicinal product)	All subjects will receive this class of medication for prophylactic coadministration with first dose of study drug for prevention of possible hypersensitivity reactions.
Group of Medicines	**Antihistamines**
Product name	Cetirizine, fexofenadine, desloratadine, diphenhydramine, dexchlorpheniramine
Designation	Pre-dose and post-dose medications
Active substance	Cetirizine hydrochloride, fexofenadine hydrochloride, desloratadine hydrochloride, loratadine hydrochloride, diphenhydramine hydrochloride;
Dose formulation	Tablet or Solution, IV
Dose strength(s)	Cetirizine: 10 mg; Fexofenadine: 60 mg; Desloratidine: 5 mg; Diphenhydramine: 25-50 mg; Dexchlorpheniramine: 2-4 mg
Route of administration	PO or IV
Dosage level(s)	Cetirizine: 10 mg PO and IV; Fexofenadine: 180 mg PO; Desloratidine: 5 mg PO; Diphenhydramine: 150-300 mg PO and IV; Dexchlorpheniramine: 8-16 mg PO
Dose regimen	Per local SmPC guidance.
Duration	Per local SmPC guidance.
Arm (subjects receiving the medicinal product)	All subjects receive this class of medication for prophylactic coadministration with first dose of study drug for prevention of possible hypersensitivity reactions. This group of medicines is also administered as post-dose (subsequent to first dose) prophylaxis for hypersensitivity reactions.
Group of Medicines	**Antipyretics**
Product name	Acetaminophen, ibuprofen, naproxen
Designation	Pre-dose and post-dose medications

Active substance	Acetaminophen, ibuprofen, naproxen sodium
Dose formulation	Tablet
Dose strength(s)	Acetaminophen: 500 mg; ibuprofen: 200 mg, naproxen: 220 mg
Route of administration	PO
Dosage level(s)	Acetaminophen: 500-1000 mg PO; ibuprofen: 200-400 mg PO; naproxen sodium: 220-440 mg PO
Dose regimen	Per local SmPC guidance.
Duration	Per local SmPC guidance.
Arm (subjects receiving the medicinal product)	All subjects will receive this class of medication for prophylactic coadministration with first dose of study drug for prevention of possible hypersensitivity reactions. This group of medicines will also be administered as post-dose (subsequent to first dose) prophylaxis for hypersensitivity reactions.
Group of Medicines	**Histamine H_2 Antagonists**
Product name	Famotidine, cimetidine, ranitidine and nizitidine
Designation	Pre-dose medications
Active substance	Famotidine, ranitidine and nizitidine
Dose formulation	Tablet or PO, Solution; Solution for injection
Dose strength(s)	Famotidine: 20 mg; Ranitidine: 150 mg and 300 mg; Nizitidine: 150 and 300 mg
Route of administration	PO and IV
Dosage level(s)	Famotidine: 20 mg PO and IV; ranitidine: 300 mg PO and IV; nizatidine: 300 mg PO and IV
Dose regimen	Per local SmPC guidance.
Duration	Per local SmPC guidance.
Arm (subjects receiving the medicinal product)	All subjects will receive this class of medication for prophylactic coadministration with first dose of study drug for prevention of possible hypersensitivity reactions.

Dosing and Administration

[0643] Subjects receive mezagitamab or placebo during the intervention period. Subjects will undergo a dosing criteria assessment prior to each dosing event; if subjects meet the dosing criteria, they will be given appropriate prophylactic medications.

Predosing Criteria Assessment

[0644] Investigators evaluate subjects before each dose on the basis of the criteria outlined in **Table 20**. If clinical parameters do not meet criteria for continued dosing, the subject's dosing must be temporarily withheld until parameters meet dosing levels or the subject must be discontinued from study dosing. Dosing may only be held for 1 week; if dosing criteria are not met at the next study visit after a missed/held dose, the subject must discontinue trial intervention.

[0645] Subjects whose clinical parameters meet the dose discontinuation criteria are permanently discontinued from dosing and advance to the SFP, completing all associated assessments.

[0646] Because immunoglobulin levels may be reduced with mezagitamab treatment, quantitative immunoglobulin levels (IgG, IgA, and IgM) are evaluated during the dosing period at a central laboratory. If any of these levels are >50% below the lower limit of normal (LLN), the investigator manages as clinically appropriate on the basis of the subject's signs and symptoms. If IgG levels are below the LLN and the subject is experiencing a severe infection, IVIg may be administered per physician discretion according to standard practice. If IVIg is given as bridging therapy, the subject may continue with dosing; otherwise, the subject is discontinued from the intervention period and enters the SFP.

Table 20. Dosing Criteria and Decisions.

	Dosing Decision		
Safety Parameter	**Continue**	**Hold [a]**	**Discontinue [b]**
Laboratory Investigations [c]			
Neutrophils	ANC ≥500/mm^3	ANC <500/mm^3	
Total lymphocyte count	≥500/mm^3	<500/mm^3.	
Clinical Events			
Anaphylaxis [d,e]			Any event
Hypersensitivity reaction other than anaphylaxis (*i.e.*, allergic reaction, CRS) [d,e]	Grade ≤2		Grade ≥3
Systemic infection [c]		Grade 2 Hold dosing until the infection is resolved.	Grade ≥3 **or** infections requiring hospitalization.

ANC: absolute neutrophil count; CRS: cytokine release syndrome; IRR: NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] Subjects whose clinical parameters meet dose hold criteria will not receive the scheduled dose of mezagitamab, and instead will return for reassessment and evaluation at the next planned visit.

[b] Subjects whose clinical parameters meet dose discontinuation criteria are to be permanently discontinued from dosing. SOC ITP therapy will be managed according to the principal investigator's discretion.

[c] Laboratory and infection grading are based on NCI CTCAE, Version 4.03.

[d] Allergic reactions (including anaphylaxis and other hypersensitivity reactions) are classified according to the World Allergy Organization Anaphylaxis Guidance (Cardona *et al.* 2020).

[e] Clinical event management guidance provided.

[f] CRS is classified in accordance with Lee et al. (Lee et al. 2014). A full cytokine panel is to be obtained for any suspected Grade ≥2 events of CRS.

Administration

[0647] All protocol-specified criteria for administration of mezagitamab or placebo must be met and documented before administration.

[0648] After completion of all screening assessments and procedures and confirmation of eligibility, subjects report to the trial site on Day 1 to begin dosing of mezagitamab or placebo in accordance with random treatment assignment. Before administration, subjects receive premedication and will complete safety assessments. Both the subject and physician are blinded to treatment assignment.

[0649] Subjects receive mezagitamab or placebo QW for 8 weeks via SC injections. Two injections are required to administer the full dose of mezagitamab or placebo at each dosing visit. On Day 1, the second of the 2 injections is administered approximately 30 minutes after the first

injection to mitigate the potential risk of hypersensitivity reaction. If the subject does not have a clinically significant hypersensitivity reaction on the first dosing day, the mezagitamab or placebo may be given without a waiting period between the 2 injections at subsequent dosing visits.

[0650] Before each dose of mezagitamab or placebo, investigators evaluate subjects according to the predosing criteria outlined in above. For the Day 1 dose, laboratory assessments may be evaluated using results obtained at screening; for all other doses, laboratory results are obtained on the day before or the day of dosing. If clinical parameters do not meet criteria for continued dosing, mezagitamab or placebo must be temporarily withheld until parameters meet dosing levels or the subject must be discontinued, as outlined above, or in accordance with the principal investigator's judgment. Dosing of mezagitamab or placebo may not otherwise be reduced or escalated for any given subject. If study dosing is held for 2 consecutive doses because of safety concerns or because the subject meets the dose hold criteria outlined above, the subject is discontinued from mezagitamab or placebo dosing and advances to the SFP.

Postdose Monitoring

[0651] After the first and second dosing events (Days 1 and 8), subjects are closely monitored in the clinic for at least 2 hours after receiving the second injection. Postdose monitoring procedures should include vital signs assessments, as well as any additional assessment and observations deemed necessary based on the principal investigator's medical judgment and as warranted by exhibited clinical signs or symptoms at each trial clinic visit. Before discharge from the clinic, the possible signs and symptoms of anaphylactic reactions and cytokine release syndrome (CRS) are reviewed with subjects. Postdose medication may be given.

Trial Intervention Dose Modification

[0652] If a subject has clinical parameters that do not meet criteria for continued dosing, dosing must be temporarily withheld until parameters meet dosing levels or the subject must be discontinued. Dosing may not otherwise be reduced or escalated for any given subject.

Prophylactic Coadministration Regimen

[0653] Pre- and postdose prophylactic medications are administered for prevention of hypersensitivity reactions; an equivalent medication can be substituted for an individual medication as needed. If any of these medications raise safety concerns for an individual subject, a potential alternative regimen may be used upon approval from the sponsor.

[0654] To prevent possible hypersensitivity reaction after the first dosing event, prophylactic medications are administered on Days 1 through 3 according to the regimen show in **Table 21**. On each dosing day other than Day 1, subjects are premedicated with an antipyretic (such as acetaminophen) and an antihistamine (such as cetirizine). Premedications are administered 1 to 3 hours before the dose of mezagitamab or placebo. On the basis of the timing of the risk of hypersensitivity reaction, this will ensure that therapeutic levels of these medications are present at the expected time of maximum exposure to mezagitamab or placebo.

Table 21. Prophylactic coadministration regimen for mezagitamab and placebo dosing.

	Dose 1			Doses 2-8
Medication	**Day 1 (Day of Dose) [a]**	**Day 2**	**Day 3**	**Day of Dose [a]**
Corticosteroid: methylprednisolone 40 mg orally [b]	X	None	None	None
Antipyretic: acetaminophen 500-1000 mg orally [b]	X	X	X	X
Antihistamines:				
Cetirizine 10 mg orally or IV [b]	X	X	X	X
Famotidine 20 mg orally or IV [b]	None	X	X	None

IV: intravenous.
[a] Prophylactic medications given on day of dosing should be administered 1 to 3 hours before mezagitamab or placebo injection.
[b] Or equivalent.

Postdose Medication

[0655] If clinically indicated and in consultation with and approval from the medical monitor or medical director, an antipyretic (acetaminophen 500-1000 mg orally, or equivalent) and an antihistamine (cetirizine 10 mg orally or intravenously, or equivalent) may be given as postdose medication on the day of dosing. Additional postdose medications may be considered for subjects with respiratory complications (*e.g.*, history of asthma or COPD).

[0656] Subjects with a higher risk of respiratory complications (*e.g.*, history of COPD, asthma) may be administered the following prophylactic medications before or after each dose of mezagitamab at the investigator's discretion and after consultation with the medical monitor and sponsor, when possible: antihistamines: oral cetirizine (10 mg) and oral famotidine (20 mg); or leukotriene-receptor antagonist: oral montelukast (10 mg). In addition, these subjects may be administered the following medications to control their asthma or COPD: subjects with asthma or COPD: a short-acting ß2-adrenergic receptor agonist, such as salbutamol (albuterol) aerosol; subjects with asthma: inhaled corticosteroids with or without long-acting β2 adrenergic receptor agonists; and subjects with COPD: long-acting bronchodilators, such as tiotropium or salmeterol, with or without inhaled corticosteroids.

Treatment of Overdose

[0657] In this trial an overdose is defined as a known deliberate or accidental administration of trial intervention, to or by the study subject, at a dose above that which was assigned to that individual subject according to the trial protocol. In the event of an overdose, close monitoring and medically-required supportive treatment are recommended. An event of overdose—with or without an associated AE—should be reported to the trial medical monitor promptly and will be entered into the electronic clinical report forms (eCRFs) as an AE.

Subject Assignment, Randomization, and Blinding

[0658] Subjects are randomly assigned to receive mezagitamab or placebo in a 2:1 ratio based on blinded randomization schedule.

[0659] This is a double-blind, placebo-controlled trial in which subjects are randomly assigned to receive mezagitamab or placebo in a 2:1 allocation ratio based on a computer-generated randomization schedule created by the sponsor or designee. Randomization is stratified by baseline platelet count ($< \text{or} \geq 1.5\times10^9$/L), splenectomy (yes or no), and categorized concomitant SOC ITP therapy. All subjects are centrally assigned to randomized trial intervention using interactive response technology (IRT).

[0660] This is a double-blind trial in which subjects and trial personnel (including investigators, site personnel, the contract research organization, the medical monitor, study clinicians, and the sponsor) are blinded to trial intervention assignments. Treatment assignments will be obtained

via IRT and in relevant study documentation. Information regarding the trial intervention assignments will be kept securely per standard operating procedures. Records of the subject number, blinded trial intervention assignment, and date the intervention was dispensed are maintained by the study site.

[0661] Placebo and mezagitamab solutions are identical in appearance and are provided in vials that are indistinguishable as to treatment assignment. Specifically, a yellow wrap-around label is applied to the vials to mask the difference between mezagitamab and placebo, and a black wrap-around label is applied at the crimp of the vial to mask the lot numbers on the vials.

[0662] In the event of a medical emergency in which the investigator believes that information concerning the trial intervention is necessary for the medical treatment of the subject (*e.g.*, to treat an AE/safety issue or to inform decisions for subsequent therapy), the following is considered: subject safety must always be the first consideration in making such a determination; the decision to break the blind must be reached by the clinician and the investigator, but the investigator (or designee) may break the blind independent of the clinician only if the investigator considers the situation to be an emergency and that it requires specific knowledge of the blinded trial intervention to properly treat the subject's adverse event/safety issue; and if the treatment of the AE/safety issue is anticipated to be the same regardless of trial intervention assignment, the blind should not be broken.

Concomitant Therapy

[0663] Subjects are instructed not to take any medications (including over-the-counter products and any herbal supplements/treatments) without first consulting with the investigator. Information about the use of concomitant medications is collected and recorded from the time informed consent is obtained throughout the duration of the trial. Prohibited concomitant therapies and permitted SOC ITP therapies are described below.

Prohibited Concomitant Therapy

[0664] In addition to being prohibited prior to study entry for the time periods specified above, subjects may not receive prohibited concomitant therapies throughout the intervention and safety follow-up periods, unless used as described in **Table 22**. Exceptions may be allowed for treatment of AEs after discussion and agreement between the sponsor and principal investigator.

[0665] Any subject who receives prohibited concomitant therapy during the intervention period is prematurely discontinued from treatment; EOI visit procedures should be completed and the subject will enter the SFP. Subjects who receive prohibited therapy during the SFP may continue trial visits.

Table 22. Prohibited concomitant therapies.

Category or Agent	Additional Considerations
Anticoagulants	
IV or SC immunoglobulins or anti-D immunoglobulins	IVIg may be given as part of a single dose of bridging therapy.
Anti-CD20 treatment or other monoclonal or polyclonal antibodies	
Recombinant human thrombopoietin (rhTPO)	
Immunosuppressants (*e.g.*, cyclophosphamide, vincristine)	Only allowed if part of SOC ITP therapy.
Live-attenuated vaccinations	

Permitted Concomitant Therapy (Stable SOC ITP Therapy)

[0666] Subjects who have received an SOC ITP therapy that has remained stable in dose and frequency for at least 4 weeks prior to Day 1 and is expected to remain stable throughout the trial may continue using this therapy throughout participation in the trial. Permitted SOC ITP therapies must be approved for use within the region in which they are administered and may include 1 medication from each of the following 3 categories: one TPO-RA (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag); and/or one oral corticosteroid given daily or every other day (not to exceed prednisone 20 mg daily or equivalent dose); and/or one of the following other medications: methotrexate, azathioprine, leflunomide, cyclosporine, fostamatinib, mycophenolate, danazol, and/or dapsone.

Bridging Therapy

[0667] Because platelet counts may not be affected until several weeks after initiation of treatment with mezagitamab, subjects may receive a single bridging therapy during the intervention period without being prematurely discontinued from the trial. Allowed bridging therapies may include 1 of the following: a one-time infusion of platelets; a single dose of IVIg (up to 1 g/kg); or an additional 20 mg of prednisone (or equivalent) per day for up to 7 days.

Because the effects of these bridging therapies are typically expected to last ≤4 weeks, long-term effects on platelet levels are not anticipated.

Rescue Therapy

[0668] At any point in the trial, subjects may receive rescue therapy, which is defined as additional dosing of concomitant medications (beyond allowed bridging therapy) in accordance with institutional practices or the physician's best medical judgment to control and manage ITP. Rescue therapies may include (but are not limited to) administration of high-dose corticosteroids or IVIg and/or increasing or adding SOC ITP therapies. If a subject receives rescue therapy during the intervention period, mezagitamab or placebo must be discontinued; the EOI visit procedures are completed and the subject enters the SFP. If any rescue therapy is administered throughout the trial, the subject is considered a nonresponder at all subsequent study timepoints.

Management of Clinical Events

[0669] Based on the mechanism of action of anti-CD38 monoclonal antibodies, potential risks with mezagitamab treatment may include hypersensitivity reactions, changes in hematologic parameters, and infections. In addition, injection site reactions are possible with medications administered subcutaneously.

Injection Site Reactions

[0670] For agents given subcutaneously, injection site reactions are possible and have been reported with anti-CD38 monoclonal antibodies. Significant injection site abnormalities have not been observed in rat or monkey nonclinical studies after SC administration of mezagitamab. Subjects in this trial are closely monitored for any injection site reaction and are managed with standard medical care.

Hypersensitivity Reactions

[0671] Hypersensitivity reactions—including infusion-related reactions, anaphylaxis, and cytokine release syndrome (CRS)—have been reported with other biologic agents and may be seen with mezagitamab.

[0672] Generally, effects of hypersensitivity can be seen in different organ systems, including skin and eye. Symptoms range from mild skin rash to more severe reactions, including fever, urticaria, wheezing, hypotension, poor perfusion, respiratory arrest, and, rarely, death. Hypersensitivity reactions involving the eye (such as eye swelling, irritation, temporary blurred vision) may also be seen. Non-anaphylactic clinical hypersensitivity occurs within the first hour, but delayed responses have also been reported in the literature with other biologic agents.

[0673] CRS represents an important hypersensitivity reaction often associated with the use of natural and bispecific mAbs used in anti-inflammatory and antitumor therapies. Onset of CRS may occur early in therapy, often after the first dose, because of a high level of activation of the immune system and engagement and proliferation of T-cells that can result in increased cytokine release.

[0674] The CRS hallmark is fever. CRS also presents with rash, urticaria, headache, chills, fatigue, nausea, and/or vomiting. Severe CRS is characterized by severe dyspnea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. The acute respiratory failure may be accompanied by such events as pulmonary interstitial infiltration or edema visible on a chest x-ray. The syndrome frequently manifests within 1 or 2 hours of initiating the first infusion. Subjects with a history of pulmonary insufficiency or those with pulmonary tumor infiltration may be at greater risk of poor outcome and should be treated with increased caution. On the basis of outcomes from studies of the anti-CD38 mAb daratumumab, subjects with preexisting COPD or asthma may be at particular risk for respiratory complications (such as bronchospasm) should an infusion or hypersensitivity reaction or CRS event occur. Therefore, if the subject's FEV_1 is <50% of predicted normal, they are excluded from study participation. Eligible subjects with a history of COPD may require additional postdose medications to manage respiratory complications. To mitigate the potential risk of hypersensitivity reactions in this study: subjects with a history of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in the mezagitamab formulation are not eligible and therefore will not be exposed to mezagitamab; for all subjects, a 3-day prophylactic coadministration regimen (premedication and postdose medication) is mandatory for the first dose of mezagitamab or placebo (a prophylactic coadministration regimen is also required before each subsequent dose for all subjects); at the first and second dosing

visits, subjects will be carefully monitored in the clinic for 2 hours after the second injection, and any AE will be managed in accordance with available guidelines or institutional standards of care. Note: additional blood pressure measurements should be assessed any time the subject complains of symptoms consistent with a hypersensitivity reaction. If the subject experiences hypotension (with or without symptoms), intensive blood pressure monitoring according to local practice should be instituted. The subject should not be released from the site until blood pressure has returned to Grade 1 or baseline for at least 1 hour.

Changes in Hematologic Parameters

[0675] Reductions in platelets, lymphocytes, neutrophils, and RBCs have occurred in nonclinical studies when mezagitamab has been administered at a dose higher than the no observed adverse effect level (NOAEL). Subjects in this trial are closely monitored for changes in hematologic parameters, including testing of hematologic parameters throughout the trial. If clinical parameters do not meet dosing criteria, study dosing must be temporarily or permanently withheld. Medical interventions may be administered according to institutional guidelines.

Infections

[0676] In a GLP-compliant, 13-week toxicology study, bacterial and/or viral infection, secondary to immune suppression, was observed in cynomolgus monkeys at IV doses of 3, 30, and 80 mg/kg administered once every 2 weeks. The NOAEL dose of 0.3 mg/kg, administered IV once every week, was not associated with infections.

[0677] Subjects in this trial will be monitored for any signs and symptoms of infections throughout the trial. If clinical parameters do not meet dosing criteria, trial intervention must be temporarily or permanently withheld. Management of infections according to standard medical care is recommended.

Discontinuation of Trial Intervention and Subject Withdrawal from Trial

Discontinuation of Trial Intervention

[0678] Trial intervention must be permanently discontinued for participants meeting any of the following criteria: pregnancy; use of rescue therapy during the intervention period; and clinical parameters meet certain criteria. Treatment with trial intervention may also be discontinued for

any of the following reasons: AE; protocol deviation; symptomatic deterioration; unsatisfactory therapeutic response; trial terminated by sponsor; withdrawal by subject; lost to follow-up; and/or other.

[0679] Once trial intervention has been discontinued, all procedures outlined for the end-of-intervention (EOI) visit will be completed as specified above; subsequently, subjects enter the SFP. Subjects who discontinue trial intervention but complete the SFP may still be eligible to enter the continuation trial if all continuation trial eligibility criteria are met.

[0680] Investigators evaluate subjects before each dose of trial intervention; if clinical parameters do not meet criteria for continued dosing, the subject's dosing must be temporarily withheld until parameters meet dosing levels. During this time, participants continue to follow all trial-related requirements and complete all other scheduled assessments. Dosing may only be held for 1 week; if dosing criteria are not met at the next study visit after a missed/held dose, the subject must discontinue trial intervention and advance to the SFP.

Participant Withdrawal from the Trial

[0681] Participants may withdraw from the trial at any time and for any reason without prejudice to their future medical care by the physician or at the institution; alternatively, they may be withdrawn at any time at the discretion of the investigator or sponsor (*e.g.*, in the interest of subject safety).

[0682] If a participant prematurely discontinues mezagitamab or placebo during the intervention period, the EOI visit procedures are performed and the participants advance to the SFP. If a participant prematurely discontinues during the SFP, the EOT visit procedures are performed.

[0683] A participant may be withdrawn from the trial for any of the following reasons: adverse event; lost to follow-up; trial terminated by sponsor; withdrawal by participant; death; and/or other.

[0684] The consequence of a participant withdrawing consent for further treatment and follow-up is that no new information is collected and added to the existing data or any database; however, data collected during participant consent must be included in the database. Every effort will be made to follow all participants for safety. Participants who discontinue/withdraw

prematurely from the trial for reasons other than safety may be replaced at the discretion of the sponsor.

Lost to Follow-Up

[0685] A participant is considered lost to follow-up if he/she repeatedly fails to attend scheduled visits and is unable to be contacted by the site. The following actions must be taken if a participant fails to return to the clinic for a required trial visit.

[0686] The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the trial.

[0687] Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented.

[0688] If the participant continues to be unreachable, they are considered to have withdrawn from the trial.

Trial Assessments and Procedures

Screening/Baseline Assessments and Procedures

[0689] Written or electronic informed consent must be obtained (signed and dated) before trial assessments and procedures can be performed.

[0690] The screening period for this study is up to 28 days (Day -28 to Day -1). Assessments and procedures are performed on schedule, within the window for each visit. Additional time allowance for most study procedures and assessments is acceptable in extenuating circumstances (*i.e.*, holidays, vacations, and other administrative reasons) on approval by the medical monitor or delegate; however, these time extensions should not deviate more than 7 days from the scheduled procedural time.

[0691] Procedures conducted as part of the participant's routine clinical management (*e.g.*, blood count) and obtained before signing of the ICF may be used for screening or baseline purposes

provided the procedures met the protocol-specified criteria and were performed within the timeframe defined above.

