METHODS FOR TREATING IMMUNE THROMBOCYTOPENIA BY ADMINISTERING (R)-2-[3-[4-AMINO-3-(2-FLUORO-4-PHENOXY-PHENYL)PYRAZOLO[3,4-D]PYRIMIDIN-1-YL]PIPERIDINE-1-CARBONYL]-4-METHYL-4-[4-(OXETAN-3-YL)PIPERAZIN-1-YL]PENT-2-ENENITRILE

This application claims priority to U.S. Provisional Application No. 62/914,688, filed on October 14, 2019, and U.S. Provisional Application No. 62/951,302, filed on December 20, 2019, the contents of each of which are incorporated herein by reference in their entirety.

Disclosed herein are methods for treating immune thrombocytopenia. BTK inhibitors and pharmaceutical compositions comprising the same are also disclosed.

Immune thrombocytopenia, commonly referred to as ITP, is a rare autoimmune disease that causes high risk for bleeding, excessive bruising, and fatigue, as well as the potential for life threatening intracranial bleeding due to destruction of platelets. ITP is characterized by immune-mediated (e.g., autoantibody-mediated) platelet destruction and impaired platelet production, resulting in thrombocytopenia, a predisposition to bleeding associated with morbidity and mortality, and adverse impact on patient quality of life (QOL).

Current therapies for adults with ITP include initial treatment with intravenous immunoglobulin (IVIG) and corticosteroids, and subsequent treatment with splenectomy, thrombopoietin receptor agonists (TPO-RAs), rituximab, fostamatinib, and other immunosuppressive therapies (such as, e.g., mycophenolate mofetil (MMF) and cyclosporine). In general, pharmacotherapy (e.g., corticosteroids, IVIG, or anti-D immunoglobulin therapy) is used for symptomatic patients with low platelet counts for reducing platelet destruction. While most patients respond initially to corticosteroids, the rate of continued remission is low. Second line therapies for ITP include rituximab and splenectomy, which are associated with risk of sepsis and immune suppression. Additionally, thrombopoietin (TPO) mimetics (Bussel 2007) are approved for the treatment of patients with chronic ITP who have not had sufficient responses to corticosteroids, IVIG, or splenectomy.

Novel, safe, and effective oral treatments to maintain platelet counts in ITP patients would represent a significant therapeutic advantage over current standard of care. Illustratively, unmet needs in relapsed and refractory ITP include: improving remission rates and durability; avoiding rapid increase of platelet counts/thrombosis risk; steroid-free regimens; and a tolerable and safe therapy that ensures good patient QOL. Thus, there is a need for novel oral therapies for treating ITP, including relapsed and refractory ITP, that address some or all of these limitations of existing therapeutic modalities.

Bruton's agammaglobulinemia tyrosine kinase (BTK) is an essential signaling element downstream of the B-cell receptor (BCR), Fc-gamma receptor (FcγR), and Fc-epsilon receptor (FcεR). BTK is a non-receptor tyrosine kinase and a member of the TEC family of kinases. BTK is essential to B cell lineage maturation, and inhibition of BTK activity in cells produces phenotypic changes consistent with blockade of the BCR. Illustratively, BTK inhibition results in the down-regulation of various B-cell activities, including cell proliferation, differentiation, maturation, and survival, and the up-regulation of apoptosis.

Rather than acting in an "on/off switch" manner, BTK may be best viewed as an immune function "modulator" (Crofford LJ et al., 2016; Pal Singh S et al., 2018). Important insights into BTK function come from loss of function analyses in humans and mice. Individuals with loss of function mutations in the BTK gene develop X-linked agammaglobulinemia (XLA), characterized by a complete absence of circulating B cells and plasma cells, and very low levels of immunoglobulins of all classes (Tsukada 1993, Vetrie 1993). This indicates the potential for BTK inhibition to suppress production of autoantibodies thought to be important in the development of autoimmune diseases, such as, e.g., ITP.