Demographics, Medical History, and Medication History

[0692] Participant demographic information are collected prior to the participant receiving the first dose of trial intervention. Demographic information includes: age/date of birth at the time of informed consent; sex; race and ethnicity; and height, weight, and smoking status of the participant at Screening.

[0693] Medical and medication history, including concurrent medical conditions, are collected and recorded. Medical history obtained includes determining whether the participant has any significant conditions or diseases relevant to the disease under study that resolved before the participant signed the ICF. The medical history assessment includes current ITP signs and symptoms, as evaluated and scored by disease activity tools, as well as previous and current ITP therapies. The complete medical history includes history of eye disease or ophthalmic clinical symptoms (including allergic reactions). If an eye exam had been conducted within the previous year, a copy of the records from the exam are provided to the site as source documentation. Coronavirus disease 2019 (COVID-19) infection and vaccination history prior to the study are recorded as part of medical history.

[0694] Ongoing conditions are considered concurrent medical conditions. Concurrent medical conditions are those significant ongoing conditions or diseases that are present when informed consent is provided. This includes clinically significant laboratory, electrocardiogram (ECG), physical examination, and/or vital signs abnormalities noted at screening examination, according the judgment of the investigator. The condition (*i.e.*, diagnosis) is described.

[0695] Prior and concomitant treatments and medications are collected and recorded. Such treatments/medications include but are not limited to: medications or vaccines; over-the-counter or prescription medicines; recreational drugs; vitamins; herbal supplements; medications relevant to the eligibility criteria; and prior ITP therapies and concomitant SOC ITP therapies.

[0696] At the time of the medical history, any available prior medication/treatment information will be collected. Prior medications/treatments are defined as those that were received within 30 days of the date of first dose of trial intervention.

[0697] Concomitant medications/treatments are defined as those given in addition to the trial intervention between the first dose of trial intervention and the end of the SFP, inclusive. These include concomitant SOC ITP therapy.

[0698] Concomitant medications may be prescribed by a physician or obtained by the participant over the counter. Medications used and therapeutic procedures completed by the participant are recorded. Information recorded includes: trade name and international nonproprietary name (if available); indication; start and end dates of the administered medication.

[0699] At each trial visit, participants are asked whether they have taken any medication or received any treatment other than the trial intervention. COVID-19 vaccination and COVID-19 treatments received during the study through SFP are recorded as concomitant medications.

[0700] The medical monitor is contacted if there are any questions regarding concomitant or prior therapy.

[0701] Information regarding ITP therapies received since the time of ITP diagnosis is collected and reported. In addition, information is collected regarding to which prior ITP therapies participants had insufficient response, adverse reaction, or contraindication and/or intolerance, and the adverse reaction, reason for the contraindication or symptoms of intolerance.

[0702] Each participant must have a documented diagnosis of primary ITP that has persisted for at least 3 months. The diagnosis is in accordance with The American Society of Hematology 2019 Guidelines for ITP or the Updated International Consensus Report on The Investigation and Management of Primary ITP, as locally applicable. Each participant must also have had documented insufficient response to prior ITP therapy, intolerance, and/or contraindication to current or other treatment.

[0703] To confirm eligibility for the study, participants' platelet counts must also meet the protocol defined criterion outlined above. Platelet count results are obtained from the clinical laboratory samples taken during the screening period.

Inclusion Criteria and Assessment

[0704] Eligibility criteria and associated trial screening assessments must be confirmed during the screening period (after a patient has signed the ICF and before receiving mezagitamab or placebo).

Efficacy Assessments and Procedures

Clinical Outcomes Assessments

[0705] WHO Bleeding Scale: The World Health Organization (WHO) Bleeding Scale is a single clinical investigator determined classification of bleeding on a simple five-point scale (Fogarty et al. 2012). The investigator asks the patient whether they experienced any bruising or bleeding within the last 7 days. Grade of bleeding ranges from 0 (no bleeding) to 1 (petechiae), 2 (mild blood loss), 3 (gross blood loss), and 4 (debilitating blood loss).

[0706] ITP-PAQ: The ITP-PAQ is a patient-reported outcome (PRO) questionnaire that assesses the effect of ITP symptoms and the disease impacts on health-related quality of life (HRQoL) in adult patients with ITP (Mathias et al. 2007a; Mathias et al. 2007b). The questionnaire consists of 44 items grouped into 10 domains/scales: symptoms (6 items); physical health-bother (3 items); fatigue/sleep (4 items); physical health-activity (2 items); fear (5 items); psychological health (5 items); work (4 items); social activity (4 items); women's reproductive health (6 items); and overall quality of life (5 items). Domain/scale scores range from 0 to 100, with higher scores representing better quality of life. The ITP-PAQ is self-administered. On the day of assessment, the ITP-PAQ is completed before the EQ-5D-5L and all vital signs, laboratory, or biomarker assessments.

[0707] EQ-5D-5L: Participants are asked to complete the EuroQol Five Dimensions (EQ-5D) questionnaire to assess HRQoL. The EQ-5D is a generic, multi-attribute, HRQoL instrument composed of a descriptive system and a visual analog scale (VAS) (The EuroQol Group 1990). The EQ-5D descriptive system has the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D 5-level version (EQ-5D-5L) is used for this study. The EQ-5D-5L is self-administered. On the day of assessment, the EQ-5D-5L is completed after the ITP-PAQ and before all vital signs, laboratory, or biomarker assessments.

Safety Assessments and Procedures

[0708] Physical Examination: A physical examination is completed per standard of care at the times specified in the Schedule of Assessments. Women of childbearing potential are asked about their menstrual history at each visit. A serum pregnancy test is conducted for delayed menses.

[0709] Vital Signs: Vital signs are evaluated at the visits specified in above and are recorded. Vital signs are also assessed at any other times at which it is clinically warranted (*e.g.*, participant is exhibiting signs or symptoms of CRS or other hypersensitivity reaction). On dosing days, vital signs are assessed before the dose; vital signs are also assessed 2 hours (±10 minutes) after dosing at Week 0 and Week 1. When vital signs are scheduled at the same time as blood sample collection, the blood sample collection takes priority, and vital signs are obtained within 0.5 hour before or after the scheduled blood draw. Vital signs evaluated include: body temperature (measurement method based on site standard of practice); respiratory rate; blood pressure (systolic and diastolic, resting more than 5 minutes); and pulse (beats per minute). The investigator assesses whether a change in vital signs from baseline is deemed clinically significant and whether the change should be considered and recorded as an AE; any such changes are closely monitored for follow-up/resolution.

[0710] Weight and Height: Height (in centimeters) is measured and recorded during screening. Weight (in kilograms) is measured and recorded at screening and at the timepoints shown above.

[0711] Electrocardiograms: A single 12-lead ECG is performed at the screening visit (for assessment of eligibility) and at the timepoints shown above and is read locally. Any ECG finding that is judged by the investigator as clinically significant (except at the screening visit) is considered an AE; as such, clinically significant findings are recorded, and the participant undergoes continued monitoring.

Clinical Laboratory Assessments

[0712] Clinical Chemistry and Hematology: Blood samples for analysis of the clinical chemistry and hematology parameters shown in **Table 23** are obtained at each visit specified above. Creatinine clearance is estimated during the screening visit using serum creatinine and the Cockroft-Gault formula.

Table 23. Clinical chemistry and hematology evaluations.

Hematology	Serum Chemistry	
Hematocrit Hemoglobin Leukocytes with differential Total lymphocyte count [a] Neutrophils [a] Platelet (count)	Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Bilirubin (total) Blood urea nitrogen Calcium	Carbon dioxide Creatinine Chloride Glucose Lactate dehydrogenase Potassium Sodium
[a] Total lymphocyte count and absolute neutrophil count are resulted as part of the leukocyte differential and will be specifically recorded in electronic data capture.		

[0713] Blood Type Assessment: Anti-CD38 monoclonal antibodies have been reported to bind to CD38 on RBCs, resulting in a positive indirect Coombs test, which may persist for up to 6 months. The determination of a subject's ABO and Rh blood type are not affected, but the RBC binding may mask detection of antibodies to minor antigens in the subject's serum (Darzalex (daratumumab) injection 2019; Regan and Markowitz 2016). It is possible that mezagitamab may affect the results of these tests. Following the recommendations for avoiding problems with blood transfusions for subjects treated with anti-CD38 antibodies (Lancman et al. 2018; Regan and Markowitz 2016), extended RBC antigen typing by phenotype or genotype testing is required for subjects as part of the screening assessments. The extended phenotype test cannot be assessed in subjects who have had a blood transfusion within 3 months prior to screening; genotyping is performed in this case. The results of these tests enables the identification of antigen-matched RBC units for subjects with known alloantibodies. The most common immunogenic antigens, including antigens in the Rh (D, E, e, C, c), Duffy (Fya, Fyb), Kidd (Jka, Jkb), Kell (K) and MNS (S, s) blood group systems, are to be tested. RBC extended antigen typing by either phenotype or genotype testing is required prior to receiving trial intervention, unless an adequate alternative local practice of cross-matching for blood transfusions is established for subjects on anti-CD38 therapy (*e.g.*, pretreating the RBC samples with polybrene or dithiothreitol (DTT) to address the CD38 antibody interference in the cross-matching before blood transfusion).

[0714] Blood Sample for CD19+ Counts: Subjects who have had prior exposure to anti-CD20 therapy and require confirmatory testing of CD19+ levels (see Exclusion Criteria) have a blood sample drawn during screening that is used to confirm eligibility via flow cytometry.

[0715] Other Screening Laboratory Tests: Blood samples collected during screening are also used for the following additional tests: coagulation (international normalized ration, INR and partial thromboplastin time; and Coombs test (both direct and indirect).

Adverse Events and Serious Adverse Events

Adverse Events of Special Interest

[0716] Adverse events of special interest (AESIs) in this study include anaphylaxis and opportunistic infections.

Pharmacokinetics

[0717] Serum samples are collected for measurement of mezagitamab concentrations at the time points specified in above. The actual date and time of each PK sample collection is recorded. The timing of PK sample collection may be modified during the study on the basis of emerging PK data if a change is considered necessary to better characterize the PK profile of mezagitamab. Additional PK samples may be requested if deemed necessary by the medical monitor for specific events of clinical interest or AEs.

Biomarkers

[0718] Biomarkers are assessed to test for correlation with safety, PK, and, if possible, with efficacy. These biomarkers are used to identify subjects who have a higher probability of response or adverse reactions to mezagitamab. The biomarker sample analysis is performed if or when required. Samples for biomarker/PD measurements are collected at the time points shown above. These measurements include:

- Anti-platelet autoantibodies: whole blood samples are collected to assess quantitative reduction in antibodies directed against platelet glycoproteins in response to total immunoglobulin reduction;

- Circulating biomarkers: serum samples for cytokines/chemokines or other soluble factors (*e.g.*, Complement C3, C4 and antiphospholipid antibodies) are collected to help identify subjects who have a higher probability of response or of experiencing adverse reactions to mezagitamab;
- Immunoprofiling: blood samples are collected for profiling of immune cells and are analyzed for the presence and changes of immune cells by flow or mass cytometry;
- Vaccine-induced protective antibodies: serum samples for vaccine-induced protective antibodies (measles, mumps, rubella, tetanus, and diphtheria) are collected before, during, and at end of treatment to monitor individual antibody reductions and potential effect on vaccine protection;
- Immature platelet fraction: blood samples are collected to analyze immature platelet fraction as a potential measure of platelet production;
- TPO: whole blood or serum samples for measurement of TPO are collected at screening and may be used to assess correlation with response to treatment;
- Vitamin B12: whole blood or serum samples for measurement of Vitamin B12 are collected at screening and may be used to assess correlation with response to treatment; and
- Reticulocyte count: corrected reticulocyte count are collected using hemoglobin and hematocrit values from the clinical samples collected at screening and may be used to assess the possible relationship of bone marrow function on response to treatment.

If a subject is exhibiting signs or symptoms possibly assessed as Grade ≥2 CRS by the investigator, a blood sample is collected and sent to a central laboratory to assess cytokine marker activity.

Immunogenicity Assessments

[0719] Antibodies to mezagitamab are evaluated in serum samples collected from all subjects according to the timepoints shown above. When collected on a dosing day, samples must be collected before mezagitamab or placebo is administered. Additionally, serum samples are

collected at the final visit from subjects who discontinue trial intervention or are withdrawn from the trial. A central laboratory assesses samples for true positivity and titer if a positive ADA is detected. Other analyses may be performed to verify the stability of antibodies to the trial intervention and/or further characterize the immunogenicity of the trial intervention.

Statistical Considerations

[0720] A statistical analysis plan (SAP) is prepared before the first subject is randomized. The SAP provides the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics, and baseline characteristics, mezagitamab exposure, prior and concomitant medications, and PK/PD. The SAP also includes a description of how missing, unused, and spurious data is addressed.

[0721] Unless otherwise specified, summary tabulations are presented by treatment group. All data listings are sorted by treatment group, site, and subject number, and will include the subject's age, sex, and race. For categorical variables, the number and percentage of subjects within each category (with a category for missing data as needed) of the parameter is presented. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values are presented.

Analysis Sets

[0722] The analysis sets are as follows:

- Enrolled set: all subjects for whom informed consent has been obtained;
- Full analysis set (FAS): all randomized subjects who have received at least 1 dose of the mezagitamab or placebo (analysis is performed according to the randomized treatment regimen regardless of the treatment regimen actually received);
- Pre-protocol analysis set (PPAS): all randomized subjects who received at least 1 dose of the mezagitamab or placebo without major protocol deviations impacting the efficacy evaluation;

- Safety analysis set (SAF): all subjects who have received at least 1 dose of the mezagitamab or placebo (analysis is performed according to the treatment regimen actually received, regardless of the randomized treatment regimen assigned);
- PK analysis set (PKAS): all subjects from the safety analysis set who have received at least 1 dose of trial intervention and have at least 1 evaluable postdose PK concentration value; and
- PD analysis set (PDAS): all subjects from the safety analysis set who have received at least 1 dose of trial intervention and have at least 1 evaluable postdose PD sample assessment.

Analyses Supporting Primary Objective(s)

[0723] The primary endpoint is durable platelet response, defined as a sustained platelet response with platelet count ≥50,000/μL on at least 4 out of 6 biweekly visits between weeks 14-24 without receipt of rescue therapy. The primary analysis of the primary endpoint is an analysis of the proportion of subjects with a durable platelet response. The primary analysis is performed on the FAS and assessed at the 2-sided alpha level of 0.05. A sensitivity analysis is performed on the PPAS.

Statistical Model, Hypothesis, and Method of Analysis

[0724] For the analysis of the primary endpoint, the proportions of subjects with a durable platelet response are compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test stratified by baseline platelet count (< or ≥ 1.5×10^9/L), splenectomy (yes or no), and categorized stable SOC ITP therapy. The treatment group difference (mezagitamab versus placebo) of proportions and associated 95% CI is provided using the CMH stratum weights. The primary efficacy endpoint is tested by the following hypothesis: H_0: $\delta = 0$, H_1: $\delta \neq 0$, where δ is the common treatment difference across strata, j=1 to m. The common treatment difference is a weighted average of the stratum-specific treatment differences. The estimate of the treatment difference along with the corresponding stratified 95% CI using the method of (Yan and Su, (2010) Stat. Biopharm. Res., 2(3), 329-35) and CMH p value is presented.

Handling of ICEs and Primary Estimands and Missing Data

[0725] The intercurrent events for the primary estimand include: use of rescue therapy; premature treatment discontinuation due to 1) met dose discontinuation criteria, 2) use of prohibited concomitant therapy, or 3) AEs or lack of efficacy; premature discontinuation from the study; and missing platelet count measurement. Subjects with intercurrent events are not considered as having a durable platelet response in the following cases (composite strategy): subject received rescue therapy or prematurely discontinued from the treatment due the reasons as specified in above ICEs at any time prior to week 14; subject received rescue therapy or prematurely discontinued from the study at any time during weeks 14-24 and had fewer than 4 visits with platelet response; or subject missed platelet count measurement during weeks 14-24 and had fewer than 4 visits with platelet response.

[0726] Subjects with missing platelet count data due to rescue therapy use or study discontinuation due to an AE or lack of efficacy are considered treatment failures, hence considered as nonresponders. Subjects with missing data due to the reasons other than these (*e.g.*, due to measurement not done, early discontinuation from study with reason of subject decision) may have platelet count data imputed by different methods (such as such as multiple imputation, worst observation carried forward).

Sensitivity Analyses

[0727] Sensitivity analyses are conducted to evaluate the robustness of the result from the primary analysis method. These analyses include various imputation methods (worst case/best case prior (multiple imputation procedures for ICEs, or using platelet values adjacent to occurrence the primary test period of ICE and multiple imputation procedures) weeks 14-week 24 for subjects with less than 4 valid platelet test results during the period) for missing platelet count measurements, as well as repeating the primary analysis in different analysis sets (*e.g.*, PPAS).

Analysis Supporting Secondary Objectives

[0728] The secondary objectives, endpoints, and associated estimands are specified above. The analysis of the rank-ordered secondary endpoints is conducted using the fixed-sequence testing procedure aligned with the endpoint order. Testing for a given endpoint will be performed only

if the null hypothesis is rejected for all previously tested endpoints. A significance level of 0.05 is used for all tests. All the secondary endpoint analyses are performed on the FAS.

Statistical Model, Hypothesis, and Method of Analysis for Secondary Endpoints

[0729] The rank-ordered secondary efficacy endpoints and the corresponding methods of analysis are described as follows.

(1) Duration of platelet response is measured by the total number of weeks for which a platelet response is attained, where platelet response is defined as a platelet count of ≥50,000/μL on the scheduled visit in the absence of any concomitant rescue therapy. The difference in the mean total number of weeks with platelet response between the mezagitamab and placebo groups, along with the corresponding treatment difference 95% CI, is derived by a student's t-test assuming a common standard deviation.

(2) Platelet response is defined as a platelet count ≥50,000/μL on at least 2 visits without a bridging therapy in the previous 4 weeks and without any previous rescue therapy. The difference in the proportions of subjects with platelet response between the mezagitamab and placebo groups, along with the associated 95% CI, is provided using the CMH stratum weights.

(3) Complete platelet response is defined as a platelet count ≥100,000/μL on at least 2 visits without use of bridging therapy in the previous 4 weeks and without any other previous rescue therapy. The difference in the proportions of subjects with a complete platelet response between the mezagitamab and placebo groups, along with the associated 95% CI, is provided using the CMH stratum weights.

(4) Clinically meaningful platelet response is defined as a platelet count ≥20,000/μL above baseline on at least 2 visits without use of bridging therapy in the previous 4 weeks and without any other previous rescue therapy. The difference in the proportions of subjects with a clinically meaningful platelet response between the mezagitamab and placebo groups, along with the associated 95% CI is provided using the CMH stratum weights.

(5) Hemostatic platelet response is defined for subjects with a baseline platelet count of <15,000/μL who achieve a platelet count of ≥30,000/μL and ≥20,000/μL above baseline on at least 2 visits without use of bridging therapy in the previous 4 weeks and without any other previous rescue therapy. The analysis of the endpoint is conducted over subjects in FAS with baseline platelet count of <15,000/μL. The difference in the proportions of subjects with a hemostatic platelet response between the mezagitamab and placebo groups, along with the associated 95% CI, is provided using the CMH stratum weights.

(6) Occurrence of rescue therapy. The difference in the proportions of subjects who received rescue therapy between the mezagitamab and placebo groups, along with the associated 95% CI, is provided using the CMH stratum weights.

(7) The time to first rescue therapy is summarized using the Kaplan-Meier method and compared using the stratified log-rank test. The treatment difference (hazard ratio, and its 95% CI) between the mezagitamab and placebo groups is estimated using the stratified Cox's regression model.

Handling of ICEs and Secondary Endpoints and Missing Data

[0730] If a subject receives rescue therapy or prematurely discontinues from the study, any platelet count measurements obtained thereafter are excluded from the analysis. In addition, any platelet count measurements obtained within 4 weeks after receiving bridging therapy are excluded from the analysis. This approach allows estimation of the treatment effect under the hypothetical situation in which the dosing schedule is adhered to without use of rescue or bridging therapy.

[0731] Subjects with missing platelet count data due to rescue therapy use or study discontinuation due to an AE or lack of efficacy are considered treatment failures, hence considered as nonresponders. Subjects with missing platelet count data due to reasons unrelated to the subject (*e.g.*, samples collected but not tested) may have platelet count data imputed using missing at random (MAR) based methods (*e.g.*, multiple imputation), worst observation carried forward, WOCF).

Analysis of Exploratory Objectives

[0732] For the exploratory objectives, summary descriptive statistics includes the number of subjects (N), mean, standard deviation, median, minimum, and maximum (range) values for continuous variables, and number and percentages of subjects in each category for categorical variables. The denominator for the percentages is based on the number of subjects in the analysis set, unless otherwise specified. Time-to-event endpoints is summarized using Kaplan-Meier methods. The 25%, 50%, and 75% percentiles, along with corresponding 95% CIs are presented.

Safety Analyses

[0733] The safety analysis is performed using the SAF and descriptively summarized by treatment group and overall; no statistical testing is performed. Safety outcome measures are as follows.

- Adverse events, which are coded using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs are defined as AEs with start dates at the time of or following the first exposure to mezagitamab or placebo. The number and percentage of subjects with TEAEs, as well as the number of events, is summarized by MedDRA system organ class (SOC) and preferred term (PT) for each treatment group and overall. TEAEs are further summarized by seriousness, severity, and relationship to mezagitamab or placebo. In addition, TEAEs related to mezagitamab or placebo, TEAEs related to COVID-19, TEAEs leading to withdrawal, treatment-emergent SAEs, and treatment-emergent deaths are similarly summarized/listed.
- Vital signs, clinical laboratory (clinical chemistry and hematology), and 12-lead ECG results (observed and changes from baseline) are summarized by study visit for each treatment group using descriptive statistics. Clinically significant abnormal values in routine laboratory parameter and vital sign results are listed or summarized descriptively when appropriate.

[0734] Exposure to study drug and reasons for discontinuation is tabulated by treatment group.

Other Analyses

PK and PD Analyses

[0735] Exploratory PK and PK/PD evaluations are performed to assess the relationship between mezagitamab plasma concentrations and selective PD measures, as data allow and as deemed appropriate. A descriptive summary of the PK concentrations and PD values is summarized, as well as individual PK concentrations and observed PD values.

[0736] Additionally, population PK analysis, exposure-efficacy, and/or exposure-safety relationship (model-based and or non-model-based) may be explored, as deemed appropriate.

Immunogenicity Analyses

[0737] Mezagitamab immunogenicity status (ADA incidence) is analyzed and summarized using descriptive statistics, as applicable, and using the safety analysis set. The effect of immunogenicity on PK, safety, and efficacy is explored.

Sample Size Determination

[0738] A total sample size of 171 subjects with an allocation ratio of 2:1 (mezagitamab:placebo) provides at least 90% power to detect a treatment difference of 40% (50% response rate for the mezagitamab group compared to 10% response rate for placebo group) at a 2-sided significance level of 0.001. This sample size was estimated based on a Chi-square exact test assuming a dropout rate (DOR) of 20% and that subjects who drop out will be imputed as nonresponders.

[0739] This study is designed to have approximately 90% power for the primary endpoint to detect a treatment difference at a highly statistically persuasive level (*i.e.*, a p-value ≤ 0.001); however, an alpha of 0.05 (2-sided) is used as the overall Type-I error rate for the purposes of demonstration of efficacy in this trial and declaring trial success.

EXAMPLE 3: A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE EFFICACY AND SAFETY OF MEZAGITAMAB SUBCUTANEOUS INJECTION IN SUBJECTS WITH PERSISTENT OR CHRONIC PRIMARY IMMUNE THROMBOCYTOPENIA

[0740] Data from the trial in participants with ITP show preliminary signs of efficacy in this population. The Phase 2 study demonstrated that weekly doses of mezagitamab 600 mg for 8 weeks was tolerable with favorable safety and promising signs of efficacy; 10/11 participants treated with mezagitamab 600 mg achieved a platelet response by week 16 vs 3/13 with placebo. Due to the heterogeneity of ITP pathogenesis and the involvement of multiple humoral and cellular pathways, there is a strong scientific rationale for utilizing mezagitamab in patients with ITP due to its multimodal mechanism of action, which may provide significant benefit, including in patients with a poor prior response to other therapies.