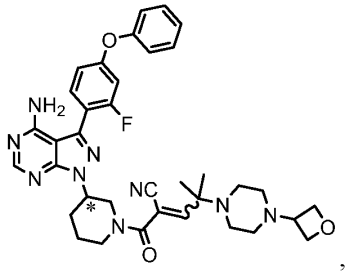
While BTK is not expressed in T cells, natural killer cells, and plasma cells and has no traceable direct functions in T cells and plasma cells (Sideras and Smith 1995; Mohamed et al., 2009), the enzyme regulates the activation of other hematopoietic cells, such as basophils, mast cells, macrophages, neutrophils, and platelets. For example, BTK plays a role in the activation of neutrophils, which are key players in the inflammatory response that contributes to wound healing but may also cause tissue damage (Volmering S et al., 2016).

Accordingly, a selective BTK inhibitor has the potential to target multiple pathways involved in inflammation and autoimmunity, including, but not limited to: blocking BCR; inhibiting plasma cell differentiation and antibody production; blocking IgG-mediated FcγR activation, phagocytosis, and inflammatory mediators in monocytes or macrophages; blocking IgE-mediated FcεR activation and degranulation in mast cells or basophils; and inhibiting activation, adhesion, recruitment, and oxidative burst in neutrophils. Based on these effects, a selective BTK inhibitor may block the initiation and progression of various inflammatory diseases and mitigate tissue damage resulting from these diseases. Although individuals with loss of function mutations in the BTK gene have decreased humoral immunity and are susceptible to pyogenic bacterial and enterovirus infections, requiring treatment with intravenous immunoglobulin, inhibition of BTK in individuals with an intact immune system is not predicted to produce similar susceptibility to infection.

Several orally administered BTK inhibitors (BTKi), including ibrutinib (PCI-32765) and spebrutinib (CC-292), are currently marketed or in clinical development for a range of indications (Lee A et al., 2017). For example, ibrutinib has provided further clinical validation of the BTK target and was recently approved for human use in mantle cell lymphoma, Waldenström's macroglobulinemia, and chronic lymphocytic leukemia by the U.S. Food and Drug Administration (FDA). Ibrutinib has also demonstrated activity in other hematological malignancies (Wang 2013, Byrd 2013, Imbruvica Package Insert, 2015). In addition, CC-292 has been reported to be well tolerated in a healthy volunteer population at doses which provide 100% occupancy of the BTK enzyme (Evans 2013). Furthermore, evobrutinib recently demonstrated efficacy for multiple sclerosis in a Phase 2 trial (Montalban X et al., 2019). Other BTKi compounds are in clinical development for various immune-mediated disorders, such as pemphigus (NCT02704429), rheumatoid arthritis (NCT03823378, NCT03682705, NCT03233230), and asthma (NCT03944707) (Montalban X et al., 2019; Norman P 2016; Tam CS et al., 2018; Crawford JJ et al., 2018; Min TK et al., 2019; Gillooly KM 2017; Nadeem A et al., 2019).

While covalent BTKi, such as ibrutinib and acalabrutinib, improved on the selectivity issues that plagued many first-generation kinase inhibitors, these inhibitors are typically irreversible, causing permanent modification of both on- and off-target kinases and side effects such as thrombocytopenia, anemia, platelet aggregation, and hepatotoxicity (RITUXAN Prescribing Information, 2018; Drug Record Kinase Inhibitors, 2019; Khan Y et al., 2019; Paydas S, 2019; IMBRUVICA, 2013; Rigg RA et al., 2016; Tang CPS et al., 2018). Thus, there is a need for treatment modalities for immune-mediated diseases, such as, e.g., ITP, based on BTKi with reduced side effects.

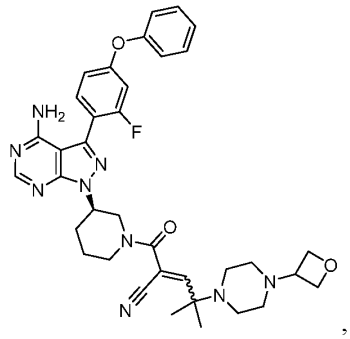
Compound (**I**) is a BTK inhibitor of the following structure:



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wherein *C is a stereochemical center. See PCT Publication No. WO 2014/039899, which is incorporated herein by reference, e.g., Example 31.

(R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, having the following structure:



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is also known as PRN1008 and rilzabrutinib. This compound has been disclosed in several patent publications, such as, e.g., PCT Publication Nos. WO 2014/039899, WO 2015/127310, WO 2016/100914, WO 2016/105531, and WO 2018/005849, the contents of each of which are incorporated by reference herein.

PRN1008 is a novel, highly selective, small molecule inhibitor of non-T cell white blood cell signaling via B-cell receptor, FCγR, and/or FcεR signaling of the BTK pathway. PRN1008 functions as a reversible covalent BTK inhibitor and forms both a non-covalent and a covalent bond with its target, allowing for enhanced selectivity and extended inhibition with low systemic exposure. In comparison to first and second generation BTKi, PRN1008 has shown minimal cross-reactivity with other molecules and is low risk for off-target effects (Smith PF et al., 2017). Importantly, PRN1008's reversible binding minimizes the likelihood of permanently modified peptides (Serafimova IM 2012). In addition, PRN1008 shows improved kinase selectivity relative to the covalent BTK inhibitor ibrutinib, with PRN1008 (1 μM) achieving > 90% inhibition for 6 kinases compared to 21 kinases for ibrutinib (1 μM) in a 251-kinase panel.

PRN1008 has shown encouraging results for the treatment of immune-mediated diseases. PRN1008 is the most advanced BTKi in development for an autoimmune disease (Phase 3, NCT03762265) and the first BTKi to be evaluated in the treatment of pemphigus, a blistering disease that, like ITP, is autoantibody-driven. In humans, PRN1008 is rapidly absorbed following oral administration, with a fast half-life (3-4 h) and variable pharmacokinetics (PK).

In Phase 1 studies of PRN1008 with 114 healthy volunteers, target BTK occupancy levels were safely and consistently exceeded, suggesting PRN1008 may be highly effective in

treating autoimmune diseases. Moreover, preclinical and clinical PK/PD data showed that treatment effects endured even after the compound was cleared from circulation, consistent with an extended target residence time (Hill R et al., 2015) and high occupancy rate (> 90% within four hours) (Smith PF et al., 2015.)

PRN1008 has also demonstrated a favorable safety profile. Based on preclinical reproductive toxicity studies, PRN1008 is not expected to harm fetal development or male fertility. In a Phase 1 study in healthy volunteers, the most commonly reported adverse events were gastrointestinal adverse events, including nausea/vomiting and diarrhea. No serious adverse events or deaths were reported, and no participants discontinued treatment due to an adverse event (Smith PF 2017).

There is preliminary evidence to support the role of BTK inhibition in patients with autoimmune cytopenias (Rogers 2016, Montillo 2017), where sequential episodes of severe autoimmune hemolytic anemia and ITP ceased after initiation of treatment with ibrutinib, a BTK/EGFR/ITK inhibitor, in patients with chronic lymphatic leukemia (CLL). Additionally, and pertinent to the treatment of ITP, PRN1008 treatment *in vitro* profoundly inhibits human B cell activation and blocks antibody (IgG, IgE) mediated activation of immune cells via Fc receptor signaling. In nonclinical studies, PRN1008 demonstrates a significant dose dependent reduction of platelet-loss (consumption) in a mouse model of immune thrombocytopenia. PRN1008 also shows rapid and significant anti-inflammatory effects in a rat collagen-induced arthritis model, a rat antibody-mediated arthus model, spontaneous canine pemphigus foliaceus, and human pemphigus vulgaris (PV).

Disclosed herein are methods for treating immune thrombocytopenia (ITP) in a human patient in need thereof comprising administering to the human patient a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (PRN1008) and pharmaceutically acceptable salts thereof once a day or twice a day for a treatment period.

In some embodiments, the treatment period is 8 days. In some embodiments, the treatment period is 28 days. In some embodiments, the treatment period is 84 days. In some embodiments, the treatment period is 168 days.

In some embodiments, the treatment period is at least 8 days. In some embodiments, the treatment period is at least 28 days. In some embodiments, the treatment period is at least 84 days. In some embodiments, the treatment period is at least 168 days.

In some embodiments, the treatment period is from 8 days to 28 days. In some embodiments, the treatment period is from 8 days to 84 days. In some embodiments, the treatment period is from 8 days to 168 days. In some embodiments, the treatment period is from 28 days to 84 days. In some embodiments, the treatment period is from 28 days to 168 days. In some embodiments, the treatment period is from 84 days to 168 days.

In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof once a day or twice a day. In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof once a day. In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof twice a day.

In some embodiments, the methods comprise administering to the human patient 300 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof twice a day.