[0741] This is a Phase 3, randomized, double-blind, placebo-controlled study. Participants are ≥18 years, with primary ITP for ≥12 months and evidence of an insufficient response or intolerance to ≥1 first-line and ≥1 second-line treatment for ITP. After screening, participants are randomized (2:1) to mezagitamab 600 mg or placebo. Study treatment is administered subcutaneously once weekly for 8 weeks, followed by biweekly monitoring visits off treatment for 8 weeks, then once weekly treatment for a further 8 weeks, for a total study duration of 24 weeks. Use of additional, stable background ITP therapy including corticosteroids, thrombopoietin receptor agonists, and fostamatinib is permitted as is use of rescue therapy (prednisone 20 mg or equivalent, intravenous immune globulin, platelet transfusion) when indicated. The primary endpoint is the durable platelet response through Week 24, defined as a platelet count ≥50,000/μL on at least 4 of the 6 weekly platelet measurements between Weeks 19 and 24. Secondary endpoints include: cumulative number of weeks through Week 24 that platelet count was ≥50,000/μL; time to first platelet count ≥50,000/μL; cumulative number of weeks through Week 24 that platelet count was ≥30,000/μL and at least double that of baseline; complete platelet response (platelet count ≥100,000/μL on ≥2 visits through Week 24); platelet response at Week 16 (platelet count ≥50,000/μL before study treatment administration at the Week 16 visit); change from baseline in the Symptoms scale score of the ITP Patient Assessment Questionnaire; occurrence of the use of rescue therapy; time to first rescue therapy; and bleeding

events based on the ITP-specific Bleeding Assessment Tool. Safety is assessed by the incidences of treatment-emergent adverse events, treatment-related adverse events, and Grade ≥3 treatment-emergent adverse events, and clinically significant abnormal laboratory test results and vital signs.

[0742] This global, registrational study involving approximately 20 countries and >100 study sites evaluates the efficacy and safety of subcutaneous mezagitamab administered via a cyclic dosing regimen as a potential novel treatment for chronic primary ITP. Endpoint evaluations include those pertaining to durability of treatment effect, safety, and impact on quality of life.

Trial Objectives, Endpoints, and Estimands

[0743] The primary objective and associate endpoint is provided in **Table 24** and the estimand framework for the primary endpoint is provided in **Table 25**.

Primary Objectives and Associated Endpoints and Estimands

Table 24. Primary Objective and Associated Endpoint

Primary Objective	Primary Endpoint
To assess the efficacy of mezagitamab compared with placebo in achieving durable platelet response in participants aged ≥18 years with persistent or chronic ITP.	Durable platelet response through Week 24, defined as platelet count ≥50,000/μL on at least 4 of the 6 weekly platelet measurements between Week 19 and Week 24.

Table 25. Estimand Framework for Primary Endpoint

Definition	The primary estimand is the comparison of the effect of mezagitamab to placebo on platelet counts.
Trial Intervention	Two cycles of mezagitamab 600 mg or placebo, separated by an 8-week dosing-free period; each cycle consists of once-weekly dosing for 8 weeks.
Population	Full analysis set.
Variable (or Endpoint)	Durable platelet response through Week 24, defined as platelet count ≥50,000/μL on at least 4 of the 6 weekly platelet measurements between Week 19 and Week 24.
Strategy for Addressing Intercurrent Event	ICEs: • Use of rescue therapy. • Premature discontinuation of IMP Strategy for addressing ICEs and missing data: The participant is considered as not having durable platelet response in the following cases (composite strategy): • Received rescue therapy. • Prematurely discontinued IMP before Week 22. • Had more than 2 missed platelet count measurements, due to any reason, between Week 19 and 24 (inclusive).
Population-Level Summary	Difference in proportions of participants with durable platelet response in the mezagitamab group compared to the placebo group.
IMP: investigational medicinal product, *i.e.*, mezagitamab or placebo	

Secondary Objectives and Associated Endpoints and Estimands

[0744] The secondary objectives and associated endpoints are provided in **Table 26**, the estimand framework for the secondary endpoints relating to platelet count thresholds is provided in **Table 27**, the estimand framework for the secondary endpoints relating to time to first platelet count ≥50,000/μL is provided is **Table 28**, the estimand framework for the secondary endpoint relating to complete platelet response is provided in **Table 29**, the estimand framework for the secondary endpoint relating to the use of rescue therapy is provided in **Table 30**, and the estimand framework for the secondary endpoint relating to participant-reported symptoms is provided in **Table 31**.

Table 26. Secondary Objectives and Associated Endpoints

Secondary Objective	Secondary Endpoint
To assess the efficacy of mezagitamab compared with placebo in achieving platelet response in participants aged ≥18 years with persistent or chronic ITP.	• The cumulative number of weeks that a platelet count was ≥50,000/μL through Week 24. • Time to first platelet count ≥50,000/μL. • The cumulative number of weeks that a platelet count was ≥30,000/μL through Week 24 and at least doubled from baseline. • Complete platelet response, defined as a platelet count ≥100,000/μL on at least 2 visits through Week 24. • Platelet response at Week 16, defined as a platelet count ≥50,000/μL before IP administration at the Week 16 visit.
To assess the use of rescue therapy in participants aged ≥18 years receiving mezagitamab compared with those receiving placebo.	• Occurrence of receiving rescue therapy. • Time to first rescue therapy.
To assess the effects of mezagitamab compared with placebo on patient-reported symptoms of ITP in participants aged ≥18 years with persistent or chronic ITP.	• Change from baseline in the Symptoms scale score of the ITP-PAQ at Week 24.
To assess the effects of mezagitamab compared with placebo on occurrence of bleeding in participants aged ≥18 years with persistent or chronic ITP.	• Presence of bleeding events, defined as Grade ≥2 in the Skin domain, or Grade ≥1 in the Mucosal domain, or Grade ≥1 in the Organ domain, in the ITP-BAT through Week 24.
To determine the PK profile of mezagitamab.	• The PK concentration during and after intervention.
To evaluate the immunogenicity of mezagitamab.	• Incidence of ADA and change in ADA titers. • Incidence of neutralizing ADA (Nab).

Table 27. Estimand Framework for Secondary Endpoints Relating to Platelet Count Thresholds

Definition	Comparison of the effect of mezagitamab with placebo on platelet counts.
Trial Intervention	Two cycles of mezagitamab 600 mg or placebo, separated by an 8-week dosing-free period; each cycle consists of once-weekly dosing for 8 weeks.
Population	Full analysis set.
Variable (or Endpoint)	• The cumulative number of weeks that a platelet count was ≥50,000/μL through Week 24. • The cumulative number of weeks that a platelet count was ≥30,000/μL through Week 24 and at least doubled from baseline.
Strategy for Addressing Intercurrent Event	ICEs: • Use of rescue therapy. • Premature discontinuation of IMP. Strategy for addressing ICEs and missing data: The participant will be considered as not having platelet count ≥50,000/μL or ≥30,000/μL at the scheduled visit in the following cases (composite strategy): • Received rescue therapy at any time before the visit. • Prematurely discontinued IMP at any time before the visit. • Missed platelet count measurement at the visit.
Population-Level Summary	Difference between participants in the mezagitamab group compared with the placebo group in the cumulative number of weeks with: • Platelet count ≥50,000/μL through Week 24. • Platelet count ≥30,000/μL through Week 24 and at least doubled from baseline.

Table 28. Estimand Framework for Secondary Endpoint Relating to Time to First Platelet Count ≥50,000/μL

Definition	Comparison of the effect of mezagitamab with placebo on platelet counts.
Trial Intervention	Two cycles of mezagitamab 600 mg or placebo, separated by an 8-week dosing-free period; each cycle consists of once-weekly dosing for 8 weeks.
Population	Full analysis set.
Variable (or Endpoint)	• Time to first platelet count ≥50,000/μL.
Strategy for Addressing Intercurrent Event	ICEs: • Use of rescue therapy. • Premature discontinuation of IMP. Strategy for addressing ICEs: The participant is considered censored at the EOT (*e.g.*, not having achieved first platelet count ≥50,000/μL) in the following cases (hypothetical strategy): • Received rescue therapy before first visit with platelet count ≥50,000/μL. • Prematurely discontinued IMP before first visit with platelet count ≥50,000/μL.
Population-Level Summary	Hazard ratio of the mezagitamab group to the placebo group.

Table 29. Estimand Framework for Secondary Endpoint Relating to Complete Platelet Response

Definition	Comparison of the effect of mezagitamab with placebo on platelet counts.
Trial Intervention	Two cycles of mezagitamab 600 mg or placebo, separated by an 8-week dosing-free period; each cycle consists of once-weekly dosing for 8 weeks.
Population	Full analysis set.
Variable (or Endpoint)	• Complete platelet response, defined as a platelet count ≥100,000/μL on at least 2 visits through Week 24. • Platelet response at Week 16, defined as a platelet count ≥50,000/μL before IP administration at the Week 16 visit.
Strategy for Addressing Intercurrent Event	ICEs: • Use of rescue therapy. • Premature discontinuation of IMP. Strategy for addressing ICEs and missing data: The participant will be considered as not having a complete platelet response or platelet response at Week 16 in the following cases (composite strategy): • Received rescue therapy before having 2 visits with platelet count ≥100,000/μL for complete platelet response or have a platelet count ≥50,000/μL at Week 16 for platelet response at Week 16. • Prematurely discontinued IMP before having 2 visits with platelet count ≥100,000/μL for complete response or have a platelet count ≥50,000/μL at Week 16 for platelet response at Week 16.
Population-Level Summary	• Difference in proportions of participants with complete platelet response in the mezagitamab group compared to the placebo group. • Difference in proportions of participants with platelet response in the mezagitamab group compared to the placebo group at Week 16.

Table 30. Estimand Framework for Secondary Endpoint Relating to Use of Rescue Therapy

Definition	Comparison of the effect of mezagitamab on the use of rescue therapy compared to placebo.
Trial Intervention	Two cycles of mezagitamab 600 mg or placebo, separated by an 8-week dosing-free period; each cycle consists of once-weekly dosing for 8 weeks.
Population	Full analysis set.
Variable (or Endpoint)	• Occurrence of receiving rescue therapy. • Time to first rescue therapy.
Strategy for Addressing Intercurrent Event	ICEs: Premature discontinuation of IMP. Strategy for addressing ICEs: • For the binary endpoint of occurrence of receiving rescue therapy, the intercurrent event will be ignored and data will be analyzed as collected (treatment policy strategy). • For the time to event endpoint of time to first rescue therapy, any participant who prematurely discontinued IMP prior to receiving rescue therapy will be censored at the time of the ICE (hypothetical strategy).
Population-Level Summary	• Difference in proportions of participants who received rescue therapy in the mezagitamab group compared to the placebo group. • Hazard ratio of the mezagitamab group to the placebo group.

Table 31. Estimand Framework for Secondary Endpoint Relating to Participant-Reported Symptoms

Definition	The effect of mezagitamab on ITP symptoms compared to placebo.
Trial Intervention	Two cycles of mezagitamab 600 mg or placebo, separated by an 8-week dosing-free period; each cycle consists of once-weekly dosing for 8 weeks.
Population	Full analysis set.
Variable (or Endpoint)	Change from baseline in the Symptoms scale score of the ITP-PAQ at Week 24.
Strategy for Addressing Intercurrent Event	ICEs: (a) Use of rescue therapy. (b) Premature discontinuation of IMP. Strategy for addressing ICEs: • For participants impacted by ICE (a), scores from the time of event through EOT will be set to worst score observed (including baseline score) for each participant (composite strategy). • For participants impacted by any ICE (b), scores from the time of event through EOT will be collected and used regardless of whether the intercurrent event occurred (treatment policy strategy).
Population-Level Summary	Difference in the change from baseline between the mezagitamab group and the placebo group.

Safety Objectives and Associated Endpoints

[0745] The safety objectives and associated endpoints are provided in **Table 32**.

Table 32. Safety Objective(s) and Associated Endpoint(s)

Safety Objective	Safety Endpoint
To evaluate the safety and tolerability of mezagitamab in participants aged ≥18 years with persistent or chronic ITP compared with those receiving placebo.	• Incidence of TEAEs by MedDRA PT occurring in ≥5% of the safety population. • Incidence of TRAEs by MedDRA PT occurring in ≥5% of the safety population. • Incidence of Grade ≥3 TEAEs by MedDRA PT. • Incidence of clinically significant abnormal laboratory test results and vital signs.

Exploratory Objectives and Associated Endpoints

[0746] The exploratory objectives and associated endpoints are provided in **Table 33**.

Table 33. Exploratory Objectives and Associated Endpoints

Exploratory Objective	Exploratory Endpoint
To determine the PD profile of mezagitamab.	• Presence of and changes in PD biomarkers (quantitative IgA, IgM, and IgG) during and after intervention.
To evaluate the effects of mezagitamab compared with placebo on bleeding in participants aged ≥18 years with persistent or chronic ITP.	• Occurrence of bleeding events by grade in each of the Skin, Mucosal, and Organ domains in the ITP-BAT through Week 24.
To evaluate the effects of mezagitamab compared with placebo on health-related quality of life in participants aged ≥18 years with persistent or chronic ITP.	• Change from baseline in the Symptoms, Fatigue/Sleep, Physical Health-Activity, Physical Health-Bother, Psychological Health, Overall Quality of Life, Social Activity, and Work scales scores of the ITP-PAQ through Week 24. • Change from baseline in the Menstrual Symptoms subscale scores of the ITP-PAQ in female participants who had at least one menstrual period within 12 months before the start of the trial through Week 24. • Change from baseline in the Fertility subscale scores of the ITP-PAQ in female participants through Week 24. • Change from baseline in the EQ-5D-5L utility index score and VAS score through Week 24.
To evaluate the immunogenicity of mezagitamab.	• Impact of immunogenicity on PK, efficacy, and safety.

Trial Design

[0747] The trial schema is shown in **Figure 12**.

[0748] Intervention Model: The intervention model for this trial is a parallel group assignment with 2 groups: experimental treatment group and placebo comparator group. Note: the use of

stable background concomitant ITP treatment is allowed in both experimental and placebo groups.

[0749] Trial Duration: The screening period is a maximum of 4 weeks. Eligible participants undergo an 8-week intervention period, an 8-week dosing-free period, and a second intervention period starting at Week 16. The overall trial duration for an individual participant is approximately 28 weeks, including screening, the first intervention period, the dosing-free period, and a second intervention period.

[0750] Method of Assignment to Trial Intervention: When a participant has completed all required screening procedures and all eligibility criteria are met, the participant is randomly assigned to 1 of the 2 trial arms for the duration of the trial. To minimize the potential for bias, treatment assignment remains double-blinded throughout the duration of the trial.

Rationale for Trial Design

[0751] Rationale for Intervention Model: The 2-arm parallel-arm design was selected for this trial to facilitate the simultaneous collection of data from participants receiving mezagitamab or receiving placebo. The random assignment to 1 of the 2 arms with stratification factors ensures that baseline characteristics that may affect trial outcomes are similar between arms. The parallel arm design is aligned with available regulatory guidance for drug development in ITP (EMA/CHMP/153191/2013 "Guideline on the clinical development of medicinal products intended for the treatment of chronic primary immune thrombocytopenia." 20 February 2014.)

[0752] Rationale for Duration: Based on results from the phase 2 trial of mezagitamab in participants with ITP described above, sustained depletion of immunoglobulin G persisted up to 8 weeks after the last (8th weekly) dose of mezagitamab, approximately in parallel with sustained PK concentrations of mezagitamab. Furthermore, the platelet levels were sustained at a level of at least 50,000/μL in approximately 64% of participants at Week 16 (compared with 8% in placebo), illustrating that mezagitamab-treated patients continue to benefit from its pharmacologic effects during the dosing-free period. Beyond Week 16, for most patients, there was a trend towards return to normal levels of the previously depleted immunoglobulins, with a corresponding loss of the durable platelet response. The goal of treatment in chronic/persistent ITP is, in part, to maintain a durable platelet count >50,000/μL long term. This treatment

regimen comprises two 8-week dosing cycles separated by an 8-week dosing-free period over the course of the 24-week trial period. This dosing regimen was designed to rapidly increase and durably maintain platelet count >50,000/μL by maintaining sustained PK concentrations and high target engagement while enabling a dosing-free period after each 8-week dosing cycle.

[0753] Rationale for Endpoints: The primary and secondary endpoints were designed to assess rapidity and durability of platelet response in alignment with the goal of treatment in ITP, namely, to achieve and maintain the platelet count above a safe level and minimize the risk for bleeding. The endpoints were designed to further characterize the nature, rapidity, magnitude and durability of ITP disease control achieved by mezagitamab relative to placebo through Week 24 of the trial. The safety endpoints were selected to provide comprehensive analysis of adverse events, immunogenicity, and other data relevant to evaluate the benefit-risk profile of treatment with mezagitamab for patients with persistent or chronic ITP. The exploratory endpoints were selected to further characterize the pharmacokinetic (PK) and pharmacodynamics (PD) of mezagitamab and the effects of treatment on symptoms and health-related quality of life.

[0754] Rationale for Comparator: No active comparator has been selected in the trial because of the unavailability of effective options for ITP patients who have an insufficient response or intolerance to available first- and second-line agents. In both trial arms, the use of concomitant ITP treatment is allowed and is individualized with the investigator having the discretion to maintain stable dosing and frequency of ongoing standard of care therapy. Additionally, participants may receive rescue therapy if their platelet count is <50,000/μL and at risk for bleeding at any point during the trial. Placebo-controlled design is aligned with available regulatory guidance (EMA/CHMP/153191/2013 "Guideline on the clinical development of medicinal products intended for the treatment of chronic primary immune thrombocytopenia." 20 February 2014 and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E10 "Choice of Control Group and Related Issues in Clinical Trials." 20 July 2000.)

[0755] Other Design Considerations: This trial collects race and ethnicity parameters. Race and ethnicity data are collected in this trial to understand how similar the trial population is to the population with ITP at large and to help researchers understand if the efficacy and/or safety of mezagitamab could be different for people of different races or ethnicities. The predosing

criteria have been designed with the mechanism of action and pharmacodynamics of mezagitamab in mind and are intended to be simple and safe to implement.

[0756] The Phase 3 cyclic dosing regimen for mezagitamab was informed by 3 factors:

- The unique mechanism of action of mezagitamab, which results in sustained depletion of long-lived plasma cells (and other immune cells) responsible for producing pathogenic antiplatelet antibodies;
- The sustained effects on platelet response up to, and in some cases, beyond 8 weeks post-dosing as seen in the phase 2 trial of mezagitamab in participants with ITP; and
- The desire for a dosing scheme that provides a durable therapeutic effect, limits the potential for safety issues by having a dosing-free period after the initial 8 doses (when immunoglobulin depletion remains in the therapeutic range), and safely affords the participant a predictable dosing-free period.

Access to Trial Intervention After End of Trial

[0757] All participants who complete the pivotal trial are able to enroll in a separate continuation trial. Participants in the continuation trial are able to receive mezagitamab regardless of treatment assignment in the pivotal trial. The continuation trial allows for continued dosing of mezagitamab for eligible participants. Continued access to mezagitamab for participants in the continuation trial is managed at the investigator's discretion to ensure optimal care.

Trial Population

[0758] Selection of Trial Population: Participants aged ≥18 years who have had a diagnosis of primary ITP for at least 3 months and an insufficient response or intolerance to at least 1 currently available first-line therapy for treatment of ITP and at least 1 currently available second-line therapy for treatment of ITP are enrolled in this trial if all selection criteria are met.

[0759] Rationale for Trial Population: The selection criteria for this trial were designed to facilitate enrollment of participants who reflect the general population of patients with persistent or chronic primary ITP who have had insufficient response or intolerance to first- and second-line ITP treatment. To reflect the broad range of therapies that patients may use in

clinical practice, participants are allowed to enter having received varying numbers of prior ITP therapies or types of therapy (with a minimum of two lines of treatment), and they are allowed to enter regardless of whether they are currently on a standard-of-care ITP treatment. Individuals who do not meet criteria for trial eligibility are enrolled via protocol waivers or exemptions.

Inclusion Criteria

[0760] An individual eligible to participate in this trial meets all the following criteria:

1. The participant is aged ≥18 years at the time of signing the ICF.
2. The participant has provided informed consent (that is, in writing, documented via a signed and dated ICF) and any required privacy authorization before the initiation of any trial procedures.
3. The participant has been diagnosed with primary ITP that has persisted for at least 3 months. Diagnosis is in accordance with The American Society of Hematology 2019 Guidelines for ITP (Neunert *et al.* Blood Adv (2019) 3 (23): 3829–3866) or the Updated International Consensus Report on The Investigation and Management of Primary ITP (Provan *et al.* Blood Adv (2019) 3 (22): 3780–3817), as locally applicable.
4. The participant's diagnosis of ITP is supported by a prior response to an ITP therapy (not including a TPO-RA), defined as having achieved a platelet count ≥50,000/mL.
5. The participant has evidence of insufficient response or intolerance to at least 1 currently available first-line therapy for treatment of ITP (for example, corticosteroids) and at least 1 currently available second-line therapy for treatment of ITP (for example, TPO-RA, rituximab, fostamatinib, mycophenolate). Insufficient response to previous treatment is defined as failure to achieve a sustained platelet count of at least 50,000/μL or doubling of baseline platelet count after an appropriate course of prior ITP treatment. Intolerance is defined as a documented side effect causing discontinuation of the therapy.

6. The participant has a mean platelet count of <30,000/μL (with individual values ≤35,000/μL) from at least 2 consecutive measurements taken at least 5 days apart between the signing of the ICF and Day 1, including at least 1 of those measurements within 7 days before the first dose of IMP (Day 1).

7. If the participant is receiving allowed standard-of-care treatment for ITP at screening and continued use is intended, treatment may continue during the trial if the dose and frequency have been stable for at least 4 weeks before receiving the first dose of IMP (*i.e.*, Day 1) and are expected to remain stable throughout the trial. Permitted concomitant treatments may include 1 medication from each of the following 3 categories:

    a. One thrombopoietin receptor agonist (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag), and/or
    b. One oral corticosteroid given daily or every other day (not to exceed prednisone 20 mg daily or equivalent dose), and/or
    c. Fostamatinib.

8. If participants do not plan to continue these agents during the trial, they are washed out.

9. If the participant is an individual with potential for pregnancy, the participant is not pregnant as confirmed by negative human chorionic gonadotropin during screening and before the first dose of trial intervention.

10. If enrolled at a site in Japan, the participant has a documented negative *Helicobacter pylori* test result at or after diagnosis of ITP or has documented history of successful *H. pylori* eradication therapy at least 12 weeks before Day 1.

Exclusion Criteria

[0761] An individual who meets any of the following criteria is excluded from participation in this trial:

1. In the investigator's opinion, the participant is unwilling and/or unable to understand and fully comply with trial procedures and requirements (including digital tools and applications).
2. The participant has secondary ITP (drug-induced or clear association with another medical condition such as autoimmune thyroid disease, systemic lupus erythematosus, *H. pylori* infection, lymphoma, chronic lymphocytic leukemia, viral infection, etc.).
3. The participant has had any thrombotic or embolic event within 12 months before signing the ICF.
4. The participant has had a splenectomy within 3 months before signing the ICF. Note: Due to increased risk of infection, splenectomized participants should be up to date with vaccinations and receiving appropriate prophylaxis.
5. The participant has active infection with hepatitis B virus, hepatitis C virus, or human immunodeficiency virus (HIV).
6. The participant has had any of the following types of infections within the specified timeframes:
    a. Active bacterial, viral, fungal infection (except for the common cold and onychomycosis), or any other serious infection within 2 weeks of signing the ICF. Any anti-infective course for infection is completed at least 2 weeks before Day 1.
    b. SARS-CoV-2 infection within 4 weeks of signing the ICF.
    c. Opportunistic infection or treatment for an opportunistic infection ≤12 weeks before signing the ICF.
7. History of malignancy (including myelodysplastic syndrome) within 5 years of signing the ICF, except for treated non-melanoma skin cancer or cervical carcinoma in situ.

8. The participant has (1) been diagnosed with or has suspected chronic obstructive pulmonary disease (COPD) or asthma and (2) has a prebronchodilatory forced expiratory volume in 1 second <50% of predicted normal at screening.

9. In the opinion of the investigator, the participant is currently experiencing any medical condition that might interfere with participation in the trial (*e.g.*, significant ocular, cardiovascular, pulmonary, hematologic, gastrointestinal, endocrinologic, hepatic, renal, neurologic, malignancy, infectious disease, immunodeficiency, or alcohol and drug abuse), that poses an added risk for the participant, or could confound the assessment of trial results.