In some embodiments, the methods comprise treating primary ITP. In some embodiments, the methods comprise treating secondary ITP. In some embodiments, the methods comprise treating chronic ITP. In some embodiments, the methods comprise treating relapsing ITP. In some embodiments, the methods comprise treating refractory ITP.

In some embodiments, the human patient has at least one characteristic prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof is administered as a monotherapy.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof is administered in combination with at least one concomitant ITP therapy.

Also disclosed herein are methods for increasing a platelet count in a human patient with immune thrombocytopenia (ITP) comprising administering to the human patient a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (PRN1008) and pharmaceutically acceptable salts thereof once a day or twice a day for a treatment period.

In some embodiments, the methods comprise increasing at least 2 consecutive platelet counts relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 2 consecutive platelet counts relative to a pre-administration baseline platelet count without requiring rescue medication.

In some embodiments, the methods comprise increasing a platelet count by at least 5,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing a platelet count by at least 10,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing a platelet count by at least 15,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing a platelet count by at least 20,000/μL relative to a pre-administration baseline platelet count.

In some embodiments, the methods comprise increasing at least 30% of platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 40% of platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 50% of platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 60% of platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 70% of platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count.

In some embodiments, the methods comprise increasing at least 2 of the final 8 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 3 of the final 8 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 4 of the final 8 platelet counts measured during the

treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 5 of the final 8 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 6 of the final 8 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 7 of the final 8 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count.

In some embodiments, the methods comprise increasing at least 2 of the final 6 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 3 of the final 6 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 4 of the final 6 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 5 of the final 6 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count.

In some embodiments, the pre-administration baseline platelet count is an average of the human patient's two most recent platelet counts prior to the start of the treatment period and the human patient's platelet count on the first day of the treatment period. In some embodiments, the pre-administration baseline platelet count is an average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart, and the human patient's platelet count on the first day of the treatment period. In some embodiments, the pre-administration baseline platelet count is an average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period, and the human patient's platelet count on the first day of the treatment period.

In some embodiments, consecutive platelet counts are measured at least 5 days apart.

In some embodiments, the treatment period is 8 days. In some embodiments, the treatment period is 28 days. In some embodiments, the treatment period is 84 days. In some embodiments, the treatment period is 168 days.

In some embodiments, the treatment period is at least 8 days. In some embodiments, the treatment period is at least 28 days. In some embodiments, the treatment period is at least 84 days. In some embodiments, the treatment period is at least 168 days.

In some embodiments, the treatment period is from 8 days to 28 days. In some embodiments, the treatment period is from 8 days to 84 days. In some embodiments, the treatment period is from 8 days to 168 days. In some embodiments, the treatment period is from 28 days to 84 days. In some embodiments, the treatment period is from 28 days to 168 days. In some embodiments, the treatment period is from 84 days to 168 days.

In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof once a day or twice a day. In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof once a day. In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof twice a day.

In some embodiments, the methods comprise administering to the human patient 300 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof twice a day.

In some embodiments, the human patient has primary ITP. In some embodiments, the human patient has secondary ITP. In some embodiments, the human patient has chronic ITP. In some embodiments, the human patient has relapsing ITP. In some embodiments, the human patient has refractory ITP.

In some embodiments, the human patient has at least one characteristic prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof is administered as a monotherapy.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof is administered in combination with at least one concomitant ITP therapy.

Also disclosed herein are methods for achieving a platelet count of at least 50,000/μL in a human patient with immune thrombocytopenia (ITP) comprising administering to the human patient a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (PRN1008) and pharmaceutically acceptable salts thereof once a day or twice a day for a treatment period.

In some embodiments, the methods comprise achieving at least 2 platelet counts of at least 50,000/μL. In some embodiments, the methods comprise achieving at least 2 platelet counts of at least 50,000/μL without requiring rescue medication.

In some embodiments, the methods comprise achieving at least 2 consecutive platelet counts of at least 50,000/μL. In some embodiments, the methods comprise achieving at least 2 consecutive platelet counts of at least 50,000/μL without requiring rescue medication.

In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 30% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 35% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 40% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 45% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 50% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 55% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 60% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 65% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 70% of platelet counts measured during the treatment period.

In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 2 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 3 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 4 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 5 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 6 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 7 of the final 8 platelet counts measured during the treatment period.

In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 2 of the final 6 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 3 of the final 6 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 4 of the final 6 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 5 of the final 6 platelet counts measured during the treatment period.

In some embodiments, the methods comprise increasing at least 30% of platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 40% of platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 50% of platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 60% of platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 70% of platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count.

In some embodiments, the methods comprise increasing at least 2 of the final 8 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing

at least 3 of the final 8 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 4 of the final 8 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 5 of the final 8 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 6 of the final 8 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 7 of the final 8 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count.

In some embodiments, the methods comprise increasing at least 2 of the final 6 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 3 of the final 6 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 4 of the final 6 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 5 of the final 6 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count.

In some embodiments, the pre-administration baseline platelet count is an average of the human patient's two most recent platelet counts prior to the start of the treatment period and the human patient's platelet count on the first day of the treatment period. In some embodiments, the pre-administration baseline platelet count is an average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart, and the human patient's platelet count on the first day of the treatment period. In some embodiments, the pre-administration baseline platelet count is an average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period, and the human patient's platelet count on the first day of the treatment period.

In some embodiments, consecutive platelet counts are measured at least 5 days apart.

In some embodiments, the treatment period is 8 days. In some embodiments, the treatment period is 28 days. In some embodiments, the treatment period is 84 days. In some embodiments, the treatment period is 168 days.

In some embodiments, the treatment period is at least 8 days. In some embodiments, the treatment period is at least 28 days. In some embodiments, the treatment period is at least 84 days. In some embodiments, the treatment period is at least 168 days.

In some embodiments, the treatment period is from 8 days to 28 days. In some embodiments, the treatment period is from 8 days to 84 days. In some embodiments, the treatment period is from 8 days to 168 days. In some embodiments, the treatment period is from 28 days to 84 days. In some embodiments, the treatment period is from 28 days to 168 days. In some embodiments, the treatment period is from 84 days to 168 days.

In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof once a day or twice a day. In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof once a day. In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof twice a day.

In some embodiments, the methods comprise administering to the human patient 300 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof twice a day.

In some embodiments, the human patient has primary ITP. In some embodiments, the human patient has secondary ITP. In some embodiments, the human patient has chronic ITP. In some embodiments, the human patient has relapsing ITP. In some embodiments, the human patient has refractory ITP.

In some embodiments, the human patient has at least one characteristic prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof is administered as a monotherapy.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof is administered in combination with at least one concomitant ITP therapy.

Also disclosed herein are methods for achieving at least one platelet count of at least 50,000/μL and increasing at least one platelet count by at least 20,000/μL in a human patient with immune thrombocytopenia (ITP) comprising administering to the human patient a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (PRN1008) and pharmaceutically acceptable salts thereof once a day or twice a day for a treatment period.

In some embodiments, the methods comprise achieving at least 2 platelet counts of at least 50,000/μL. In some embodiments, the methods comprise achieving at least 2 platelet counts of at least 50,000/μL without requiring rescue medication.

In some embodiments, the methods comprise achieving at least 2 consecutive platelet counts of at least 50,000/μL. In some embodiments, the methods comprise achieving at least 2 consecutive platelet counts of at least 50,000/μL without requiring rescue medication.

In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 30% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 35% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 40% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 45% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 50% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 55% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 60% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 65% of platelet counts measured during the treatment period. In some embodiments, the methods comprise

achieving a platelet count of at least 50,000/μL in at least 70% of platelet counts measured during the treatment period.

In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 2 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 3 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 4 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 5 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 6 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 7 of the final 8 platelet counts measured during the treatment period.

In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 2 of the final 6 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 3 of the final 6 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 4 of the final 6 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 5 of the final 6 platelet counts measured during the treatment period.

In some embodiments, consecutive platelet counts are measured at least 5 days apart.

In some embodiments, the treatment period is 8 days. In some embodiments, the treatment period is 28 days. In some embodiments, the treatment period is 84 days. In some embodiments, the treatment period is 168 days.

In some embodiments, the treatment period is at least 8 days. In some embodiments, the treatment period is at least 28 days. In some embodiments, the treatment period is at least 84 days. In some embodiments, the treatment period is at least 168 days.

In some embodiments, the treatment period is from 8 days to 28 days. In some embodiments, the treatment period is from 8 days to 84 days. In some embodiments, the treatment period is from 8 days to 168 days. In some embodiments, the treatment period is from 28 days to 84 days. In some embodiments, the treatment period is from 28 days to 168 days. In some embodiments, the treatment period is from 84 days to 168 days.