10. In the opinion of the investigator, the participant has a serious medical or psychiatric illness that could potentially interfere with the completion of treatment according to this protocol.

11. The participant has received anti-CD20 treatment within 12 months before screening and either of the following applies:

    a. The last dose was received within 6 months before screening.
    b. The last dose was received between 6 and 12 months before screening and the participant has a CD19+ count below the lower limit of normal.

12. The participant has received any monoclonal or polyclonal antibody for immunomodulation within 6 months before Day 1.

13. The participant has been exposed to mezagitamab or participated in any other investigational drug trial (including prior other anti-CD38 or vaccine trials) or has been exposed to another investigational agent within 4 weeks or 5 half-lives, whichever is longer, before Day 1.

14. The participant has used anticoagulants (*e.g.*, vitamin K antagonists, direct oral anticoagulants) within 3 weeks prior to the first dose of trial treatment.

15. The participant has received a live or live-attenuated vaccine within 4 weeks prior to the first dose of trial treatment or has any live or live-attenuated vaccine planned during the trial.

16. The participant has used the following immunosuppressive agents as specified prior to the first dose of trial treatment: alkylating agents (*e.g.*, cyclophosphamide) within 8 weeks, vinca alkaloids (*e.g.*, vincristine) within 4 weeks, sulfones (*e.g.*, dapsone) within 3 weeks, antiproliferative agents: (*e.g.*, mycophenolate mofetil and azathioprine) within 2 weeks, and calcineurin inhibitors: (*e.g.*, cyclosporine) within 2 weeks.

17. The participant has used intravenous immunoglobulin (IVIg), SC immunoglobulin, recombinant human thrombopoietin, anti-D immunoglobulin treatment, or efgartigimod within 4 weeks before signing the ICF or it is expected that any treatment for thrombocytopenia other than the participant's standard-of-care ITP therapy (*e.g.*, rescue therapy, administration of blood products) may be used between screening and Day 1.

18. The participant has a history of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in the mezagitamab/placebo formulation.

19. The participant has any of the following clinically significant laboratory abnormalities at screening:

    a. Alanine aminotransferase or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN).
    b. Total bilirubin >1.5 × ULN. (Note: Participants with a diagnosis of Gilbert syndrome are not excluded based on this criterion.)
    c. Absolute neutrophil count <1000/mm^3.
    d. Hemoglobin <9 g/dL.
    e. IgG <500 mg/dL.
    f. Lymphocyte count <500/mm^3.
    g. Estimated glomerular filtration rate <30 mL/min.

20. Is capable of breastfeeding but does not agree to forego breastfeeding from first dose of IMP through 30 days after the last dose of IMP.

21. The participant is an individual with potential for pregnancy but does not agree to use at least 1 form of highly effective contraception and 1 barrier method of

contraception (preferably male condom) when engaging in heterosexual sex until at least 150 days after the last dose of IMP.

22. The participant is a sexually active, non-sterilized individual who produces sperm but does not agree to use a barrier method (preferably male condom) combined with at least 1 form of highly effective contraception for any partner(s) with potential for pregnancy when engaging in heterosexual sex until at least 150 days after the last dose of mezagitamab.

Screen Failure Categorization, Information Collection, and Other Procedures

[0762] All An individual who has provided informed consent to participate in the trial may be categorized as a screen failure for any of the following reasons: (i) did not meet entrance criteria; (ii) adverse event; (iii) lost to follow-up; (iv) pregnancy; (v) withdrawal by participant; (vi) met eligibility criteria but not needed; (vii) trial terminated by sponsor; (viii) other.

[0763] Participants are not considered screen failures if they were randomized but not treated.

[0764] Information about screen failures is collected via the electronic case report forms (eCRFs), including participant identification, screening disposition (including the reason for screen failure), demography, inclusion/exclusion criteria, and AEs (if applicable). If a potential participant experiences a serious adverse event (SAE) during screening, all of the participant's screening eCRFs is available for collection.

Trial Intervention and Concomitant Therapy

[0765] This trial has the following Investigational Medicinal Products: (i) mezagitamab (experimental therapy); and (ii) placebo (control) (**Table 34**). This trial uses the following Auxiliary Medicinal Product(s): (a) corticosteroids; (b) antipyretics; (c) antihistamines; (d) leukotriene receptor agonists; (e) intravenous immunoglobulin infusion therapy; and (f) platelet transfusion (**Table 35**).

Table 34. Description of Trial Intervention

Product name	**Mezagitamab**	**Placebo**
Designation	Investigational medicinal product (IMP) (investigational product)	IMP (placebo)

Identification in the Protocol	Mezagitamab	Placebo
Active Substance	Mezagitamab	None
Dose Formulation	Solution for injection	Solution for injection (to match mezagitamab solution for injection)
Dose Strength(s)	150 mg/mL	NA
Route of Administration	SC injection	SC injection
Dosage Level(s)	600 mg (as two 300 mg vials)	Placebo volume to match mezagitamab 600 mg (as two 300 mg vials)
Dose Regimen	QW	QW
Duration	8 weeks per cycle	8 weeks per cycle
Arm (participants receiving the medicinal product)	First intervention period: Random assignment for all participants Second intervention period: Participants who received mezagitamab in the first intervention period.	First intervention period: Random assignment for all participants Second intervention period: Participants who received placebo in the first intervention period.

Table 35. Table of Auxiliary Medicinal Products

Medication Type	**Corticosteroid**	**Antipyretics**	**Antihistamines**	**Leukotriene-receptor agonist**	**Short-acting ß2-adrenergic receptor agonist**	**Long-acting ß2-adrenergic receptor agonist**	**Intravenous Ig Infusion Therapy**	**Platelet Transfusion**	**Corticosteroid**
Designation	AxMP (other – premedication)	AxMP (other – premedication)	AxMP (other – premedication)	AxMP (other – premedication)	AxMP (other – premedication)	AxMP (other – premedication)	AxMP (rescue medicine)	AxMP (rescue medicine)	AxMP (rescue medication)
Identification in the Protocol	**ATC Class** Methyl-prednisolone [a] H02AB04 Additional allowed equivalents: Dexamethasone H02AB02; Hydrocortisone H02AB09: Prednisolone H02AB06; Prednisone H02AB07	**INN/active substance** Paracetamol (acetaminophen)	**INN/active substance** 1st choice: Cetirizine 2nd choice (equivalent medications. if first choice not available): Desloratidine Fexofenadine Loratidine Chlorpheneramine Hydroxyzine Diphenydramine Famotidine	**INN/active substance** 1st choice: Montelukast 2nd choice (equivalent medications. if first choice not available): Zafirlukast	**ATC Class** R03AC Selective beta-2-adrenoreceptor agonists	**ATC Class** R03AK Selective beta-2-adrenoreceptor agonists	**ATC Class** Human normal Ig (IVIg)	**ATC Class** Thrombocytes	**ATC Class** Prednisone H02AB07 Additional allowed equivalents: Methyl-prednisolone H02AB04 Dexamethasone H02AB02: Hydrocortisone H02AB09; Prednisolone H02AB06
ATC Code	H02AB04 or H02AB02, H02AB09; H02AB06; H02AB07 Selected glucocortico-steroids	NA (classified as INN/Active Substance)	NA (classified as INN/Active Substance)	NA (classified as INN/Active Substance)	R03AC	R03AK	J06BA02 Immunoglobulins, normal human, for intravascular administration.	B05AX02 Thrombocytes	H02AB04 or H02AB02, H02AB09; H02AB06; H02AB07 Selected glucocortico-steroids

Medication Type	Corticosteroid	Antipyretics	Antihistamines	Leukotriene-receptor agonist	Short-acting ß2-adrenergic receptor agonist	Long-acting ß2-adrenergic receptor agonist	Intravenous Ig Infusion Therapy	Platelet Transfusion	Corticosteroid
Active Substance	NA (ATC Class Identification)	Paracetamol (acetaminophen)	**1st choice: Cetirizine** 2nd choice (equivalent medications): Desloratadine Fexofenadine Loratadine Chlorpheniramine Hydroxyzine Diphenhydramine Famotidine	**1st choice: Montelukast** 2nd choice (equivalent medications): Zafirlukast	NA (ATC Class Identification)	NA (ATC Class Identification)	NA (classified as per ATC Code)	NA (classified as per ATC Code)	NA (ATC Class Identification)
Dose Formulation	NA (ATC Code Identification)	Capsule. (Coated) Tablet	Tablet	Tablet	NA (ATC Class Identification)	NA (ATC Class Identification)	NA (ATC Code Identification)	NA (ATC Code Identificatio n)	NA (ATC Code Identification)

Medication Type	Corticosteroid	Antipyretics	Antihistamines	Leukotriene-receptor agonist	Short-acting ß2-adrenergic receptor agonist	Long-acting ß2-adrenergic receptor agonist	Intravenous Ig Infusion Therapy	Platelet Transfusion	Corticosteroid
Dose Strength(s)	NA (ATC Code Identification)	325 mg 500 mg	Cetirizine: 10 mg If first choice not available: Equivalent medications: Desloratadine: 5 mg or Fexofenadine: 180 mg or Loratadine: 10 mg or Chlorpheniramine: 24 mg or Hydroxyzine: 75-100 mg or Diphenhydramine: 25-50 mg PO or Famotidine: 20 mg	Montelukast: 10 mg If first choice not available: Equivalent medications: Zafirlukast: 40 mg	NA (ATC Code Identification)	NA (ATC Code Identification)	NA (ATC Code Identification)	NA (ATC Code Identification)	NA (ATC Code Identification)
Route of Administration	PO	PO	PO	PO	III	III	IV	IV	PO
Dosage Level(s)	As indicated in product label	As indicated in product label	As indicated in product label	As indicated in product label	As indicated in product label	As indicated in product label	As indicated in product label	As indicated in product label	As indicated in product label
Dose Regimen	Per product labelling	Per product labelling	Per product labelling	Per product labelling	Per product labelling	Per product labelling	Per product labelling		
Duration	As needed (per product labelling)	As needed (per product labelling)	As needed (per product labelling)	As needed (per product labelling)	As needed (per product labelling)	As needed (per product labelling)	As needed (per product labelling)	As needed (per product labelling)	As needed (per product labelling)

AxMP: auxiliary medicinal product; ATC: Anatomical Therapeutic Chemical; EEA: European Economic Area; EU: European Union; Ig: immunoglobulin; IH: inhaler; INN: international nonproprietary name; IV: intravenous; IVIg: intravenous immunoglobulin; NA: not applicable; PO: oral; QD: daily
a Methylprednisolone or equivalent used per institutional standards or investigator discretion.

Rationale for Trial Intervention

[0766] The selected dosing regimen for this phase 3 trial in patients with persistent or chronic ITP is an 8-week course of 600 mg QW subcutaneous administration, followed by an 8-week dosing-free period, followed by an 8-week course of 600 mg QW subcutaneous administration. This dosing regimen is designed to provide sustained mezagitamab drug concentrations and maintain high target engagement (*i.e.*, receptor occupancy) over entire study duration. The regimen also considers the mechanism of action of mezagitamab and its ability to deplete multiple components of both the humoral and cellular immune system, which are responsible for heterogeneous ITP pathogenesis. The depleted cells include, but are not limited to, plasma cells, NK cells, and a subset of B and T cells. The depletion of some of these cells is beneficial in the long-term management of ITP, but also may be associated with risk for infection, if excessive.

[0767] The dosing schedule also acknowledges the chronic nature of ITP and that in most cases patients require long-term treatment. Thus, the cyclic regimen, based on its mechanism of action and targeted pharmacodynamic effect, maximizes the potential for patient benefit in a difficult-to-treat refractory ITP population, without significant tolerability or safety concerns. This regimen also safely affords the ITP patient some predictable time off therapy. Additionally, the dosing regimen with mezagitamab is intended to align with the goals of treatment in ITP, namely rapid and durable platelet response, and is supported by the totality of available nonclinical and clinical safety/efficacy data, including results of clinical pharmacology and quantitative assessments.

[0768] A fixed dose **is** administered in this trial, as body weight is not expected to have a clinically significant factor on the disposition of mezagitamab. As mezagitamab is a mAb, the anticipated elimination routes are via proteolytic catabolism and intracellular degradation after binding to its target. Both of these clearance mechanisms are not thought to be significantly influenced by body weight. Additionally, the Vd of mAbs is generally limited to the volume of the blood and extracellular fluids, such that body composition is a less important determinant of Vd compared with small molecule drugs (Hendrikx et al. 2017, Fixed Dosing of Monoclonal Antibodies in Oncology, Oncologist, incorporated herein by reference in its entirety).

Dosing and Administration

[0769] Participants receive mezagitamab or placebo during the intervention periods. Participants undergo a predosing criteria assessment before each dosing event; if participants meet the predosing criteria, they are given appropriate prophylactic.

Predosing Criteria Assessment

[0770] Investigators evaluate participants before each mezagitamab/placebo dose on the basis of the predosing criteria. For the first dose of each trial intervention period, laboratory assessments for the predosing criteria may be evaluated using results obtained within the previous 7 days; for all other doses, laboratory results are obtained on the day before or the day of dosing.

[0771] If clinical parameters do not meet criteria for continued dosing, the participant's dosing is temporarily withheld until parameters meet dosing levels or the participant is discontinued from trial dosing or in accordance with the investigator's judgment.

[0772] Participants whose clinical parameters meet the dose discontinuation criteria are permanently discontinued from dosing. In addition to the dose discontinuation criteria shown in **Table 36**, participants should be permanently discontinued from trial dosing in any of the circumstances described below.

Table 36. Predosing Assessment Criteria

Safety Parameter	Dosing Decision	
	Hold [a]	Discontinue [b]
Laboratory Investigations		
Platelet count	≥250,000/μL	
Absolute neutrophil count	<750/mm^3	
Absolute lymphocyte count	<500/mm^3	
Absolute IgG [c]	≤1/2 of LLN	
Clinical Events		
Anaphylaxis		Any event
Hypersensitivity reaction other than anaphylaxis (*i.e.*, allergic reaction, CRS) [d, e]		Grade ≥3
Systemic infection	Grade 2 or 3 Hold dosing until the infection is resolved.	Grade >3 **or** opportunistic infections requiring hospitalization.

CRS: cytokine release syndrome; LLN: lower limit of normal; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] Participants whose clinical parameters, as shown in the above table, meet dose hold criteria do not receive the scheduled dose; instead, they return for reassessment and evaluation at the next planned visit.

[b] Participants whose clinical parameters meet dose discontinuation criteria are to be permanently discontinued from mezagitamab/placebo. Standard-of-care ITP therapy is managed according to the investigator's discretion.

[c] Quantitative immunoglobulins are tested at a central laboratory and sites are blinded to the results. Sites are notified if the dose hold criterion is met.

[d] Allergic reactions (including anaphylaxis and other hypersensitivity reactions) are classified according to the World Allergy Organization Anaphylaxis Guidance (Cardona et al., 2020. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J. 13(10), 100472).

[e] CRS is classified in accordance with . Infection grading is based on NCI CTCAE, version 6.0.

Mezagitamab/Placebo Administration

[0773] Mezagitamab or placebo is administered only to eligible participants under the supervision of the investigator or properly trained site staff according to the trial delegation log.

[0774] After completion of all screening assessments and procedures and confirmation of eligibility, participants begin dosing of mezagitamab or placebo (in accordance with random treatment assignment) on Day 1 at the trial site. The participant and all site personnel are blinded to treatment assignment. Before the start of mezagitamab or placebo administration, participants receive premedication and complete safety assessments.

[0775] Before each dose of mezagitamab or placebo, investigators evaluate participants according to the predosing criteria; clinical parameters meet the criteria for dosing before mezagitamab or placebo is administered.

[0776] During each intervention period, participants receive mezagitamab or placebo once weekly for 8 weeks via SC injections. Two injections are required to administer the full dose of mezagitamab or placebo at each dosing visit. On the first dose of each intervention period, the second of the 2 injections is administered approximately 30 minutes after the first injection to mitigate the potential risk of hypersensitivity reaction. If the participant does not have a clinically significant hypersensitivity reaction (per the investigator's judgment) on the first dosing day of each intervention period, the mezagitamab or placebo may be given without a waiting period between the 2 injections at subsequent dosing visits in that intervention period.

Postdose Monitoring

[0777] After the first and second mezagitamab or placebo dosing events of each cycle, participants are closely monitored in the clinic for at least 2 hours after receiving the second injection. Postdose monitoring procedures includes vital signs assessments, as well as any additional assessment and observations deemed necessary based on the investigator's medical judgment and as warranted by exhibited clinical signs or symptoms at each trial clinic visit. Before discharge from the clinic, the possible signs and symptoms of anaphylactic reactions and cytokine release syndrome are reviewed with participants. Postdose medication may be given.

Prophylactic Coadministration

[0778] Pre- and postdose prophylactic medications are administered to all participants, regardless of treatment assigned, for prevention of hypersensitivity reactions; an equivalent medication can be substituted for an individual medication as needed. If any of these medications raise safety concerns for an individual participant, a potential alternative regimen may be used after approval from the sponsor or designee.

[0779] Prophylactic Coadministration Regimen: To prevent possible hypersensitivity reaction after dosing events, prophylactic medications are administered according to the schedule outlined in **Table 37**. Premedications are administered approximately 1 to 3 hours before the dose of mezagitamab/placebo. Based on the timing of the risk of hypersensitivity reaction, this ensures

that therapeutic levels of these medications are present at the expected time of maximum mezagitamab exposure.

Table 37. Prophylactic Coadministration Regimen for Mezagitamab or Placebo Dosing

	Dose 1 of Each Intervention Period			Doses 2-8 of Each Intervention Period
		If Clinically Indicated:		
Medication	**Day 1 (Day of Dose) [a]**	**Day 2**	**Day 3**	**Day of Dose [a]**
Corticosteroid: methylprednisolone 40 mg orally [c]	X	None	None	None
Antipyretic: acetaminophen 500-1000 mg orally [c]	X	X	X	X
Antihistamines:				
Cetirizine 10 mg orally or IV [c]	X	X	X	X
Famotidine 20 mg orally or IV [c]	None	X	X	None
Day numbers in this table are relative to the start of each intervention period. [a] Prophylactic medications given on day of dosing are administered approximately 1 to 3 hours before mezagitamab or placebo injection. [c] Or equivalent.				

[0780] Postdose Medication: If clinically indicated, and in consultation with and approval from the medical monitor or medical director, an antipyretic (acetaminophen 500-1000 mg orally, or equivalent) and an antihistamine (cetirizine 10 mg orally or intravenously, or equivalent) is given as postdose medication on the day of dosing; these medications also may be be given on Days 2 and 3 (Week 0) and Days 114 and 115 (Week 16). Additional postdose medications may be considered for participants with respiratory complications (*e.g.*, history of asthma or COPD).

[0781] Additional Considerations for Participants with Respiratory Complications: Participants with a higher risk of respiratory complications (*e.g.*, history of COPD, asthma) may be administered the following prophylactic medications before or after each dose of mezagitamab or placebo at the investigator's discretion and after consultation with the medical monitor and/or sponsor, when possible: (i) antihistamines, oral cetirizine (10 mg) and oral famotidine (20 mg) or equivalent; (ii) leukotriene-receptor antagonist, oral montelukast (10 mg) or equivalent.

[0782] In addition, it is expected that participants with respiratory complications defer to their prescribed treatment and continue to use medications as prescribed to control their asthma or

COPD. In the event that recommendations are needed for prophylactic administration for participants with respiratory complications, the following are permitted medications for control of asthma or COPD. Asthma: Short-acting ß2-adrenergic receptor agonist, such as salbutamol (albuterol) aerosol; inhaled corticosteroids with or without long-acting β2 adrenergic receptor agonists. COPD: Short-acting ß2-adrenergic receptor agonist, such as salbutamol (albuterol) aerosol; long-acting bronchodilators, such as tiotropium or salmeterol, with or without inhaled corticosteroids.

[0783] Trial Intervention Dose Modification: If a participant has clinical parameters that do not meet the criteria for continued dosing, mezagitamab/placebo is temporarily withheld or discontinued. Dosing of mezagitamab or placebo may not otherwise be reduced or escalated for any given participant.

Participant Assignment, Randomization, and Blinding

[0784] Participant Assignment: Participants are randomly assigned on Day 1 to receive mezagitamab or placebo in a 2:1 ratio for both intervention periods based on a blinded randomization.

[0785] Randomization: This is a double-blind, placebo-controlled trial. Participants are randomly assigned to a trial arm on Day 1, based on a computer-generated randomization schedule generated by IRT using a validated software package. Randomization is stratified by baseline platelet count ($< \text{or} \geq 15{,}000/\mu L$ based on local laboratory results), splenectomy status (yes or no), and use of background concomitant standard-of-care ITP therapy (yes or no). All participants are centrally assigned to randomized trial intervention using IRT.

[0786] Blinding and Unblinding: This is a double-blind trial in which participants and trial personnel (including investigators, site personnel, the contract research organization (CRO), the medical monitor, trial clinicians, and the sponsor) are blinded to trial intervention assignments. Placebo and mezagitamab solutions are identical in appearance and are provided in vials that are indistinguishable as to treatment assignment. Specifically, a yellow wrap-around label will be applied to the vials to mask the difference between mezagitamab and placebo, and a black wrap-around label will be applied at the crimp of the vial to mask the lot numbers on the vials.

[0787] Emergency Unblinding: In case of an emergency, the investigator has the sole responsibility for determining if unblinding of an individual participant's intervention assignment is warranted. Participant safety is always the first consideration in making such a determination. The trial intervention blind is not broken by the investigator unless information concerning the trial intervention is necessary for the medical treatment of the participant. In the event of a medical emergency, the medical monitor and the sponsor's trial clinician are contacted, if possible, before the trial intervention blind is broken to discuss the need for unblinding. If the investigator decides that unblinding is warranted, the investigator makes every effort to contact the sponsor before unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. The investigator initiates unblinding using the IRT.

Concomitant Therapy

Prohibited Concomitant Therapy

[0788] In addition to participants not being permitted to receive prohibited concomitant therapies before trial entry for the time periods, participants do not receive prohibited concomitant therapies throughout the dosing and dosing-free periods unless used as described in **Table 38**. Exceptions are allowed for treatment of adverse events (AEs) after discussion and agreement between the sponsor and investigator.

[0789] It is preferred that participants remain on a standard-of-care ITP therapy that has been stable for at least 4 weeks prior to the first dose of trial treatment. If there is not a plan to continue use of such agents at the time of randomization, then washout of the agent is required as specified below. At a minimum, washout of any agent prior to Day 1 is 5 half-lives or 2 weeks, whichever is longer, unless specified.

[0790] Any participant who receives prohibited concomitant therapy during an intervention period that is not a rescue therapy or background standard-of-care allowed is prematurely discontinued from treatment at the discretion of the sponsor. Receipt of the prohibited concomitant medication requires immediate discontinuation of mezagitamab/placebo. If a participant is discontinued, the EOT (Week 24) assessments are completed. Participants who receive prohibited therapy during the dosing free period continue trial visits.

Table 38. Prohibited Concomitant Therapies

Category or Agent	Washout Period	Additional Considerations
Anticoagulants	3 weeks prior to first dose of trial treatment	
IVIg or anti-D immunoglobulins	4 weeks prior to first dose of trial treatment	IVIg may be given as rescue therapy
Recombinant human thrombopoietin (rhTPO)	4 weeks prior to first dose of trial treatment	
Efgartigimod	4 weeks prior to first dose of trial treatment	If received during intervention period then participant is discontinued.
Anti-CD20 or other anti-B-cell monoclonal or polyclonal antibodies	6 months prior to first dose of trial treatment If the last dose was received between 6 and 12 months prior to first dose of trial treatment, the participant must have a CD19+ count above the lower limit of normal.	If received during intervention period then participant is discontinued.
Alkylating agents (*e.g.*, cyclophosphamide)	8 weeks prior to first dose of trial treatment	If received during intervention period then participant is discontinued.
Antiproliferative agents (*e.g.*, mycophenolate mofetil and azathioprine)	2 weeks prior to first dose of trial treatment	If received during intervention period then participant is discontinued.
Calcineurin inhibitors (*e.g.*, cyclosporine)	2 weeks prior to first dose of trial treatment	If received during intervention period then participant is discontinued.
Sulfones (*e.g.*, dapsone)	3 weeks prior to first dose of trial treatment	If received during intervention period then participant is discontinued.
Vinca alkyloids (*e.g.*, vincristine)	4 weeks prior to first dose of trial treatment	If received during intervention period then participant is discontinued.
Live or live-attenuated vaccinations	4 weeks prior to first dose of trial treatment	
Investigational agents	5 half-lives or 4 weeks prior to trial treatment, whichever is longer	If received during intervention period then participant is discontinued.
Other agents used to treat ITP, including traditional medicine or supplements	5 half-lives or 2 weeks prior to trial treatment, whichever is longer	If received during intervention period then participant is discontinued.
ICF: informed consent form; ITP: immune thrombocytopenia; IVIg: intravenous immunoglobulin.		

Permitted Concomitant Therapy

[0791] Participants who received a standard-of-care ITP therapy that has remained stable in dose and frequency for at least 4 weeks before Day 1 and is expected to remain stable throughout the trial continue using this therapy throughout participation in the trial.

[0792] Permitted standard of care ITP therapies are approved for use within the region in which they are administered and may include 1 medication from each of the following 3 categories:

- One thrombopoietin receptor agonist (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag), and/or
- One oral corticosteroid given daily or every other day (not to exceed prednisone 20 mg daily or equivalent dose), and/or
- Fostamatinib.

[0793] If there is not a plan to continue standard-of-care ITP therapy at the time of randomization, washout of these agents is required prior to first dose of trial treatment. Required washout periods are as follows:

- 3 weeks prior to first dose of trial treatment: romiplostim
- 2 weeks prior to first dose of trial treatment: other thrombopoietin receptor agonists (*e.g.*, eltrombopag, avatrombopag and hetrombopag), corticosteroids and fostamatinib.

Rescue Therapy

[0794] If a participant's platelet count is <50,000/μL at any point during the trial, rescue therapy is given if either of the following criteria are met:

- Participant is at immediate risk of bleeding or has clinically significant active bleeding.
- Participant requires surgery that cannot be postponed until after trial completion.

[0795] The allowed rescue therapy includes one of the following at a given time:

- A platelet transfusion.

- IVIg: up to 1 g/kg total, given over 1 to 5 days. (Japan-specific note: IVIg treatment of 200 to 400 mg/kg for up to 5 days is allowed as a one time bridge therapy in Japan.)
- Corticosteroids: 20 mg of prednisone (or equivalent) per day for up to 7 days.

Management of Potential Risks

[0796] Mezagitamab is a human IgG1 mAb directed against human CD38. Based on the mechanism of action of anti-CD38 mAbs, potential risks with mezagitamab treatment include hypersensitivity reactions, changes in hematologic parameters, and infections. Additional information about management of these clinical events is included below.

[0797] In addition, injection site reactions are possible with medications administered subcutaneously; additional information about monitoring and management is presented below.

Injection Site Reactions

[0798] For agents given subcutaneously, injection site reactions are possible and have been reported with anti-CD38 mAbs (Chari et al., 2018, Subcutaneous Daratumumab in Patients with Relapsed or Refractory Multiple Myeloma: Part 2 Safety and Efficacy Update of the Open-Label, Multicenter, Phase 1b Study (PAVO). Abstract No. 1995. Blood, 132(Suppl 1), which is incorporated by reference herein in its entirety). Significant injection site abnormalities have not been observed in rat or monkey nonclinical studies after SC administration of mezagitamab. Participants in this trial are closely monitored for any injection site reaction and are managed with standard medical care.

Hypersensitivity Reactions

[0799] Hypersensitivity reactions, including infusion-related reactions, anaphylaxis, and cytokine release syndrome (CRS), have been reported with other biologic agents and may be seen with mezagitamab. Generally, effects of hypersensitivity can be seen in different organ systems, including skin and eye. Symptoms range from mild skin rash to more severe reactions, including fever, urticaria, wheezing, hypotension, poor perfusion, respiratory arrest, and, rarely, death (Chen et al., 2021, Daratumumab-induced transient myopic shift and its proposed mechanisms. Clin. Exp. Ophthalmol., 49(1), 81-3; Isabwe et al., 2018, Hypersensitivity reactions

to therapeutic monoclonal antibodies: Phenotypes and endotypes. J. Allergy Clin. Immunol., 142(1), 159-70.e2, each of which is herein incorporated by reference in its entirety). Hypersensitivity reactions involving the eye (such as eye swelling, irritation, temporary blurred vision) may also be seen. Nonanaphylactic clinical hypersensitivity occurs within the first hour, but delayed responses have also been reported in the literature with other biologic agents (Ellis and Day, 2003, Diagnosis and management of anaphylaxis. CMAJ, 169(4), 307-11, which is herein incorporated by reference in its entirety).

[0800] CRS represents an important hypersensitivity reaction often associated with the use of mAbs used in anti-inflammatory and antitumor therapies (Bugelski *et al.*, 2009, Monoclonal antibody-induced cytokine-release syndrome. Expert Rev Clin Immunol, 5(5), 499-521; Lee et al., 2014, Current concepts in the diagnosis and management of cytokine release syndrome. Blood, 124(2), 188-95; and Rituxan (rituximab) Injection for Intravenous Use 2019, Prescribing Information. South San Francisco, CA: Genentech, Inc., each of which is herein incorporated by reference in their entirety). Onset of CRS may occur early in therapy, often after the first dose (Lee et al. 2014; Rituxan (rituximab) Injection for Intravenous Use 2019; and Winkler et al., 1999, Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). Blood, 94(7), 2217-24, each of which is incorporated by reference herein in its entirety), because of a high level of activation of the immune system and engagement and proliferation of T cells that can result in increased cytokine release.

[0801] The CRS hallmark is fever. CRS also presents with rash, urticaria, headache, chills, fatigue, nausea, and/or vomiting (Bugelski *et al.*, 2009; Lee et al. 2014). Severe CRS is characterized by severe dyspnea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. The acute respiratory failure may be accompanied by such events as pulmonary interstitial infiltration or edema visible on a chest x-ray. The syndrome frequently manifests within 1 or 2 hours of initiating the first infusion. Participants with a history of pulmonary insufficiency or those with pulmonary tumor infiltration may be at greater risk of poor outcome and should be treated with increased caution. On the basis of outcomes from studies of the anti-CD38 mAb daratumumab, participants with preexisting COPD or asthma may be at particular risk for respiratory complications (such as

bronchospasm) should a hypersensitivity reaction or CRS event occur (Delforge and Ludwig, 2017, How I manage the toxicities in myeloma drugs. Blood (ASH Annual Meeting Abstracts), 129, 2359-67, which is incorporated herein by reference in its entirety). Therefore, if the participant's FEV1 (forced expiratory volume in one second) is <50% of predicted normal, they are excluded from clinical trial participation. Eligible participants with a history of COPD may require additional postdose medications to manage respiratory complications (Darzalex (daratumumab) injection, 2019, Prescribing Information. Horsham, PA, US: Janssen Biotech, Inc., which is incorporated herein by reference in its entirety). To mitigate the potential risk of hypersensitivity reactions in this clinical trial:

- Participants with a history of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in the mezagitamab formulation are not eligible and therefore are not exposed to mezagitamab.
- For all participants, a prophylactic premedication regimen is required before each dosing event. Additional postdose medication can be administered as described above.
- After the first and second mezagitamab or placebo dosing visits of each cycle, *i.e.*, the Week 0 and 1 doses and the Week 16 and 17 doses, participants are carefully monitored in the clinic for 2 hours after the second injection, and any AE is managed in accordance with available guidelines or institutional standards of care (Lieberman et al., 2005, The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol, 115(3 Suppl 2), S483-523; and Sampson et al., 2006, Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol, 117(2), 391-7, each of which is herein incorporated by reference in its entirety).

[0802] Additional blood pressure measurements are assessed any time the participant complains of symptoms consistent with a hypersensitivity reaction. If the participant experiences hypotension (with or without symptoms), intensive blood pressure monitoring according to local

practice is instituted. The participant is not released from the site until blood pressure has returned to Grade 1 or baseline for at least 1 hour.

[0803] Management Recommendations for Hypersensitivity Reactions (Other than CRS): Participants are carefully monitored for signs and symptoms of potential systemic hypersensitivity reactions, including CRS, allergic reactions, or anaphylaxis; management recommendations for CRS are described below. Signs and symptoms of systemic hypersensitivity reactions include rash, urticaria, fever, and/or bronchospasm. Depending on the severity of the reaction, management of hypersensitivity reactions may include discontinuation of mezagitamab/placebo and/or the administration of appropriate medical therapy, including an eye examination, if appropriate/applicable. Recommendations for the management of hypersensitivity reactions (Sampson *et al.* 2006) are presented in **Table 39**.

Table 39. Management Recommendations for Hypersensitivity Reactions (Other Than CRS)

Grade	Clinical Trial Management	Participant Support
1	If full dose of IMP has not been administered, hold dosing until symptoms resolve, at which time the remainder of the dose may be administered.	Monitor closely until resolution of symptoms.
2	If full dose of IMP has not been administered, hold dosing until symptoms resolve, at which time the remainder of the dose may be administered.	Administer appropriate symptomatic and prophylactic medical care; consider postdose medications. For allergic reaction, provide symptomatic treatment (*e.g.*, antihistamines, nonsteroidal anti-inflammatory drugs, epinephrine) as medically appropriate and consider postdose medications.
≥3[a]	Discontinue IMP dosing and complete EOT assessments	Provide symptomatic treatment, including epinephrine, until symptoms resolve. Consider hospitalization as appropriate.
CRS: cytokine release syndrome; EOT: end of trial; IMP: investigational medicinal product. [a] Including any diagnosis of anaphylaxis according to .		

[0804] Management Recommendations for CRS: Immediate clinical assessment and management of symptoms is key to symptom management. Participants are monitored in the

clinic for at least 2 hours after the first and second mezagitamab or placebo dosing visits of each cycle, *i.e.*, the Week 0 and Week 1 doses and the Week 16 and Week 17 doses. Medical symptomatic treatment according to guidelines or institutional standard of care is recommended (Lee et al. 2019). Before discharge from the clinic, the possible signs and symptoms of CRS and anaphylactic reactions are reviewed with participants. Additionally, participants receive information about what to do if emergency care is needed. The grading system for CRS is shown in **Table 40** and additional guidance for clinical trial management and participant support for CRS by grade is presented in **Table 41**.

Table 40. Grading System for CRS

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever [a]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or [b]		
Hypoxia	None	Requiring low-flow nasal cannula [c] or blow-by	Requiring high-flow nasal cannula [c], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (*e.g.*, CPAP, BiPAP, intubation and mechanical ventilation)

ASTCT: American Society for Transplantation and Cellular Therapy; BiPAP: bilevel positive airway pressure; CPAP: continuous positive airway pressure; CRS: cytokine release syndrome; CTCAE: Common Terminology Criteria for Adverse Events.

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

By convention, Grade 5 CRS is defined as death due to CRS in which another cause is not the principal factor leading to this outcome.

[a] Fever is defined as temperature ≥38 °C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

[c] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Source: Adapted from Table 2 ASTCT CRS Consensus Grading in Lee, D. W., Santomasso, B. D., Locke, F. L., Ghobadi, A., Turtle, C. J., Brudno, J. N., et al. 2019. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant,* 25(4), 625-38. (Lee et al. 2019)

Table 41. Management Recommendations for CRS

Grade	Definition	Clinical Trial Management	Participant Support
1	Fever, constitutional symptoms	Hold dosing until symptoms resolve; resume IMP dose after symptom resolution.	Provide vigilant supportive symptomatic treatment, which may include antipyretics, analgesics, and antihistamines.
2	Hypotension, hypoxia, organ toxicity	Discontinue IMP dosing and advance to the end of clinical trial visit procedures.	Provide vigilant supportive symptomatic treatment, which may include antipyretics, analgesics, and antihistamines, with or without tocilizumab or equivalent
≥3	Hypotension, hypoxia, and severe organ toxicity	Discontinue trial dosing and advance to the end of clinical trial visit procedures.	Provide vigilant supportive care, including but not limited to tocilizumab, antipyretics, analgesics, and antihistamines, as medically indicated (Lee et al. 2014).
CRS: cytokine release syndrome; IMP; investigational medicinal product.			

Changes in Hematologic Parameters

[0805] Reductions in platelets, lymphocytes, neutrophils, and red blood cells (RBCs) have occurred in nonclinical studies when mezagitamab has been administered at a dose higher than the no-observed-adverse-effect level. In clinical studies, hematologic parameters have been closely monitored. Participants in this trial are closely monitored for changes in hematologic parameters, including testing of hematologic parameters throughout the trial. If clinical parameters do not meet dosing criteria, clinical trial dosing is temporarily or permanently withheld as outlined above. Medical interventions may be administered according to institutional guidelines.

Infections

[0806] Participants in this trial are monitored for any signs and symptoms of infections throughout the trial. If clinical parameters do not meet dosing criteria, trial intervention is temporarily or permanently withheld as outlined above. Management of infections according to standard medical care is recommended. Investigators ensure that participants who have had splenectomies are up to date in their vaccinations and are receiving appropriate prophylaxis (Lee 2020).

Discontinuation of Trial Intervention and Participant Withdrawal from Trial

Criteria for Permanent Discontinuation of Trial Intervention

[0807] Trial intervention is permanently discontinued for any of the following reasons: pregnancy, and/or clinical parameters meeting criteria outlined above.

[0808] Treatment with trial intervention is also discontinued for any of the following reasons: AE; protocol deviation; symptomatic deterioration; trial termination by sponsor; withdrawal by participant; lost to follow-up; other.

[0809] If early termination occurs, the participant is subsequently encouraged to complete the remaining trial visits with a modified schedule of activities (without dosing-related activities) and completes the EOT assessments, unless the participant withdraws consent for participation or is lost to follow-up, or the trial is terminated. The primary reason for trial intervention discontinuation is recorded. Participants who discontinue/withdraw prematurely from trial intervention for reasons other than safety may be replaced at the discretion of the sponsor.

[0810] Participants who discontinue trial intervention but complete the EOT (Week 24) assessments may still be eligible to enter the continuation trial if all continuation trial eligibility criteria are met.

Temporary Discontinuation or Interruption of Trial Intervention

[0811] Investigators evaluate participants before each dose of trial intervention; if clinical parameters do not meet criteria for continued dosing, the participant's dosing is temporarily withheld until parameters meet dosing levels. During this time, participants continue to follow

all trial-related requirements and complete all other scheduled assessments. Dosing may be temporarily withheld for dose hold criteria and may be resumed once the dose hold criteria are no longer met.

Trial Stopping Rules

[0812] The study is completed as planned unless one or more of the following criteria are met, which will necessitate a temporary suspension or termination of the study: (1) Two (2) or more participants experience ≥ CTCAE Grade 4 hematological events (neutropenia, lymphocytopenia, or anemia) that are considered related to the study drug and confirmed by the investigator; and/or (2) A cumulative total of five (5) or more participants experience ≥ CTCAE Grade 4 systemic infections that are considered related to the study drug and confirmed by the investigator.

[0813] Dosing is paused or suspended at the discretion of the internal safety review committee to review safety data if any of the above stopping criteria are met.

Trial Assessments and Procedures

Screening/Baseline Assessments and Procedures

[0814] Written or electronic informed consent are obtained (signed and dated) before trial assessments and procedures are performed. The screening period for this trial is up to 28 days (Day -28 to Day -1). Assessments and procedures should be performed on schedule. Additional time allowance for most trial procedures and assessments is acceptable in extenuating circumstances (*i.e.*, holidays, vacations, and other administrative reasons) on approval by the medical monitor or delegate; however, these time extensions do not deviate more than 7 days from the scheduled procedural time.

[0815] Procedures conducted as part of the participant's routine clinical management (*e.g.*, blood count) and obtained before signing of the ICF are used for screening or baseline purposes provided the procedures met the protocol-specified criteria and are performed. Assessments performed during the screening period are captured in a screening eligibility checklist, which require review by the medical monitor or sponsor prior to randomization.

Demographics, Medical History, and Medication History

[0816] Demographics: Participant demographic information is collected prior to the participant receiving the first dose of trial intervention. Demographic information obtained includes: (i) age/date of birth at the time of informed consent; (ii) sex; (iii) race (where permitted or required); (iv) ethnicity (where permitted or required), Hispanic or Latino/Not Hispanic or Latino; and (v) height and weight of the participant at screening. Race and ethnicity data are collected in this trial to understand how similar the enrolled population is to the population with ITP at large and to help researchers understand if the efficacy and/or safety of mezagitamab could be different for people of different races or ethnicities.

[0817] ITP History: Current ITP signs and symptoms, as evaluated and scored by disease activity tools, are recorded. Information regarding prior ITP history, including the date of diagnosis, is recorded.

[0818] Medical History: Medical and medication history, including concurrent medical conditions, are collected and recorded in the participant's source documents and in the eCRFs. Medical history obtained includes determining whether the participant has any significant conditions or diseases relevant to the disease under study that resolved before the participant signed the ICF. The complete medical history includes history of eye disease or ophthalmic clinical symptoms (including allergic reactions). If an eye examination has been conducted within the previous year, a copy of the records from the examination is provided to the site as source documentation. COVID-19 infection and vaccination history prior to the trial is recorded as part of medical history. Ongoing conditions are considered concurrent medical conditions. Concurrent medical conditions are those significant ongoing conditions or diseases that are present when informed consent is provided. This includes clinically significant laboratory, electrocardiogram (ECG), physical examination, and/or vital signs abnormalities noted at screening examination, according to the judgment of the investigator. The condition (*i.e.*, diagnosis) is described.

[0819] Prior and Concomitant Treatments/Medications: Prior and concomitant treatments and medications are collected and recorded in the participant's source document and in the eCRF. Such treatments/medications include but are not limited to medications or vaccines; over-the-

counter or prescription medicines; recreational drugs; vitamins; herbal supplements (note that traditional medicine or supplements being used for the purpose of managing platelets or ITP are prohibited); medications relevant to the eligibility criteria; and prior and concomitant ITP medications.

[0820] Prior medications/treatments are defined as those that were received within 30 days before the date of first dose of trial intervention. At the time of medical history recording, any available prior medication/treatment information is collected. Concomitant medications/treatments are defined as those given in addition to the trial intervention between the first dose of trial intervention and Week 24, inclusive. These include concomitant standard-of-care ITP therapy, prophylactic and postdose medications for hypersensitivity, and rescue therapy. Concomitant medications may be prescribed by a physician or obtained by the participant over the counter.

[0821] At each trial visit, participants are asked whether they have taken any medication or received any treatment other than the trial intervention. Information recorded includes trade name and/or international nonproprietary name (if available); indication; start and end dates of the administered medication.

[0822] Prior ITP Therapy: Information regarding ITP therapies received since the time of ITP diagnosis is collected and reported in the source and eCRF. In addition, the prior ITP therapies to which participants had insufficient response or intolerance are documented (*see* inclusion criterion 5). The reason for discontinuation of a prior ITP therapy is also recorded.

Efficacy Assessments and Procedures

Platelet Count

[0823] Blood samples for evaluation of platelet count are collected as part of the hematology laboratory assessments. Central laboratory results are used for the primary analysis of efficacy endpoints relating to platelet counts. If both central laboratory and local laboratory results are available for the same participant at the same visit then the central laboratory platelet count is used for the efficacy analysis. In cases where the central laboratory platelet count is not available, the local laboratory data is used. If neither central nor local laboratory platelet counts are available, the platelet count is treated as missing. The missing handling strategy is

implemented for the relevant endpoints. Additionally, various sensitivity analyses (*e.g.*, using only central laboratory data or local laboratory data) are carried out to assess the robustness of primary analysis of the endpoints relating to platelet counts.

Clinical Outcomes Assessments

[0824] Participants complete all clinical outcome assessments (COAs) on an electronic device on site, preferably before site personnel perform any clinical and laboratory assessments to avoid biasing the participant's response.

[0825] ITP-PAQ: The ITP Patient Assessment Questionnaire (ITP-PAQ) is a 44-item PRO measure that assesses disease-specific health-related quality of life (HRQoL) that includes 10 scales: Symptoms, Fatigue/Sleep, Physical Health – Bother, Physical Health – Activity, Emotional Health – Psychological, Emotional Health – Fear, Overall Quality of Life (QoL), Social Activity, Women's Reproductive Health (including Fertility subscale and Menstrual Symptoms subscale), and Work. The recall period varies from over the past 4 weeks, at present, or since diagnosis in adults with chronic ITP, and "thinking about your last period" for the Menstrual Symptoms subscale in the Women's Reproductive Health scale. Each item is rated on a Likert-type scale containing 4 to 7 responses. All item scores are transformed to a 0 to 100 continuum and are weighted equally to derive individual scale scores. Higher scores indicate better health status (Mathias et al., 2007, A disease-specific measure of health-related quality of life for use in adults with immune thrombocytopenic purpura: its development and validation. Health Qual Life Outcomes, 5, 11; and Mathias et al., 2007, A disease-specific measure of health-related quality of life in adults with chronic immune thrombocytopenic purpura: psychometric testing in an open-label clinical trial. Clin Ther, 29(5), 950-62, each of which is herein incorporated by reference in its entirety).

[0826] The minimal important difference (MID) was estimated to be 8 points in the Symptoms, Physical Health – Bother, Emotional Health – Psychological, Overall QoL, Social Activity, and Women's Reproductive Health (including Fertility subscale and Menstrual Symptoms subscale), and 10 points in the Physical Health – Activity and Fatigue/Sleep scale. There are no established MIDs for the Work and Emotional Health – Fear scales (Mathias et al., 2009, Evaluating clinically meaningful change on the ITP-PAQ: preliminary estimates of minimal important

differences. Curr Med Res Opin, 25(2), 375-83, which is incorporated herein by reference in its entirety).

[0827] EQ-5D-5L: The EQ-5D-5L is a generic PRO measure assessing general HRQoL, composed of a descriptive system and a visual analog scale (VAS) (The EuroQol Group 1990). The recall period is "at present". The EQ-5D descriptive system has the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ VAS records the trial participant's self-rated health on a vertical VAS, where 100 indicates 'The best health you can imagine' and 0 indicates 'The worst health you can imagine'.

[0828] Patient Global Impressions of Severity: The Patient Global Impression of Severity (PGI-S) is a 4-point, single-item PRO assessing the participant's overall perception of the severity of their ITP-related symptoms and fatigue over the past 4 weeks. There are two separate PGI-S questionnaires: PGI-S: ITP Symptoms and PGI-S: ITP Fatigue, each containing a single item. The PGI-S items is used as anchor scales to estimate meaningful within-patient change thresholds to aid score interpretation of the Symptoms and the Fatigue/Sleep scales of the ITP-PAQ.

[0829] Patient Global Impressions of Change: The Patient Global Impression of Change (PGI-C) is a 7-point, single-item PRO assessing the participant's overall perception of change in their ITP-related symptoms and fatigue since they received their first injection in the trial. There are two separate PGI-C questionnaires: PGI-C: ITP Symptoms and PGI-C: ITP Fatigue, each containing a single item. The PGI-C items are used as anchor scales to estimate meaningful within-patient change thresholds to aid score interpretation of the Symptoms and Fatigue/Sleep scales of the ITP-PAQ.

[0830] ITP-BAT: The Immune Thrombocytopenia-specific Bleeding Assessment Tool (ITP-BAT) (Rodeghiero et al., 2013, Standardization of bleeding assessment in immune thrombocytopenia: report from the International Working Group. Blood, 121(14), 2596-606, which is herein incorporated by reference in its entirety) is a clinician-reported outcome measure assessing severity of bleeding manifestations grouped into three major domains: skin (S), visible

mucosae (M), and organs (O), with gradation of severity (SMOG). Grading is based on physical examination at the time of the visit by the ITP-BAT certified rater per trial training and on patient's history supplemented by available medical reports. Severity is graded from 0 to 3 or 4, with Grade 5 indicating fatal bleeding. Each type of bleeding is graded based on the worst bleeding manifestation that occurred during each observation period or in the 15 days preceding the first visit. Bleeding manifestations reported by the patient but not visible at the time of data collection are graded 1.

Safety Assessments and Procedures

Physical Examination

[0831] A physical examination is completed per standard of care.