In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof once a day or twice a day. In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof once a day. In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof twice a day.

In some embodiments, the methods comprise administering to the human patient 300 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof twice a day.

In some embodiments, the human patient has primary ITP. In some embodiments, the human patient has secondary ITP. In some embodiments, the human patient has chronic ITP. In some embodiments, the human patient has relapsing ITP. In some embodiments, the human patient has refractory ITP.

In some embodiments, the human patient has at least one characteristic prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof is administered as a monotherapy.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof is administered in combination with at least one concomitant ITP therapy.

Also disclosed herein are methods for achieving a platelet count of at least 30,000/μL in a human patient with immune thrombocytopenia (ITP) comprising administering to the human patient a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (PRN1008) and pharmaceutically acceptable salts thereof once a day or twice a day for a treatment period.

In some embodiments, the treatment period is 8 days. In some embodiments, the treatment period is 28 days. In some embodiments, the treatment period is 84 days. In some embodiments, the treatment period is 168 days.

In some embodiments, the treatment period is at least 8 days. In some embodiments, the treatment period is at least 28 days. In some embodiments, the treatment period is at least 84 days. In some embodiments, the treatment period is at least 168 days.

In some embodiments, the treatment period is from 8 days to 28 days. In some embodiments, the treatment period is from 8 days to 84 days. In some embodiments, the treatment period is from 8 days to 168 days. In some embodiments, the treatment period is from 28 days to 84 days. In some embodiments, the treatment period is from 28 days to 168 days. In some embodiments, the treatment period is from 84 days to 168 days.

In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof once a day or twice a day. In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof once a day. In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof twice a day.

In some embodiments, the methods comprise administering to the human patient 300 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof twice a day.

In some embodiments, the human patient has primary ITP. In some embodiments, the human patient has secondary ITP. In some embodiments, the human patient has chronic ITP. In some embodiments, the human patient has relapsing ITP. In some embodiments, the human patient has refractory ITP.

In some embodiments, the human patient has at least one characteristic prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof is administered as a monotherapy.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof is administered in combination with at least one concomitant ITP therapy.

Example Embodiments 1:

Without limitation, some embodiments of the disclosure include:

1. A method for treating immune thrombocytopenia (ITP) in a human patient in need thereof comprising administering to the human patient a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (PRN1008) and pharmaceutically acceptable salts thereof once a day or twice a day for a treatment period, wherein the human patient has at least one characteristic chosen from:

an average plasma count of from 3,000/μL to 33,000/μL for a most recent platelet count prior to the start of the treatment period, a second most recent platelet count prior to the start of the treatment period, and a platelet count on the first day of the treatment period;

a history of taking at least 4 prior ITP therapies prior to the start of the treatment period; and

splenectomy prior to the start of the treatment period.

2. A method for increasing a platelet count in a human patient with immune thrombocytopenia (ITP) comprising administering to the human patient a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (PRN1008) and pharmaceutically acceptable salts thereof once a day or twice a day for a treatment period, wherein the human patient has at least one characteristic chosen from:

an average plasma count of from 3,000/μL to 33,000/μL for a most recent platelet count prior to the start of the treatment period, a second most recent platelet count prior to the start of the treatment period, and a platelet count on the first day of the treatment period;

a history of taking at least 4 prior ITP therapies prior to the start of the treatment period; and

splenectomy prior to the start of the treatment period.

3. The method according to Embodiment 2, wherein increasing the platelet count comprises increasing a platelet count by at least 20,000/μL relative to a pre-administration baseline platelet count.

4. The method according to Embodiment 2 or 3, wherein increasing the platelet count comprises increasing at least 50% of platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count.

5. The method according to any of Embodiments 2-4, wherein increasing the platelet count comprises increasing at least 2 consecutive platelet counts relative to a pre-administration baseline platelet count.

6. The method according to any of Embodiments 3-5, wherein the pre-administration baseline platelet count is an average of the human patient's two most recent platelet counts prior to the start of the treatment period and the human patient's platelet count on the first day of the treatment period.