Vital Signs

[0832] Vital signs are evaluated at the visits specified above and are recorded in the source documentation. Vital signs are also assessed at any other times at which it is clinically warranted (*e.g.*, participant is exhibiting signs or symptoms of CRS or other hypersensitivity reaction). On dosing days, vital signs are assessed before the dose; vital signs are also assessed 2 hours (±15 minutes) after dosing at Week 0 and Week 1. When vital signs are scheduled at the same time as blood sample collection, the blood sample collection takes priority, and vital signs are obtained within 0.5 hours after the blood sample collection. Vital signs to be evaluated include body temperature (measurement method based on site standard of practice); respiratory rate; blood pressure (systolic and diastolic, resting more than 5 minutes); and pulse (beats per minute).

[0833] The investigator assesses whether a change in vital signs from baseline is deemed clinically significant and whether the change is considered and recorded as an AE; any such changes are closely monitored for follow-up/resolution.

[0834] Height is measured and recorded during screening. Weight is measured and recorded at screening and at the timepoints specified above. A participant has weight and height measured while wearing indoor clothing and with shoes off. Weight is collected in kilograms (kg). Height is recorded in centimeters (cm).

Electrocardiograms

[0835] A single ECG (at least 12 leads) is performed at the screening visit (for assessment of eligibility) and at the additional timepoints specified above and is read locally. Additional ECGs are performed at the investigator's discretion. Each ECG recording is performed according to standard institutional practice. Any ECG finding that is judged by the investigator as clinically significant (except at the screening visit) is considered an AE; as such, clinically significant findings are recorded on the source documentation, and the participant undergoes continued monitoring.

Clinical Laboratory Assessments

[0836] Clinical Chemistry and Hematology: Blood samples for analysis of the clinical chemistry and hematology parameters shown in **Table 42**.

Table 42. Clinical Chemistry and Hematology Tests

Hematology	**Serum Chemistry**	
Hematocrit	Albumin	Chloride
Hemoglobin	Alkaline phosphatase (ALP)	Glucose
Total leukocyte count	Alanine aminotransferase (ALT)	Lactate dehydrogenase (LDH)
Total lymphocyte count [a]	Aspartate aminotransferase (AST)	Potassium
Neutrophils (ANC) [a]	Bilirubin (total)	Sodium
Platelet count	Blood urea nitrogen (BUN)	
	Calcium	
	Bicarbonate (HCO_3)	
	Creatinine	
[a] The leukocyte differential will be performed and the total lymphocyte count and absolute neutrophil count will be specifically recorded.		

[0837] Creatinine clearance is estimated during the screening visit using serum creatinine and the Cockroft-Gault formula:

$$\text{Estimated creatinine clearance} = [(140 - \text{Age}) * \text{Mass(kg)}\ ] / [72 * \text{serum creatinine(mg/dL)}]$$

[0838] For female participants, the result of the formula above is multiplied by 0.85. For transgender participants, use the sex at birth for participants not using hormone therapy or for

participants who have used hormone therapy for <6 months; use the current gender for participants who have used hormone therapy for ≥6 months.

[0839] Blood Type Assessment: Anti-CD38 monoclonal antibodies have been reported to bind to CD38 on RBCs, resulting in a positive indirect Coombs test, which may persist for up to 6 months. The determination of a patient's ABO and Rh blood type are not affected, but the RBC binding may mask detection of antibodies to minor antigens in the patient's serum (Darzalex (daratumumab) injection 2019; Regan and Markowitz 2016). It is possible that mezagitamab may affect the results of these tests.

[0840] Following the recommendations for avoiding problems with blood transfusions for patients treated with anti-CD38 antibodies (Lancman et al., 2018, Blood transfusion management for patients treated with anti-CD38 monoclonal antibodies. Front Immunol, 9, 2616; and Regan and Markowitz, 2016, Mitigating the Anti-CD38 Interference with Serology Testing. Advancing Transfusion and Cellular Therapies Worldwide Association Bulletin #16-02, 1-4, each of which is herein incorporated by reference in its entirety), extended RBC antigen typing by phenotype or genotype testing is required for participants as part of the screening assessments. The extended phenotype test cannot be assessed in participants who have had a blood transfusion within 3 months prior to the signing of the ICF; genotyping is performed in this case.

[0841] The results of these tests enable the identification of antigen-matched RBC units for participants with known alloantibodies. The most common immunogenic antigens, including antigens in the Rh (D, E, e, C, c), Duffy (Fya, Fyb), Kidd (Jka, Jkb), Kell (K) and MNS (S, s) blood group systems, are to be tested (Lancman et al. 2018). RBC extended antigen typing by either phenotype or genotype testing is required prior to receiving trial intervention, unless an adequate alternative local practice of cross-matching for blood transfusions is established for clinical trial participants on anti-CD38 therapy (*e.g.*, pretreating the RBC samples with polybrene or dithiothreitol to address the CD38 antibody interference in the cross-matching before blood transfusion).

[0842] Crossmatching for Blood Transfusions During the Trial: To prevent delays in obtaining RBCs if a participant requires a blood transfusion, the transfusion service is informed that the participant is on anti-CD38 therapy. Recommendations for crossmatching, including the use of

dithiothreitol-treated cells; providing antigen-matched RBC units; or using un-crossmatched ABO/RhD-compatible blood (in the event of an emergency) have been reported elsewhere, including the Advancing Transfusion and Cellular Therapies Worldwide Bulletin #16-02 (Regan and Markowitz 2016).

[0843] Blood Sample for CD19+ Counts: Participants who have had prior exposure to anti-CD20 therapy between 6 and 12 months before screening and require confirmatory testing of CD19+ levels have a blood sample drawn during screening that is used to confirm eligibility via flow cytometry.

[0844] Hepatitis B, Hepatitis C, and HIV Tests: At screening, hepatitis B surface antigen, hepatitis B core antibody (HBcAb) (total or IgG), and hepatitis B surface antibody are assessed in all participants (mandatory). Participants with positive HBcAb are further tested for hepatitis B virus DNA (**Table 43**).

Table 43. Eligibility Based on Serology Markers for Hepatitis B Infection

Test Results				Eligibility
HBsAg	**HBcAb**	**HBV DNA**	**HBsAb**	
+	+ or –	n/a	+ or –	Not eligible
-	+	Detectable	+ or –	Not eligible
-	+	-	+ or –	Eligible
-	-	n/a [a]	+ or –	Eligible

HBcAb: hepatitis B core antibody; HBsAb: hepatitis B surface antibody; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus.
[a] For sites in Japan only: HBV-DNA testing is done if there is no apparent hepatitis B vaccination history.

[0845] For hepatitis C status at screening, a hepatitis C antibody (HCAb) test is performed for all patients. A positive HCAb result triggers a follow-on nucleic acid test according to **Table 44**.

Table 44. Eligibility Based on Serology Markers for Hepatitis C Infection

HCAb Test Result	Previous History of Curative Treatment for HCV?	HCV RNA PCR Test Result	Eligibility
-	N/A	N/A	Eligible
+	Yes	-	Eligible
		+	Not eligible
	No	N/A	Not eligible

HCAb Test Result	Previous History of Curative Treatment for HCV?	HCV RNA PCR Test Result	Eligibility
HCAb: hepatitis C antibody; HCV: hepatitis C virus; N/A: not available; PCR: polymerase chain reaction; RNA: ribonucleic acid.			

[0846] An HIV (HIV-1 and HIV-2) antibody test is also performed at screening for all patients (mandatory). Patients who test positive are excluded from the trial.

Adverse Events (AEs) and Serious Adverse Events (SAEs)

Definitions of AE and SAE

[0847] Adverse Event (AE) Definition: An AE is any untoward medical occurrence in a clinical trial participant, temporally associated with the use of the trial intervention, whether or not the occurrence is considered related to the trial intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the trial intervention. An untoward finding generally may necessitate therapeutic intervention, require an invasive diagnostic procedure, or require discontinuation or a change in dose of trial intervention or a concomitant medication. (Repeated or additional noninvasive testing (*e.g.*, laboratory or ECG retests) for verification, evaluation, or monitoring of an abnormality is not considered a therapeutic intervention.)

[0848] Serious Adverse Event (SAE) Definition: SAEs are events that meet both the AE definition described above and as amended (described below) and the following criteria for seriousness. An SAE is defined as any untoward medical occurrence that meets 1 or more of the criteria listed:

a) Results in death;

b) Is life threatening (the term life threatening in the definition of serious refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe);

c) Requires inpatient hospitalization or prolongation of existing hospitalization;

d) Results in persistent or significant disability/incapacity;

e) Is a congenital anomaly/birth defect; and/or

f) Other situations (medically significant event):

1) Is an important medical event;

2) May require intervention to prevent one of the outcomes listed above;

3) May expose the participant to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization;

4) Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition; these events are usually considered serious;

5) Is a suspected transmission of any infectious agent via an authorized medicinal product; and/or

6) Alanine aminotransferase (ALT)/AST ≥3× ULN and total bilirubin >2× ULN or INR >1.5× ULN for which an alternative etiology has not been found.

Additional details and clarifications for SAEs are described below.

Identifying AEs and SAEs

[0849] The investigator and any qualified designees are responsible for identifying events that meet the definition of an AE or SAE. AEs are assessed at the frequency shown in the SoA using open questions asked of the participant by the investigator or trial personnel. AEs may also be spontaneously reported at any time or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE.

Recording of AEs and SAEs

[0850] Recording of AEs: All AEs are recorded on the appropriate page of the eCRF. When possible, signs and symptoms indicating a common underlying pathology are noted as a single

comprehensive event. For both serious and nonserious AEs, the investigator determines: (1) Severity (toxicity grade) for each AE, including any lab abnormality, is determined using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 6.0; (2) Relationship (*i.e.*, causality) of the event to trial intervention administration, is determined by the investigator responding yes (related) or no (unrelated) to this question: Is there a reasonable possibility that the AE is associated with the trial intervention? (the trial intervention includes mezagitamab/placebo and, if used, AxMP); and (3) Outcome at the time of recording, assessed as recovered/resolved, recovered/resolved with sequelae, recovering/resolving, not recovered/not resolved, fatal, or unknown.

[0851] Recording of SAEs: SAEs are recorded in the eCRF through Week 24. For participants who move into the continuation trial, SAEs occurring after Week 24 are recorded in the continuation trial. For participants who do not move into the continuation trial, SAEs occurring after Week 24 are captured on the paper-based SAE form only. Further details on assessing severity and causality of AEs and SAEs are described below.

Adverse Events of Special Interest

[0852] Adverse events of special interest (AESIs) in this trial include anaphylaxis and opportunistic infections. AESIs are recorded as AEs in the eCRF from the signing of the ICF. If an AESI occurs during the intervention period or the dosing-free period, it is recorded on the SAE Form (for events that meet the SAE definition) or the AE Form (for nonserious events). A description of each AESI, including Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) to be used for confirmation and method of confirmation, is presented in **Table 45**.

Table 45. AESIs

Event	MedDRA PT/SMQ	Method of Confirmation
Opportunistic infection	Opportunistic infections (narrow)	As assessed by investigator and coded to the MedDRA SMQ
Anaphylaxis	Anaphylactic reaction (narrow), Anaphylactic/Anaphylactoid shock condition (narrow)	As assessed by investigator and coded to the MedDRA SMQ
MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SMQ: Standardized MedDRA Query.		

Disease-Related Events or Outcomes Not Qualifying as AEs or SAEs

[0853] For this study, "thrombocytopenia" or "low platelet count" are not recorded as an AE, as all patients are required to have thrombocytopenia at study entry.

Special Situations

[0854] Special situations may or may not be associated with an AE/SAE but are not, in and of themselves, AEs. If special situation results in an SAE, the SAE should be reported. The following classes of special situations might occur: (1) Abuse – persistent or sporadic intentional excessive use of medicinal products accompanied by harmful physical or phycological effects; (2) Misuse – situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol-specified dose, route of administration, and/or indication; (3) Medication Error– An unintentional error in the drug treatment process (prescribing, dispensing or administration, including incorrect dose or poor-quality administration) of a medicinal product while in the control of trial site staff or a participant that leads to harm or has the potential to lead to harm; (4) Overdose – the administration of a quantity of medicinal product given per administration or per day, which is above the maximal recommended dose according to the protocol; (5) Pregnancy.

Pharmacokinetics

[0855] Serum samples are collected for measurement of mezagitamab concentrations at the time points specified in the SoA. The actual date and time of each PK sample collection is recorded. The timing (but not the total number of PK sample collections) may be modified during the clinical trial on the basis of emerging PK data if a change is considered necessary to better characterize the PK profile of mezagitamab.

Biomarkers

[0856] Quantitative IgA, IgM, and IgG are evaluated as PD biomarkers.

[0857] Exploratory biomarkers are tested and evaluated for correlation with safety, PK, and efficacy. These biomarkers are used to identify participants who have a higher probability of response or adverse reactions to mezagitamab. The biomarker sample analysis is performed if or

when required. Because new techniques are continually developed, the method and laboratory recommended for the biomarker analysis may be updated.

[0858] Serum aliquots are made according to the sample management plan and may be used for non-genetic exploratory analysis in the future. Exploratory biomarker analysis does not involve genetic analysis.

[0859] Measurements include absolute quantification and relative frequency determination of lymphocytes (T cells, B cells, and NK cells).

Immunogenicity Assessments

[0860] Antibodies to mezagitamab are evaluated in serum samples collected from all participants. When collected on a dosing day, samples are collected before mezagitamab or placebo is administered. Additionally, serum samples are collected at the final visit from participants who discontinue trial intervention or are withdrawn from the trial. Any remaining serum collected may be used for exploratory biomarker work.

[0861] The immunogenicity assessment is performed by a sponsor's designated central laboratory with a tiered approach. All samples are first tested by an anti-drug antibody (ADA) assay. The ADA positive samples are further assessed for ADA titer and for the presence or absence of neutralizing antibodies. Other analyses may be performed to further characterize the ADA antibodies if needed.

Statistical Considerations

[0862] A statistical analysis plan (SAP) is prepared before the first participant is randomized and finalized before database lock. The SAP provide the statistical methods and definitions for analysis of the efficacy and safety data as well as describe the approaches to be taken for summarizing other trial information such as participant disposition, demographics and baseline characteristics, mezagitamab or placebo exposure, prior and concomitant medications, and protocol-specified PK, PD, and immunogenicity objectives. The SAP also includes a description of how missing, unused, and spurious data will be addressed. Deviations from the statistical analyses outlined below are indicated in the SAP; any further modifications are noted in the final clinical study report (CSR).

[0863] Following the completion of the trial and the collection and verification of all final data, the database is locked, and the analysis is conducted on all participant data at the time the trial ends. All statistical analysis will be performed using Statistical Analysis System (SAS) software (SAS Institute, Cary, North Carolina) version 9.4 or higher, unless otherwise specified.

[0864] Summary tabulations are presented by treatment arm, unless otherwise indicated.

[0865] For categorical variables, the number and percentage of participants within each category (with a category for missing data as needed) of the parameter is presented. For continuous variables, the number of participants, mean, median, SD, minimum, and maximum values are presented.

Analysis Sets

[0866] The analysis sets are defined as shown in **Table 46**.

Table 46. Analysis Set Definitions

Analysis Set	Definition
Enrolled set	All participants for whom informed consent has been obtained.
Full analysis set (FAS)	All randomized participants. Analysis is performed according to the randomized treatment regimen regardless of the treatment regimen actually received.
Per-protocol analysis set (PPAS)	All randomized participants who received at least 1 dose of IMP without major protocol deviations impacting the efficacy evaluation.
Safety analysis set (SAF)	All participants who received at least 1 dose of IMP. Analysis is performed according to the treatment regimen actually received, regardless of the randomized treatment regimen assigned.
PK analysis set (PKAS)	All participants from the safety analysis set who received at least 1 dose of IMP and have at least 1 evaluable postdose PK concentration value.
PD analysis set (PDAS)	All participants from the safety analysis set who received at least 1 dose of trial intervention and have at least 1 evaluable postdose PD sample assessment.
IMP: investigational medicinal product; PD: pharmacodynamic; PK: pharmacokinetic;	

Analyses Supporting Primary Objective

[0867] The primary endpoint is durable platelet response through Week 24, defined as platelet count ≥50,000/μL on at least 4 of the 6 weekly platelet measurements between Week 19 and Week 24. Central laboratory results are intended to be used for the primary analysis. If both

central laboratory results and local laboratory results are available for the same participant at the same visit, central laboratory platelet counts will be used. In cases where the central laboratory platelet count is not available, the local laboratory data will be used. If neither central nor local laboratory platelet counts are available, the platelet count will be treated as missing. The associated estimand is described above. The primary analysis is performed on the full analysis set (FAS) and assessed at the 2 sided alpha level of 0.05.

[0868] Statistical Model, Hypothesis, and Method of Analysis: For the analysis of the primary endpoint, the proportions of participants with a durable platelet response is compared between treatment arms using the Cochran-Mantel-Haenszel (CMH) test stratified by baseline platelet count ($< \text{or} \geq 15{,}000/\mu L$), splenectomy status (yes/no), and use of background concomitant standard-of-care ITP therapy (yes or no). The treatment arm difference (mezagitamab versus placebo) of proportions and associated 95% confidence interval (CI) are provided using the CMH stratum weights. The primary efficacy endpoint is tested by the following hypothesis:

$$H_0: \delta = 0$$

$$H_1: \delta \neq 0$$

Where δ is the common treatment difference across strata. The common treatment difference is a weighted average of the stratum-specific treatment differences. The estimate of the treatment difference along with the corresponding stratified 95% CI using the stratified Newcombe confidence interval method of Yan and Su (Yan and Su, 2010, Stratified Wilson and Newcombe confidence intervals for multiple binomial proportions. Stat Biopharm Res, 2(3), 329-35, which is herein incorporated by reference in its entirety) and CMH p-value is presented.

[0869] Handling of Missing Data: For primary analysis, the platelet count data is considered missing only if both central and local laboratory data are not available. Any missing data for the primary endpoint will be handled in concordance with the estimands specified above. The imputation methods for sensitivity analysis are described below and in detail in the SAP.

[0870] Sensitivity Analysis: Sensitivity analyses are conducted to evaluate the robustness of the result from the primary analysis method. These analyses includse various assumptions for the missing data mechanisms (missing at random, missing not at random) and different imputation methods (multiple imputation procedures for intercurrent events, or using platelet values adjacent

to the primary test period of Weeks 19 to 24 for participants with fewer than 4 valid platelet test results during the period, or using platelet count results from the local laboratory if both central and local laboratory data are available) for missing platelet count measurements, as well as repeating the primary analysis in different analysis sets (*e.g.*, per protocol analysis set). Sensitivity analyses and imputation methods are described in detail in the SAP.

[0871] Subgroup Analyses: To assess the consistency in the treatment effects across different subgroup levels, the following subgroup analysis are evaluated for the primary endpoint: (1) age (18 to <65, 65 to <75, ≥75 years); (2) sex (Male, Female); (3) region (China, European Union, Japan, US, rest of world); (4) race (Asian – Chinese, Asian – Japanese, Asian – other, Black/African American, White, Other); (5) ethnicity (Hispanic or Latino, not Hispanic or Latino); (6) baseline weight (<50 kg, 50 to <75 kg, 75 to <120 kg, ≥120 kg); (7) prior therapy (splenectomy (Yes/No), rituximab (Yes/No), or use of background concomitant ITP therapy (Yes or No); (8) number of prior ITP therapies (≥3, or <3)); (9) baseline platelet count (≥15,000/μL, <15,000/μL); (10) duration of ITP at trial entry (<3 years, ≥3 years); and (11) time since diagnosis (chronic, persistent).

[0872] Adjustment for Multiple Testing: The hypothesis testing of the primary and secondary efficacy endpoints is adjusted for multiple comparisons using the fixed-sequence testing procedure to control the family-wise Type I error rate at 2-sided $\alpha = 5\%$ level. The testing is done in the order of primary efficacy endpoint and rank-ordered secondary endpoints. Testing for a given endpoint is performed only if the null hypothesis is rejected for all previously tested endpoints. The test for the primary endpoint is conducted first at the 5% significance level and, if significant, the secondary endpoints are similarly tested at the 5% significance level in the rank-ordered sequence.

Analysis Supporting Secondary Objectives

[0873] The secondary objectives, endpoints, and associated estimands are specified above. All the secondary endpoint analyses are performed on the FAS.

[0874] Statistical Model, Hypothesis, and Method of Analysis for Secondary Endpoints: The rank-ordered secondary efficacy endpoints and the corresponding methods of analysis are described below:

1. The cumulative number of weeks that a platelet count was ≥50,000/μL through Week 24. The difference in the mean total number of weeks with platelet response between the mezagitamab and placebo groups, along with the corresponding treatment difference 95% CI, is derived by analysis of variance (ANOVA) approach. The ANOVA model includes factors for treatment group and each randomization stratum (*i.e.*, baseline platelet count (< or ≥ 15,000/μL), splenectomy status (yes or no), and use of background concomitant standard-of-care ITP therapy (yes or no)).

2. Time to first platelet count ≥50,000/μL. The difference is summarized using the Kaplan-Meier method and compared using the stratified log-rank test. The treatment difference (hazard ratio, and its 95% CI) between the mezagitamab and placebo groups is estimated using the stratified Cox's regression model. The strata are based on the randomization stratification factors.

3. The cumulative number of weeks that a platelet count was ≥30,000/μL through Week 24 and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy. The difference in the mean total number of weeks with platelet response between the mezagitamab and placebo groups, along with the corresponding treatment difference 95% CI, are derived by ANOVA approach. The ANOVA model includes factors for treatment group and each randomization stratum.

4. Complete platelet response, defined as a platelet count ≥100,000/μL on at least 2 visits through Week 24. The difference in the proportions of participants with a complete platelet response between the mezagitamab and placebo groups, along with the associated 95% CI, are provided using the CMH stratum weights. The strata is based on the randomization stratification factors.

5. Platelet response at Week 16, defined as a platelet count ≥50,000/μL before IP administration at the Week 16 visit. The difference in the proportions of participants with a platelet response between the mezagitamab and placebo groups, along with the associated 95% CI, are provided using the CMH stratum weights. The strata are based on the randomization stratification factors.

6. Occurrence of receiving rescue therapy. The difference in the proportions of participants who received rescue therapy between the mezagitamab and placebo groups, along with the associated 95% CI, are provided using the CMH stratum weights. The strata are based on the randomization stratification factors. Rescue therapy is defined above.

7. Time to first rescue therapy is summarized using the Kaplan-Meier method and compared using the stratified log-rank test. The treatment difference (hazard ratio, and its 95% CI) between the mezagitamab and placebo groups is estimated using the stratified Cox's regression model. The strata are based on the randomization stratification factors.

8. Change from baseline on the Symptoms scale score of the ITP Patient Assessment Questionnaire at Week 24 is analyzed by a linear mixed model for repeated measures. The model includes factors for treatment group, study visit, treatment-by-study visit interaction, and each randomization stratum. The treatment difference in least squares means and 95% CIs is estimated for each time point. As a supportive analysis, the change from baseline is compared between the two groups at each time point using a non-parametric test.

[0875] The non-rank-ordered secondary efficacy endpoint and the corresponding methods of analysis are described below:

- Presence of bleeding event. Bleeding events are defined as Grade $\geq$2 in the Skin domain, or Grade $\geq$1 in the Mucosal domain, or Grade $\geq$1 in the Organ domain, in the ITP-BAT through Week 24. The proportions of participants with a bleeding event on each of the three ITP-BAT domains is summarized by treatment group and assessment visit. No statistical testing is done for this endpoint.
- The PK concentration during and after intervention.
- Incidence of ADA and change in ADA titers.
- Incidence of NAb.

PK and PD Analyses

[0876] PK and PK/PD evaluations are performed to assess the relationship between mezagitamab serum concentrations and selective PD measures, as data allow and as deemed appropriate. A descriptive summary of the PK concentrations and PD values is summarized. Individual PK concentrations and observed PD values are summarized in the listing.

[0877] Additionally, population PK analysis, exposure-efficacy, and/or exposure-safety relationship (model-based and or non-model-based) is explored, as deemed appropriate. If performed, the detailed analysis plan is summarized separately in the modeling analysis plan (MAP). The results of this analysis (if performed) are reported separately outside of the CSR.

Immunogenicity Analyses

[0878] Mezagitamab immunogenicity status (ADA incidence) is analyzed and summarized using descriptive statistics, as applicable, and using the safety analysis set (SAF). The effect of immunogenicity on PK, safety, and efficacy is evaluated (as data allow).

Safety Analyses

[0879] The safety analysis is performed using the SAF and descriptively summarized by treatment group and overall; no statistical testing is performed. Safety outcome measures are as follows:

- Adverse events, which are coded using MedDRA. Treatment-emergent adverse events (TEAEs) are defined as AEs with start dates at the time of or following the first exposure to IMP (mezagitamab or placebo). The number and percentage of participants with TEAEs, as well as the number of events, are summarized by MedDRA system organ class (SOC) and preferred term (PT) for each treatment group and overall. TEAEs are further summarized by seriousness, severity, and relationship to IMP. In addition, TEAEs related to IMP, TEAEs related to COVID-19, TEAEs leading to discontinuation from IMP, treatment emergent SAEs, and treatment-emergent deaths are similarly summarized/listed.

- Treatment-emergent AESIs include anaphylaxis and opportunistic infection. The PTs are from MedDRA. Standardized MedDRA Queries (SMQs) are used to identify an SMQ defined potential risk. AESIs are summarized separately by SOC and PT.
- Vital signs, clinical laboratory (clinical chemistry and hematology), and 12-lead ECG results (observed and changes from baseline) are summarized by trial visit for each treatment group using descriptive statistics. Clinically significant abnormal values in routine laboratory parameter and vital sign results are listed or summarized descriptively when appropriate.
- Exposure to trial drug and reasons for discontinuation from IMP are tabulated by treatment group.

Sample Size Determination

[0880] A total sample size of 171 participants with an allocation ratio of 2:1 (mezagitamab:placebo) provides at least 90% power to detect a treatment difference of 40% (50% response rate for the mezagitamab group compared to 10% response rate for placebo group) at a 2-sided significance level of 0.001. This sample size was estimated based on a Chi-square test assuming a dropout rate of 20% and that the participants who drop out would be imputed as non-responders.

[0881] The assumption for the effect size was based on results from the Phase 2 trial, as well as the literature from similar studies of participants with ITP (Broome et al. 2023; Bussel et al. 2018). The assumption for the dropout rate was based on observed dropout rate in Phase 2 Part A, as well as estimates from literature (Broome et al., 2023, Efficacy and safety of the neonatal Fc receptor inhibitor efgartigimod in adults with primary immune thrombocytopenia (ADVANCE IV): a multicentre, randomised, placebo-controlled, phase 3 trial. Lancet, 402(10413), 1648-59; Bussel et al., 2009, Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial. Lancet, 373(9664), 641-8; and NDA Multi-disciplinary Review and Evaluation, NDA 20929, for fostamatinib, 2018, each of which is herein incorporated by reference in its entirety).

[0882] This trial is designed to have approximately 90% power for the primary endpoint to detect a treatment difference at a highly statistically persuasive level (*i.e.*, a p-value ≤0.001); however, an alpha of 0.05 (2-sided) is used as the overall Type-I error rate for the purposes of demonstration of efficacy in this trial and declaring trial success.

Adverse Events and Serious Adverse Events – Definitions, Severity, and Causality

Further Details and Clarifications on the AE Definition

[0883] Pretreatment Event Definition: A pretreatment event is any untoward medical occurrence in a participant who has signed informed consent to participate in a trial but before administration of any trial intervention; it does not necessarily have to have a causal relationship with trial intervention.

Severity

[0884] Severity (toxicity grade) for each AE, including any lab abnormality, is determined using the NCI CTCAE, version 6.0.

Causality

[0885] Relationship of the event to trial intervention administration (*i.e.*, its causality) is determined by the investigator responding yes (related) or no (unrelated) to this question: Is there a reasonable possibility that the AE is associated with the trial intervention?

EXAMPLE 4: A PHASE 3, OPEN-LABEL, MULTICENTER TRIAL TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF MEZAGITAMAB SUBCUTANEOUS INJECTION IN ADULTS WITH CHRONIC PRIMARY IMMUNE THROMBOCYTOPENIA

[0886] Participants who complete the EOT assessments of the Phase 3 trial may participate in the continuation trial if eligibility criteria are met. Participants who completed the Phase 2 trial may participate in the continuation trial if eligibility criteria are met.

[0887] Treatment courses include 8 weeks intervention consisting of mezagitamab 600 mg QW SC for 8 doses per cycle administered. This is followed by an 8-week dosing-free period,

constituting a 16-week treatment course. On-demand treatment courses will be repeated whenever necessary if as needed when the criteria are met.

Primary and Secondary Objectives and Endpoints

Table 47. Primary Objectives and Endpoints

Primary Objective	Primary Endpoint
Safety: To evaluate the long-term safety and tolerability of mezagitamab in participants ≥18 years of age with chronic primary ITP.	• Occurrence of TEAEs and serious TEAEs • Occurrence of TEAEs leading to permanent withdrawal of mezagitamab.

Table 48. Secondary Objectives

Secondary Objective	Secondary Endpoint
Efficacy: To evaluate the long-term efficacy of mezagitamab in participants ≥18 years of age with chronic primary ITP.	• Duration of platelet response, measured by: o The cumulative number of weeks on which platelet count was ≥30,000/μL throughout the trial. o The cumulative number of weeks on which platelet count was ≥50,000/μL throughout the trial. • Duration between on-demand treatment courses (in weeks). • Time to initiation of the first on-demand treatment course (in weeks). • Occurrence of complete response defined as achieving platelet counts ≥100,000/μL on at least 2 visits. • Occurrence of ITP remission defined as: all platelet counts ≥50,000/μL for at least 24 weeks after any mezagitamab treatment cycle in the absence of further therapy for ITP.
To evaluate the reduction in concomitant ITP medications in participants ≥18 years of age with chronic primary ITP.	Reduction in dose and/or frequency of concomitant ITP medications through the trial.
To assess the use of rescue therapy in participants ≥18 years of age.	Use of rescue therapy.
To collect PK concentration of mezagitamab.	The PK concentration at selected timepoints during and after intervention.
To characterize the immunogenicity for mezagitamab.	Occurrence of ADA and NAb.

Incorporation by Reference

[0888] The contents of all references (including literature references, patents, patent applications, and websites) cited throughout this application, excluding contents inconsistent with this disclosure, are hereby expressly incorporated by reference in their entirety for any purpose, as are the references cited therein, to the same extent as if each individual reference was specifically and individually indicated to be incorporated by reference in its entirety for any purposes.

Equivalents

[0889] The disclosure may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting of the disclosure. Scope of the disclosure is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are therefore intended to be embraced herein. Modifications for carrying out the disclosure that are obvious to persons of skill in the art are intended to be within the scope of the appended claims.

We Claim:

1. A method of treating immune thrombocytopenia (ITP) in a subject in need thereof, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof.

2. A method of treating immune thrombocytopenia (ITP) in a subject in need thereof, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8.

3. The method of claim 1 or 2, wherein the isolated antibody or antigen binding fragment thereof is administered in a dosage of from about 100 mg to about 600 mg; optionally wherein the isolated antibody or antigen binding fragment thereof is administered subcutaneously.

4. A method of treating immune thrombocytopenia (ITP) in a subject in need thereof, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

5. A method of reducing the level of plasmablasts, plasma cells, and/or NK cells in a subject diagnosed with immune thrombocytopenia (ITP), the method comprising administering

to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

6. A method of reducing the level of immunoglobulin(s) in a subject diagnosed with immune thrombocytopenia (ITP), the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

7. The method of claim 6, wherein the immunoglobulin is one or more selected from the group consisting of IgA, IgG, and IgM.

8. The method of claim 6 or 7, wherein administering the isolated antibody or antigen binding fragment thereof results in a reduction in immunoglobulin(s) in three weeks or less, two weeks or less, or one week or less.

9. The method of any one of claims 6-8, wherein the immunoglobulin(s) are reduced by at least about 10%, at least about 20%, at least about 30%, at least about 40%, or at least about 50% relative to baseline levels of the immunoglobulin(s).

10. A method of increasing platelet counts in a subject in need thereof, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen

binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

11. A method of achieving platelet response in a subject in need thereof, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof.

12. The method of claim 11, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

13. The method of claim 11 or 12, wherein the platelet response is defined as a platelet count of $\geq$50,000/μL and/or wherein the platelet response is defined as a platelet count of $\geq$30,000/μL and at least doubled from baseline.

14. The method of any one of claims 11-13, wherein the platelet response is defined as a platelet count of $\geq$50,000/μL at about 16 weeks after the administering.

15. The method of any one of claims 11-14, the method achieves a platelet response in three weeks or less, two weeks or less, or one week or less.

16. The method of any one of claims 11-15, wherein administering the isolated antibody or antigen binding fragment thereof results in a platelet response for at least about 2 cumulative number of weeks, at least about 4 cumulative number of weeks, at least about 8

cumulative number of weeks, at least about 10 cumulative number of weeks, at least about 12 cumulative number of weeks, at least about 14 cumulative number of weeks, at least about 16 cumulative number of weeks, at least about 18 cumulative number of weeks, or at least about 20 cumulative number of weeks from baseline to about 24 weeks after the administering.

17. A method of achieving a durable platelet response in a subject in need thereof, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

18. The method of claim 17, wherein the durable platelet response is measured as the cumulative number of weeks in which platelet count is sustained (e.g., ≥30,000/μL or ≥50,000/μL); optionally wherein the durable platelet response is defined as a platelet count of ≥50,000/μL on at least 2 of 6 weekly platelet measurements from about 10 weeks to about 24 weeks after the administering; optionally wherein the durable platelet response is defined as a platelet count of ≥50,000/μL on at least 4 of 6 weekly platelet measurements from about 19 weeks to about 24 weeks after the administering; and optionally wherein the platelet response is sustained for at least about 2 weeks, at least about 4 weeks, at least about 6 weeks, at least about 8 weeks, at least about 10 weeks, at least about 12 weeks, at least about 14 weeks, or at least about 16 weeks after the administration of the isolated human anti-CD38 antibody or antigen binding fragment thereof.

19. A method of achieving complete platelet response in a subject in need thereof, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a

CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

20. The method of claim 19, wherein the complete platelet response is defined as a platelet count of ≥100,000/μL in at least one measurement from baseline to about 24 weeks after the administering; optionally wherein the complete platelet response is defined as a platelet count of ≥100,000/μL in at least two measurements from baseline to about 24 weeks after the administering.

21. The method of claim 19 or 20, wherein the complete platelet response is measured on at least two visits from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks.

22. A method of achieving a clinically meaningful platelet response in a subject in need thereof, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

23. The method of claim 22, wherein the clinically meaningful platelet response is defined as a platelet count ≥20,000/μL above baseline.

24. The method of claim 22 or 23, wherein the clinically meaningful platelet response is measured in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks.

25. A method of achieving hemostatic platelet response in a subject in need thereof having a baseline platelet count of <15,000/μL, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

26. The method of claim 25, wherein the hemostatic platelet response is defined as a platelet count of ≥30,000/μL and ≥20,000/μL above baseline.

27. The method of claim 25 or 26, wherein the hemostatic platelet response is measured in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks.

28. A method of reducing the level of anti-platelet autoantibodies in a subject diagnosed with immune thrombocytopenia (ITP), the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO:8 ; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

29. A method of reducing immune thrombocytopenia (ITP) disease activity and/or progression in a subject diagnosed with ITP, the method comprising administering to the subject

an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

30. The method of claim 29, wherein the ITP disease activity and/or progression is measured by one or more assessments selected from the group consisting of World Health Organization (WHO) Bleeding Scale, Immune Thrombocytopenic Purpura Subject Assessment Questionnaire (ITP-PAQ), and 5-Level EuroQol Five Dimensions (EQ-5D-5L);

optionally wherein the ITP disease activity and/or progression is measured by a change from baseline in Symptoms, Fatigue/Sleep, Physical Health-Activity, Physical Health-Bother, Psychological Health, Overall Quality of Life, Social Activity, and/or Work scales scores of the ITP-PAQ from baseline to about 24 weeks after the administering;

optionally wherein the ITP disease activity and/or progression is measured by a change from baseline in the Menstrual Symptoms subscale scores of the ITP-PAQ from baseline to about 24 weeks after the administering in a female subject who had at least one menstrual period within 12 months before the receiving the isolated antibody;

optionally wherein the ITP disease activity and/or progression is measured by a change from baseline in the Fertility subscale scores of the ITP-PAQ in a female subject from baseline to about 24 weeks after the administering;

optionally wherein the ITP disease activity and/or progression is measured by a change from baseline in the EQ-5D-5L utility index score and/or VAS score from baseline to about 24 weeks after the administering.

31. The method of claim 29 or 30, wherein the ITP disease activity and/or progression is measured by a change in a Symptoms Scale Score of ITP-PAQ from baseline to about 24 weeks after the administering.

32. A method of reducing bleeding events in a subject diagnosed with immune thrombocytopenia (ITP), the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

33. The method of claim 32, wherein the bleed events are measured by Immune Thrombocytopenia-specific Bleeding Assessment Tool (ITP-BAT).

34. The method of claim 32 or 33, wherein the bleeding events comprise Grade $\geq$2 in the Skin domain, Grade $\geq$1 in the Mucosal domain, and/or Grade $\geq$1 in the Organ domain.

35. A method of achieving immune thrombocytopenia (ITP) remission in a subject diagnosed with ITP, the method comprising administering to the subject an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of from about 100 to about 600 mg.

36. The method of claim 35, wherein ITP remission is defined as all platelet counts ≥50,000/μL for at least about 12 or at least about 24 weeks after any treatment cycle with isolated antibody or antigen binding fragment thereof in the absence of other therapy for ITP.

37. A method of treating immune thrombocytopenia (ITP) in a subject diagnosed with ITP, the method comprising administering to the subject an isolated human anti-CD38 antibody, wherein the isolated antibody comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8, wherein:

the ITP is chronic primary ITP or persistent primary ITP;

the subject has had an insufficient response or intolerance to other therapy;

the other therapy is a first-line ITP therapy and/or a second-line ITP therapy, wherein the other therapy comprises one or more of a corticosteroid, immunoglobulins, splenectomy, a thrombopoietin receptor agonist (TPO-RA) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag), rituximab, fostamatinib, and background ITP medication(s) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag, methotrexate, azathioprine, leflunomide, cyclosporine, fostamatinib, mycophenolate, danazol, dapsone, methylprednisolone, hydrocortisone, cortisone, prednisolone, prednisone, and/or dexamethasone);

the isolated antibody is subcutaneously administered in a dosage of about 600 mg in a course of once per week for 8 weeks;

optionally wherein the isolated antibody is further administered in more than one course of once per week for 8 weeks; and/or optionally wherein the isolated antibody is further not administered for a period of 8 weeks.

38. The method of any one of the preceding claims, wherein the subject in need thereof is diagnosed with immune thrombocytopenia (ITP); optionally wherein the ITP is primary ITP; optionally wherein the ITP is persistent ITP; optionally wherein the ITP is chronic ITP; optionally wherein the ITP is persistent or chronic primary ITP;

optionally wherein the primary ITP has persisted for at least about 3 months;

optionally wherein the subject has had a prior response to other therapy excluding a thrombopoietin receptor agonist (TPO-RA), wherein the prior response is defined as achieving a platelet count of ≥50,000/mL;

optionally wherein the subject has a baseline mean platelet count of <30,000/μL from at least 2 consecutive measurements taken at least about 5 days apart; optionally wherein the baseline mean platelet count comprises individual values ≤35,000/μL;

optionally wherein the subject has had an insufficient response or intolerance to other therapy; optionally wherein the other therapy is a first-line ITP therapy and/or a second-line ITP therapy; optionally wherein the other therapy comprises one or more of a corticosteroid, immunoglobulins, splenectomy, a thrombopoietin receptor agonist (TPO-RA) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag), rituximab, fostamatinib, and background ITP medication(s) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag, methotrexate, azathioprine, leflunomide, cyclosporine, fostamatinib, mycophenolate, danazol, dapsone, methylprednisolone, hydrocortisone, cortisone, prednisolone, prednisone, and/or dexamethasone); optionally wherein the insufficient response to other treatment is defined as failure to achieve a sustained platelet count of at least 50,000/μL or doubling of baseline platelet count after an appropriate course of the other therapy; and optionally wherein the intolerance to other therapy is defined as a documented side effect causing discontinuation of the therapy.

39. The method of any one of the preceding claims, wherein the isolated antibody or antigen binding fragment thereof further comprises one or more engineered glycoforms, wherein the engineered glycoform comprises glycosylation of one or more polypeptides, optionally wherein the glycosylation is N-linked glycosylation or O-linked glycosylation, and optionally wherein the glycosylation is N-linked glycosylation.

40. The method of any one of the preceding claims, wherein the variable heavy chain region of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 90% to SEQ ID NO: 9, and/or the variable light chain region of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 90% to SEQ ID NO: 10;

optionally wherein the variable heavy chain region of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 9, and/or the variable light chain region of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 10;

optionally wherein the variable heavy chain region of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 99% to SEQ ID NO: 9, and/or the variable light chain region of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 99% to SEQ ID NO: 10;

optionally wherein the heavy chain of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 11; and/or the light chain of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 12;

optionally wherein the heavy chain of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 14; and/or the light chain of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 12;

optionally wherein the isolated antibody or antigen binding fragment thereof interacts with at least K121, F135, Q139, D141, E239, W241, C275, K276, F284, P291 and E292 of SEQ ID NO: 1 and SEQ ID NO: 2, based on human sequence numbering;

optionally wherein the isolated antibody or antigen binding fragment thereof binds to human CD38 (SEQ ID NO: 1) with a KD of 10^{-8} M or a greater affinity, and wherein the affinity is measured by a standard Biacore® assay;

optionally wherein the variable heavy chain region comprises SEQ ID NO: 9 and the variable light chain region comprises SEQ ID NO: 10;

optionally wherein the isolated antibody or antigen binding fragment thereof comprises a heavy chain as set forth in SEQ ID NO: 11 and a light chain as set forth in SEQ ID NO: 12; and

optionally wherein the isolated antibody or antigen binding fragment thereof comprises a heavy chain as set forth in SEQ ID NO: 14 and a light chain as set forth in SEQ ID NO: 12.

41. The method of any one of the preceding claims, wherein the isolated antibody or antigen binding fragment thereof further comprises an Fc domain, optionally wherein the Fc domain is a human Fc domain or a variant Fc domain; and

optionally wherein the isolated antibody or antigen binding fragment is a human IgG antibody, optionally wherein the human IgG antibody is a human IgG1 antibody.

42. The method of any one of the preceding claims, wherein the subject receives background ITP medication(s);

optionally wherein the background ITP medication(s) is one or more selected from the group consisting of a thrombopoietin receptor agonist (TPO-RA), a corticosteroid, an immunosuppressant, and an inhibitor; and

optionally wherein the background ITP medication(s) is one or more selected from the group consisting of romiplostim, eltrombopag, avatrombopag, hetrombopag, methotrexate, azathioprine, leflunomide, cyclosporine, fostamatinib, mycophenolate, danazol, dapsone, methylprednisolone, hydrocortisone, cortisone, prednisolone, prednisone, and dexamethasone.

43. The method of claim 42, wherein the background ITP medication(s) is administered in combination with the isolated antibody or antigen binding fragment thereof.

44. The method of any one of the preceding claims, wherein the subject in need thereof has a baseline mean platelet count of less than or equal to about 40×10^9/L, less than or equal to about 35×10^9/L, less than or equal to about 30×10^9/L, less than or equal to about 25×10^9/L, or less than or equal to about 20×10^9/L.

45. The method of any one of the preceding claims, wherein the subject in need thereof has an ITP disease duration of at least about 0.1 years, at least about 0.3 years, at least about 0.5 years, at least about 1 year, at least about 5 years, or at least about 10 years.

46. The method of any one of the preceding claims, wherein administering the isolated antibody or antigen binding fragment thereof results in a length of platelet response of at

least about 1 week, at least about 5 weeks, at least about 10 weeks, at least about 15 weeks, at least about 20 weeks, or at least about 25 weeks, wherein the length of the platelet response is defined as the sum of all weeks in which the subject achieves a platelet response, and wherein the platelet response is defined as a platelet count of ≥50,000/μL.

47. The method of any one of the preceding claims, wherein administering the isolated antibody or antigen binding fragment thereof results in a platelet response, wherein the platelet response is defined as a platelet count of ≥50,000/μL and/or wherein the platelet response is defined as a platelet count of ≥30,000/μL and at least doubled from baseline;

optionally wherein the platelet response is defined as a platelet count of ≥50,000/μL at about 16 weeks after the administering;

optionally wherein administering the isolated antibody or antigen binding fragment thereof results in a platelet response in three weeks or less, two weeks or less, or one week or less;

optionally wherein administering the isolated antibody or antigen binding fragment thereof results in a platelet response for at least 2 cumulative number of weeks, at least 4 cumulative number of weeks, at least 8 cumulative number of weeks, at least 10 cumulative number of weeks, at least 12 cumulative number of weeks, at least 14 cumulative number of weeks, at least 16 cumulative number of weeks, at least 18 cumulative number of weeks, or at least 20 cumulative number of weeks from baseline to about 24 weeks after the administering.

48. The method of any one of the preceding claims, wherein administering the isolated antibody or antigen binding fragment thereof results in a durable platelet response, wherein the durable platelet response is measured as the cumulative number of weeks in which platelet count is sustained (e.g., ≥30,000/μL or ≥50,000/μL); optionally wherein the durable platelet response is defined as a platelet count of ≥50,000/μL on at least 2 of 6 weekly platelet measurements from about 10 weeks to about 24 weeks after the administering; optionally wherein the durable platelet response is defined as a platelet count of ≥50,000/μL on at least 4 of 6 weekly platelet measurements from about 19 weeks to about 24 weeks after the administering; optionally wherein the platelet response is sustained for at least about 2 weeks, at least about 4 weeks, at least about 6 weeks, at least about 8 weeks, at least about 10 weeks, at least about 12

weeks, at least about 14 weeks, or at least about 16 weeks after the administration of the isolated human anti-CD38 antibody or antigen binding fragment thereof.

49. The method of any one of the preceding claims, wherein administering the isolated antibody or antigen binding fragment thereof results in a complete platelet response, wherein the complete platelet response is defined as a platelet count of ≥100,000/μL in at least one measurement from baseline to about 24 weeks after the administering; optionally wherein the complete platelet response is defined as a platelet count of ≥100,000/μL in at least two measurements from baseline to about 24 weeks after the administering.

50. The method of any one of the preceding claims, wherein administering the isolated antibody or antigen binding fragment thereof results in a clinically meaningful platelet response, wherein the clinically meaningful platelet response is defined as a platelet count of ≥20,000/μL above baseline in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks.

51. The method of any one of the preceding claims, wherein administering the isolated antibody or antigen binding fragment thereof results in a hemostatic platelet response, wherein the hemostatic platelet response is defined as a platelet count of ≥30,000/μL and ≥20,000/μL above baseline in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a in the previous four weeks and the subject has a baseline platelet count of <15,000/μL.

52. The method of any one of the preceding claims, wherein administering the isolated antibody or antigen binding fragment thereof results in a platelet count of >10,000/μL, >20,000/μL, >30,000/μL, >40,000/μL, >50,000/μL, >60,000/μL, >70,000/μL, >80,000/μL, >90,000/μL, or >100,000/μL; optionally wherein administering the isolated antibody or antigen binding fragment thereof results in a platelet count of >50,000/μL; optionally wherein administering the isolated antibody or antigen binding fragment thereof results in a platelet count of >100,000/μL.

53. The method of any one of the preceding claims, wherein administering the isolated antibody or antigen binding fragment thereof results in less than 75%, less than 50%, or

less than 25% incidence of use of a rescue therapy; optionally wherein the subject has not received a rescue therapy in the previous four weeks; optionally wherein the method does not include the use of a rescue therapy.