7. A method for achieving a platelet count of at least 50,000/μL in a human patient with immune thrombocytopenia (ITP) comprising administering to the human patient a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (PRN1008) and pharmaceutically acceptable salts thereof once a day or twice a day for a treatment period, wherein the human patient has at least one characteristic chosen from:

an average plasma count of from 3,000/μL to 33,000/μL for a most recent platelet count prior to the start of the treatment period, a second most recent platelet count prior to the start of the treatment period, and a platelet count on the first day of the treatment period;

a history of taking at least 4 prior ITP therapies prior to the start of the treatment period; and

splenectomy prior to the start of the treatment period.

8. The method according to Embodiment 7, wherein achieving a platelet count comprises achieving at least 2 platelet counts of at least 50,000/μL.

9. The method according to Embodiment 7 or 8, wherein achieving a platelet count comprises achieving at least 2 consecutive platelet counts of at least 50,000/μL.

10. The method according to any of Embodiments 7-9, wherein achieving a platelet count comprises achieving a platelet count of at least 50,000/μL in at least 50% of platelet counts measured during the treatment period.

11. The method according to any of Embodiments 7-10, wherein achieving a platelet count comprises achieving a platelet count of at least 50,000/μL in at least 4 of the final 8 platelet counts measured during the treatment period.

12. The method according to any of Embodiments 7-11, wherein achieving a platelet count comprises achieving a platelet count of at least 50,000/μL in at least 4 of the final 6 platelet counts measured during the treatment period.

13. A method for achieving at least one platelet count of at least 50,000/μL and increasing at least one platelet count by at least 20,000/μL in a human patient with immune thrombocytopenia (ITP) comprising administering to the human patient a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (PRN1008) and pharmaceutically acceptable salts thereof once a day or twice a day for a treatment period, wherein the human patient has at least one characteristic chosen from:

an average plasma count of from 3,000/μL to 33,000/μL for a most recent platelet count prior to the start of the treatment period, a second most recent platelet count prior to the start of the treatment period, and a platelet count on the first day of the treatment period;

a history of taking at least 4 prior ITP therapies prior to the start of the treatment period; and

splenectomy prior to the start of the treatment period.

14. The method according to Embodiment 13, wherein achieving a platelet count comprises achieving at least 2 platelet counts of at least 50,000/μL.

15. The method according to Embodiment 13 or 14, wherein achieving a platelet count comprises achieving at least 2 consecutive platelet counts of at least 50,000/μL.

16. The method according to any of Embodiments 13-15, wherein achieving a platelet count comprises achieving a platelet count of at least 50,000/μL in at least 50% of platelet counts measured during the treatment period.

17. The method according to any of Embodiments 13-16, wherein achieving a platelet count comprises achieving a platelet count of at least 50,000/μL in at least 4 of the final 8 platelet counts measured during the treatment period.

18. The method according to any of Embodiments 13-17, wherein achieving a platelet count comprises achieving a platelet count of at least 50,000/μL in at least 4 of the final 6 platelet counts measured during the treatment period.

19. The method according to any of Embodiments 13-18, wherein achieving a platelet count comprises increasing at least 50% of platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count.

20. The method according to Embodiment 19, wherein the pre-administration baseline platelet count is an average of the human patient's two most recent platelet counts prior to the start of the treatment period and the human patient's platelet count on the first day of the treatment period.

21. A method for achieving a platelet count of at least 30,000/μL in a human patient with immune thrombocytopenia (ITP) comprising administering to the human patient a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (PRN1008) and pharmaceutically acceptable salts thereof once a day or twice a day for a treatment period, wherein the human patient has at least one characteristic chosen from:

an average plasma count of from 3,000/μL to 33,000/μL for a most recent platelet count prior to the start of the treatment period, a second most recent platelet count prior to the start of the treatment period, and a platelet count on the first day of the treatment period;

a history of taking at least 4 prior ITP therapies prior to the start of the treatment period; and

splenectomy prior to the start of the treatment period.

22. The method according to Embodiment 21, wherein achieving a platelet count comprises achieving a platelet count of at least 30,000/μL in at least 50% of platelet counts measured during the treatment period

23. The method according to Embodiment 21 or 22, wherein achieving a platelet count comprises achieving a platelet count of at least 30,000/μL in at least 75% of platelet counts measured during the treatment period

24. The method according to any of Embodiments 1-23, wherein consecutive platelet counts are measured at least 5 days apart.