54. The method of any one of the preceding claims, wherein administering the isolated antibody or antigen binding fragment thereof results in a reduction in ITP disease activity and/or progression in a subject diagnosed with ITP;

optionally wherein the ITP disease activity and/or progression is measured by one or more assessments selected from the group consisting of World Health Organization (WHO) Bleeding Scale, Immune Thrombocytopenic Purpura Subject Assessment Questionnaire (ITP-PAQ), and 5-Level EuroQol Five Dimensions (EQ-5D-5L); optionally wherein the ITP disease activity and/or progression is measured by a change in a Symptoms Scale Score of ITP-PAQ from baseline to about 24 weeks after the administering;

optionally wherein the ITP disease activity and/or progression is measured by a change from baseline in Symptoms, Fatigue/Sleep, Physical Health-Activity, Physical Health-Bother, Psychological Health, Overall Quality of Life, Social Activity, and/or Work scales scores of the ITP-PAQ from baseline to about 24 weeks after the administering;

optionally wherein the ITP disease activity and/or progression is measured by a change from baseline in the Menstrual Symptoms subscale scores of the ITP-PAQ from baseline to about 24 weeks after the administering in a female subject who had at least one menstrual period within 12 months before the receiving the isolated antibody;

optionally wherein the ITP disease activity and/or progression is measured by a change from baseline in the Fertility subscale scores of the ITP-PAQ in a female subject from baseline to about 24 weeks after the administering;

optionally wherein the ITP disease activity and/or progression is measured by a change from baseline in the EQ-5D-5L utility index score and/or VAS score from baseline to about 24 weeks after the administering;

optionally wherein the ITP disease activity and/or progression is measured by a change in a Symptoms Scale Score of ITP-PAQ from baseline to about 24 weeks after the administering.

55. The method of any one of the preceding claims, wherein administering the isolated antibody or antigen binding fragment thereof results in a reduction in bleeding events in the subject;

optionally wherein the bleed events are measured by Immune Thrombocytopenia-specific Bleeding Assessment Tool (ITP-BAT);

optionally wherein the bleeding events comprise Grade ≥2 in the Skin domain, Grade ≥1 in the Mucosal domain, and/or Grade ≥1 in the Organ domain.

56. The method of any one of the preceding claims, wherein administering the isolated antibody or antigen binding fragment thereof results in ITP remission, optionally wherein ITP remission is defined as all platelet counts ≥50,000/μL for at least about 12 or at least about 24 weeks after any treatment cycle with the isolated antibody or antigen binding fragment thereof in the absence of other therapy for ITP.

57. The method of any one of the preceding claims, wherein administering the isolated antibody or antigen binding fragment thereof results in a reduction in immunoglobulin(s); optionally wherein the immunoglobulin is one or more selected from the group consisting of IgA, IgG, and IgM;

optionally wherein administering the isolated antibody or antigen binding fragment thereof results in a reduction in immunoglobulin(s) in three weeks or less, two weeks or less, or one week or less; and

optionally wherein the immunoglobulin(s) are reduced by at least about 10%, at least about 20%, at least about 30%, at least about 40%, or at least about 50% relative to baseline levels of the immunoglobulin(s).

58. The method of any one of the preceding claims, wherein administering the isolated antibody or antigen binding fragment thereof results in less than 10% incidence of grade 3 or 4 of one or more treatment-related adverse events (TRAEs) or treatment-emergent adverse events (TEAEs);

optionally wherein the TRAEs or TEAEs are selected from the group consisting of gingival bleeding, heavy menstrual bleeding, haematochezia, mouth haemorrhage, haematoma,

traumatic haematoma, epistaxis, petechiae, ecchymosis, conjunctival haemorrhage, blood urine, and haemorrhagic ovarian cyst; and

optionally wherein a TRAE or TEAE resulting from administering the isolated antibody or antigen binding fragment thereof has a maximum intensity of Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or Grade 2.

59. The method of any one of the preceding claims, wherein administering the isolated antibody or antigen binding fragment thereof results in a reduction in dose and/or frequency of use of background ITP medication(s).

60. The method of any one of the preceding claims, wherein the isolated antibody or antigen binding fragment thereof is administered in a dosage selected from the group consisting of about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, and about 600 mg; optionally wherein the isolated antibody or antigen binding fragment thereof is administered in a dosage of about 100 mg; optionally wherein the isolated antibody or antigen binding fragment thereof is administered in a dosage of about 300 mg; and optionally wherein the isolated antibody or antigen binding fragment thereof is administered in a dosage of about 600 mg.

61. The method of any one of the preceding claims, wherein the isolated antibody or antigen binding fragment thereof is administered once every week, once every two weeks, once every three weeks or once every four weeks;

optionally wherein (a) the isolated antibody is administered once per week for from 1 week to 16 weeks; (b) the isolated antibody is not administered for a period of from 1 week to 16 weeks; and (c) the isolated antibody is administered once per week for from 1 week to 16 weeks;

optionally wherein (a) the isolated antibody is administered once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; and (c) the isolated antibody is administered once per week for 8 weeks;

optionally wherein (a) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; and (c) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks;

optionally wherein (a) the isolated antibody is administered once per week for from 1 week to 16 weeks; (b) the isolated antibody is not administered for a period of from 1 week to 16 weeks; (c) the isolated antibody is administered once per week for from 1 week to 16 weeks; and (d) the isolated antibody is not administered for a period of from 1 week to 16 weeks;

optionally wherein (a) the isolated antibody is administered once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; (c) the isolated antibody is administered once per week for 8 weeks; and (d) the isolated antibody is not administered for a period of 8 weeks;

optionally wherein (a) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; (c) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks; and (d) the isolated antibody is not administered for a period of 8 weeks.

62. The method of any one of the preceding claims, wherein the isolated antibody or antigen binding fragment thereof is administered in the form of a pharmaceutically acceptable composition, and optionally wherein the pharmaceutically acceptable composition comprises the isolated antibody or antigen binding fragment thereof and at least one pharmaceutically acceptable carrier, excipient, or stabilizer.

63. The method of any one of the preceding claims, wherein the isolated antibody or antigen binding fragment thereof comprises a heavy chain as set forth in SEQ ID NO: 11 and a light chain as set forth in SEQ ID NO: 12; and wherein the antibody or antigen binding fragment thereof is subcutaneously administered once per week for 8 weeks, or

wherein the isolated antibody or antigen binding fragment thereof comprises a heavy chain as set forth in SEQ ID NO: 14 and a light chain as set forth in SEQ ID NO: 12; and

wherein the antibody or antigen binding fragment thereof is subcutaneously administered once per week for 8 weeks.

64. The method of any one of the preceding claims, wherein the isolated antibody or antigen binding fragment thereof is mezagitamab.

65. The method of any one of the preceding claims, wherein the isolated antibody or antigen binding fragment thereof is from about 2 times to about 4 times more efficacious than fostamatinib and/or efgartigimod; optionally wherein the isolated antibody or antigen binding fragment thereof results in from about 2 times to about 4 times more durable platelet response as compared to fostamatinib and/or efgartigimod.

66. A unit dosage form comprising an isolated antibody or antigen binding fragment thereof that comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; wherein the isolated antibody or antigen binding fragment thereof binds to human CD38 (SEQ ID NO: 1), and the unit dosage form is formulated for subcutaneous administration of the isolated antibody or antigen binding fragment thereof at a dosage of from about 100 mg to about 600 mg in the treatment of ITP.

67. A unit dosage form comprising an isolated human anti-CD38 antibody that comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8; wherein the isolated antibody or antigen binding fragment thereof binds to human CD38 (SEQ ID NO: 1), and the unit dosage form is formulated for subcutaneous administration of the isolated antibody or antigen binding fragment thereof at a dosage of about 600 mg in a course of once per week for 8 weeks in the treatment of chronic primary ITP or persistent primary ITP in a

subject that has had an insufficient response or intolerance to other therapy; wherein the other therapy is a first-line ITP therapy and/or a second-line ITP therapy, wherein the other therapy comprises one or more of a corticosteroid, immunoglobulins, splenectomy, a thrombopoietin receptor agonist (TPO-RA) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag), rituximab, fostamatinib, and background ITP medication(s) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag, methotrexate, azathioprine, leflunomide, cyclosporine, fostamatinib, mycophenolate, danazol, dapsone, methylprednisolone, hydrocortisone, cortisone, prednisolone, prednisone, and/or dexamethasone); optionally wherein the isolated antibody is further administered in more than one course of once per week for 8 weeks; and/or optionally wherein the isolated antibody is not further administered for a period of 8 weeks.

68. The unit dosage form of claim 66 or 67, wherein the isolated antibody or antigen binding fragment thereof further comprises one or more engineered glycoforms, wherein the engineered glycoform comprises glycosylation of one or more polypeptides, optionally wherein the glycosylation is N-linked glycosylation or O-linked glycosylation, and optionally wherein the glycosylation is N-linked glycosylation.

69. The unit dosage form of any one of claims 66-68, wherein the variable heavy chain region of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 90% to SEQ ID NO: 9, and/or the variable light chain region of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 90% to SEQ ID NO: 10;

optionally wherein the variable heavy chain region comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 9, and/or the variable light chain region comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 10;

optionally wherein the variable heavy chain region comprises an amino acid sequence having an identity of at least 99% to SEQ ID NO: 9, and/or the variable light chain region comprises an amino acid sequence having an identity of at least 99% to SEQ ID NO: 10;

optionally wherein the heavy chain of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 11,

and/or the light chain of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 12;

optionally wherein the heavy chain of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 14, and/or the light chain of the isolated antibody or antigen binding fragment thereof comprises an amino acid sequence having an identity of at least 95% to SEQ ID NO: 12;

optionally wherein the isolated antibody or antigen binding fragment thereof interacts with at least K121, F135, Q139, D141, E239, W241, C275, K276, F284, P291 and E292 of SEQ ID NO: 1 and SEQ ID NO: 2, based on human sequence numbering;

optionally wherein the isolated antibody or antigen binding fragment thereof binds to human CD38 (SEQ ID NO: 1) with a KD of 10^{-8} M or a greater affinity, and wherein the affinity is measured by a standard Biacore® assay;

optionally wherein the variable heavy chain region comprises SEQ ID NO: 9 and the variable light chain region comprises SEQ ID NO: 10;

optionally wherein the isolated antibody or antigen binding fragment thereof comprises a heavy chain as set forth in SEQ ID NO: 11 and a light chain as set forth in SEQ ID NO: 12; and

optionally wherein the isolated antibody or antigen binding fragment thereof comprises a heavy chain as set forth in SEQ ID NO: 14 and a light chain as set forth in SEQ ID NO: 12.

70. The unit dosage form of any one of claims 66-69, wherein the isolated antibody or antigen binding fragment thereof further comprises an Fc domain, optionally wherein the Fc domain is a human Fc domain or a variant Fc domain; and

optionally wherein the isolated antibody or antigen binding fragment is a human IgG antibody, optionally wherein the human IgG antibody is a human IgG1 antibody.

71. The unit dosage form of any one of claims 66-70, wherein the isolated antibody or antigen binding fragment thereof is used in combination with one or more background ITP medication(s);

optionally wherein the background ITP medication(s) is one or more selected from the group consisting of a thrombopoietin receptor agonist (TPO-RA), a corticosteroid, an immunosuppressant, and an inhibitor; and

optionally wherein the background ITP medication(s) is one or more selected from the group consisting of romiplostim, eltrombopag, avatrombopag, hetrombopag, methotrexate, azathioprine, leflunomide, cyclosporine, fostamatinib, mycophenolate, danazol, dapsone, methylprednisolone, hydrocortisone, cortisone, prednisolone, prednisone, and dexamethasone.

72. The unit dosage form of any one of claims 66-71, wherein administering the isolated antibody or antigen binding fragment thereof results in:

a length of platelet response of at least about 1 week, at least about 5 weeks, at least about 10 weeks, at least about 15 weeks, at least about 20 weeks, or at least about 25 weeks, wherein the length of the platelet response is defined as the sum of all weeks in which the subject achieves a platelet response, and wherein the platelet response is defined as a platelet count of ≥50,000/μL; and/or

a platelet response, wherein the platelet response is defined as a platelet count of ≥50,000/μL; optionally wherein the platelet response is defined as a platelet count of ≥30,000/μL and at least doubled from baseline; optionally wherein the platelet response is defined as a platelet count of ≥50,000/μL at about 16 weeks after the administering; optionally wherein the platelet response is achieved in three weeks or less, two weeks or less, or one week or less; and optionally wherein administering the isolated antibody or antigen binding fragment thereof results in a platelet response for at least 2 cumulative number of weeks, at least 4 cumulative number of weeks, at least 8 cumulative number of weeks, at least 10 cumulative number of weeks, at least 12 cumulative number of weeks, at least 14 cumulative number of weeks, at least 16 cumulative number of weeks, at least 18 cumulative number of weeks, or at least 20 cumulative number of weeks from baseline to about 24 weeks after the administering; and/or

a durable platelet response, wherein the durable platelet response is measured as the cumulative number of weeks in which platelet count is sustained (e.g., ≥30,000/μL or ≥50,000/μL); optionally wherein the durable platelet response is defined as a platelet count of ≥50,000/μL on at least 2 of 6 weekly platelet measurements from about 10 weeks to about 24

weeks after the administering; optionally wherein the durable platelet response is defined as a platelet count of ≥50,000/μL on at least 4 of 6 weekly platelet measurements from about 19 weeks to about 24 weeks after the administering; optionally wherein the platelet response is sustained for at least about 2 weeks, at least about 4 weeks, at least about 6 weeks, at least about 8 weeks, at least about 10 weeks, at least about 12 weeks, at least about 14 weeks, or at least about 16 weeks after the administration of the isolated human anti-CD38 antibody or antigen binding fragment thereof; and/or

a complete platelet response, wherein the complete platelet response is defined as a platelet count of ≥100,000/μL in at least one measurement from baseline to about 24 weeks after the administering; optionally wherein the complete platelet response is defined as a platelet count of ≥100,000/μL in at least two measurements from baseline to about 24 weeks after the administering; and/or

a clinically meaningful platelet response, wherein the clinically meaningful platelet response is defined as a platelet count of ≥20,000/μL above baseline in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks; and/or

a hemostatic platelet response, wherein the hemostatic platelet response is defined as a platelet count of ≥30,000/μL and ≥20,000/μL above baseline in at least two measurements from baseline to about 24 weeks after the administering, wherein the subject has not received a rescue therapy in the previous four weeks and the subject has a baseline platelet count of <15,000/μL; and/or

a platelet count of >10,000/μL, >20,000/μL, >30,000/μL, >40,000/μL, >50,000/μL, >60,000/μL, >70,000/μL, >80,000/μL, >90,000/μL, or >100,000/μL; optionally wherein administering the isolated antibody or antigen binding fragment thereof results in a platelet count of >50,000/μL; optionally wherein administering the isolated antibody or antigen binding fragment thereof results in a platelet count of >100,000/μL; and/or

a reduction in immunoglobulin(s); optionally wherein the immunoglobulin is one or more selected from the group consisting of IgA, IgG, and IgM; optionally wherein the reduction in immunoglobulin(s) is achieved in three weeks or less, two weeks or less, or one week or less;

and optionally wherein the immunoglobulin(s) are reduced by at least about 10%, at least about 20%, at least about 30%, at least about 40%, or at least about 50% relative to baseline levels of the immunoglobulin(s); and/or

less than 75%, less than 50%, or less than 25% incidence of use of a rescue therapy; and/or

a reduction in ITP disease activity and/or progression in a subject diagnosed with ITP; optionally wherein the ITP disease activity and/or progression is measured by one or more assessments selected from the group consisting of World Health Organization (WHO) Bleeding Scale, Immune Thrombocytopenic Purpura Subject Assessment Questionnaire (ITP-PAQ), and 5-Level EuroQol Five Dimensions (EQ-5D-5L); optionally wherein the ITP disease activity and/or progression is measured by a change in a Symptoms Scale Score of ITP-PAQ from baseline to about 24 weeks after the administering; optionally wherein the ITP disease activity and/or progression is measured by a change from baseline in Symptoms, Fatigue/Sleep, Physical Health-Activity, Physical Health-Bother, Psychological Health, Overall Quality of Life, Social Activity, and/or Work scales scores of the ITP-PAQ from baseline to about 24 weeks after the administering; optionally wherein the ITP disease activity and/or progression is measured by a change from baseline in the Menstrual Symptoms subscale scores of the ITP-PAQ from baseline to about 24 weeks after the administering in a female subject who had at least one menstrual period within 12 months before the receiving the isolated antibody; optionally wherein the ITP disease activity and/or progression is measured by a change from baseline in the Fertility subscale scores of the ITP-PAQ in a female subject from baseline to about 24 weeks after the administering; optionally wherein the ITP disease activity and/or progression is measured by a change from baseline in the EQ-5D-5L utility index score and/or VAS score from baseline to about 24 weeks after the administering; and optionally wherein the ITP disease activity and/or progression is measured by a change in a Symptoms Scale Score of ITP-PAQ from baseline to about 24 weeks after the administering; and/or

a reduction in bleeding events in the subject; optionally wherein the bleed events are measured by Immune Thrombocytopenia-specific Bleeding Assessment Tool (ITP-BAT); optionally wherein the bleeding events comprise Grade $\geq$2 in the Skin domain, Grade $\geq$1 in the Mucosal domain, and/or Grade $\geq$1 in the Organ domain; and/or

ITP remission, optionally wherein ITP remission is defined as all platelet counts ≥50,000/μL for at least about 12 or at least about 24 weeks after any treatment cycle with the isolated antibody or antigen binding fragment thereof in the absence of other therapy for ITP.

73. The unit dosage form of any one of claims 66-72, wherein administering the isolated antibody or antigen binding fragment thereof results in less than 10% incidence of grade 3 or 4 of one or more treatment-related adverse events (TRAEs) or treatment-emergent adverse events (TEAEs);

optionally wherein the TRAEs or TEAEs are selected from the group consisting of gingival bleeding, heavy menstrual bleeding, haematochezia, mouth haemorrhage, haematoma, traumatic haematoma, epistaxis, petechiae, ecchymosis, conjunctival haemorrhage, blood urine, and haemorrhagic ovarian cyst;

optionally wherein a TRAE or TEAE resulting from administering the isolated antibody or antigen binding fragment thereof has a maximum intensity of Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or Grade 2; and

optionally wherein administering the isolated antibody or antigen binding fragment thereof results in a reduction in dose and/or frequency of use of background ITP medication(s).

74. The unit dosage form of any one of claims 66-73, wherein the isolated antibody or antigen binding fragment thereof is administered in a dosage selected from the group consisting of about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, and about 600 mg; optionally wherein the isolated antibody or antigen binding fragment thereof is administered in a dosage of about 100 mg; optionally wherein the isolated antibody or antigen binding fragment thereof is administered in a dosage of about 300 mg; and optionally wherein the isolated antibody or antigen binding fragment thereof is administered in a dosage of about 600 mg.

75. The unit dosage form of any one of claims 66-74, wherein the dosage is a dosage administered once every week, once every two weeks, once every three weeks or once every four weeks;

optionally wherein (a) the isolated antibody is administered once per week for from 1 week to 16 weeks; (b) the isolated antibody is not administered for a period of from 1 week to 16 weeks; and (c) the isolated antibody is administered once per week for from 1 week to 16 weeks;

optionally wherein (a) the isolated antibody is administered once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; and (c) the isolated antibody is administered once per week for 8 weeks;

optionally wherein (a) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; and (c) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks;

optionally wherein (a) the isolated antibody is administered once per week for from 1 week to 16 weeks; (b) the isolated antibody is not administered for a period of from 1 week to 16 weeks; (c) the isolated antibody is administered once per week for from 1 week to 16 weeks; and (d) the isolated antibody is not administered for a period of from 1 week to 16 weeks;

optionally wherein (a) the isolated antibody is administered once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; (c) the isolated antibody is administered once per week for 8 weeks; and (d) the isolated antibody is not administered for a period of 8 weeks;

optionally wherein (a) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks; (b) the isolated antibody is not administered for a period of 8 weeks; (c) the isolated antibody is administered at a dosage of from about 100 mg to about 600 mg once per week for 8 weeks; and (d) the isolated antibody is not administered for a period of 8 weeks.

76. The unit dosage form of any one of claims 66-75, further comprising at least one pharmaceutically acceptable carrier, excipient, or stabilizer.

77. The unit dosage form of any one of claims 66-76, wherein the isolated antibody or antigen binding fragment thereof comprises a heavy chain as set forth in SEQ ID NO: 11 and a

light chain as set forth in SEQ ID NO: 12; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered once per week for 8 weeks, or

wherein the isolated antibody or antigen binding fragment thereof comprises a heavy chain as set forth in SEQ ID NO: 14 and a light chain as set forth in SEQ ID NO: 12; and wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered once per week for 8 weeks.

78. The unit dosage form of any one of claims 66-77, wherein the isolated antibody or antigen binding fragment thereof is administered to a subject once a week for 8 weeks; optionally wherein the isolated antibody or antigen binding fragment thereof is subcutaneously administered in a dosage of about 600 mg; optionally wherein the isolated antibody or antigen binding fragment thereof is mezagitamab; optionally wherein the ITP is persistent or chronic ITP in an adult human; optionally wherein the subject is an adult; and optionally wherein the subject has had an insufficient response or intolerance to other therapy.

79. The unit dosage form of any one of claims 66-78, wherein the isolated antibody or antigen binding fragment thereof is mezagitamab.

80. The unit dosage form of any one of claims 66-79, wherein the ITP is primary ITP; optionally wherein the ITP is persistent ITP; optionally wherein the ITP is chronic ITP; and optionally wherein the ITP is persistent or chronic primary ITP;

optionally wherein the primary ITP has persisted for at least about 3 months;

optionally wherein the subject has had a prior response to other therapy excluding a thrombopoietin receptor agonist (TPO-RA), wherein the prior response is defined as achieving a platelet count of $\geq$50,000/mL;

optionally wherein the subject has a baseline mean platelet count of <30,000/μL from at least 2 consecutive measurements taken at least about 5 days apart; optionally wherein the baseline mean platelet count comprises individual values $\leq$35,000/μL;

optionally wherein the unit dosage form is administered to a subject having an insufficient response or intolerance to other therapy; optionally wherein the other therapy is a first-line ITP therapy and/or a second-line ITP therapy; optionally wherein the other therapy

comprises one or more of a corticosteroid, immunoglobulins, splenectomy, a thrombopoietin receptor agonist (TPO-RA) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag), rituximab, fostamatinib, and background ITP medication(s) (*e.g.*, romiplostim, eltrombopag, avatrombopag, hetrombopag, methotrexate, azathioprine, leflunomide, cyclosporine, fostamatinib, mycophenolate, danazol, dapsone, methylprednisolone, hydrocortisone, cortisone, prednisolone, prednisone, and/or dexamethasone); optionally wherein the insufficient response to other treatment is defined as failure to achieve a sustained platelet count of at least 50,000/μL or doubling of baseline platelet count after an appropriate course of the other therapy; and optionally wherein the intolerance to other therapy is defined as a documented side effect causing discontinuation of the therapy.

81. The unit dosage form of any one of claims 66-80, wherein the unit dosage form is administered to a subject having a baseline mean platelet count of less than or equal to about 40×10^9/L, less than or equal to about 35×10^9/L, less than or equal to about 30×10^9/L, less than or equal to about 25×10^9/L, or less than or equal to about 20×10^9/L.

82. The unit dosage form of any one of claims 66-81, wherein the unit dosage form is administered to a subject having an ITP disease duration of at least about 0.1 years, at least about 0.3 years, at least about 0.5 years, at least about 1 year, at least about 5 years, or at least about 10 years.

83. The unit dosage form of any one of claims 66-82, wherein the isolated antibody or antigen binding fragment thereof is from about 2 times to about 4 times more efficacious than fostamatinib and/or efgartigimod; optionally wherein the isolated antibody or antigen binding fragment thereof results in from about 2 times to about 4 times more durable platelet response as compared to fostamatinib and/or efgartigimod.

84. An isolated human anti-CD38 antibody or antigen binding fragment thereof for use in the treatment of immune thrombocytopenia (ITP), wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a

CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8.

85. A pharmaceutical composition comprising an isolated human anti-CD38 antibody or antigen binding fragment thereof for treating immune thrombocytopenia (ITP) comprising an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8.

86. A medicament for treating immune thrombocytopenia (ITP) comprising an isolated human anti-CD38 antibody or antigen binding fragment thereof, wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8.

87. Use of an isolated human anti-CD38 antibody or antigen binding fragment thereof in the manufacture of a medicament for treating immunoglobulin A nephropathy (IgAN), wherein the isolated antibody or antigen binding fragment thereof comprises a variable heavy (VH) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 3, a CDR2 having the amino acid sequence of SEQ ID NO: 4, and a CDR3 having the amino acid sequence of SEQ ID NO: 5; and a variable light (VL) chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 6, a CDR2 having the amino acid sequence of SEQ ID NO: 7, and a CDR3 having the amino acid sequence of SEQ ID NO: 8.