25. The method according to any of Embodiments 1-24, wherein the human patient has an average plasma count of from 3,000/μL to 33,000/μL for the most recent platelet count prior to the start of the treatment period, the second most recent platelet count prior to the start of the treatment period, and the platelet count on the first day of the treatment period.

26. The method according to any of Embodiments 1-24, wherein the human patient has an average plasma count of from 3,000/μL to 15,000/μL for the most recent platelet count prior to the start of the treatment period, the second most recent platelet count prior to the start of the treatment period, and the platelet count on the first day of the treatment period.

27. The method according to any of Embodiments 1-26, wherein the human patient has a history of taking at least 4 prior ITP therapies prior to the start of the treatment period.

28. The method according to any of Embodiments 1-27, wherein the human patient had a splenectomy prior to the start of the treatment period.

29. The method according to any of Embodiments 1-28, wherein the human patient has primary ITP.

30. The method according to any of Embodiments 1-28, wherein the human patient has secondary ITP.

31. The method according to any of Embodiments 1-28, wherein the human patient has chronic ITP.

32. The method according to any of Embodiments 1-28, wherein the human patient has relapsing ITP.

33. The method according to any of Embodiments 1-32, wherein the human patient has refractory ITP.

34. The method according to any of Embodiments 1-33, wherein the human patient has no available and approved therapeutic options.

35. The method according to any of Embodiments 1-34, wherein the human patient has a platelet count of less than 30,000/μL prior to the start of the treatment period.

36. The method according to any of Embodiments 1-35, wherein the human patient has 2 platelet counts of less than 30,000/μL prior to the start of the treatment period.

37. The method according to any of Embodiments 1-36, wherein the human patient has 2 platelet counts of less than 30,000/μL prior to the start of the treatment period, wherein the 2 counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period.

38. The method according to any of Embodiments 1-37, wherein the at least 4 prior ITP therapies are chosen from corticosteroids, thrombopoietin receptor agonists, intravenous immunoglobulin, anti-D immunoglobulin, and rituximab.

39. The method according to any of Embodiments 1-38, wherein the treatment period is at least 8 days.

40. The method according to any of Embodiments 1-38, wherein the treatment period is at least 28 days.

41. The method according to any of Embodiments 1-38, wherein the treatment period is at least 84 days.

42. The method according to any of Embodiments 1-38, wherein the treatment period is at least 168 days.

43. The method according to any of Embodiments 1-42, comprising administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof once a day or twice a day.

44. The method according to any of Embodiments 1-43, comprising administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof once a day.

45. The method according to any of Embodiments 1-43, comprising administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof twice a day.

46. The method according to any of Embodiments 1-42, comprising administering to the human patient 300 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof twice a day.

47. The method according to any of Embodiments 1-46, wherein the at least one compound is administered as a monotherapy.

48. The method according to any of Embodiments 1-46, wherein the at least one compound is administered in combination with at least one concomitant ITP therapy.

49. The method according to Embodiment 48, wherein the at least one concomitant ITP therapy is chosen from corticosteroids and thrombopoietin receptor agonists.

50. The method according to Embodiment 48 or 49, wherein the at least one concomitant ITP therapy is chosen from corticosteroids, eltrombopag, and romiplostim.

51. The method according to any of Embodiments 1-50, wherein the at least one compound comprises at least one compound chosen from the (E) isomer of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and pharmaceutically acceptable salts thereof.

52. The method according to any of Embodiments 1-50, wherein the at least one compound comprises at least one compound chosen from the (Z) isomer of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and pharmaceutically acceptable salts thereof.

53. The method according to any of Embodiments 1-50, wherein the at least one compound comprises a mixture of (E) and (Z) isomers of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile or a pharmaceutically acceptable salt of the foregoing.

54. The method according to any of Embodiments 1-53, wherein the at least one compound is orally administered to the human patient.

55. The method according to any of Embodiments 1-54, wherein the at least one compound is administered to the human patient in the form of at least one tablet.

56. The method according to any of Embodiments 1-55, wherein the at least one compound is administered with a glass of water.

57. The method according to any of Embodiments 1-56, wherein the at least one compound is administered with food.

58. The method according to any of Embodiments 1-56, wherein the at least one compound is administered without food.

Example Embodiments 2:

Without limitation, some embodiments of the disclosure include:

1. A method for treating immune thrombocytopenia in a human patient comprising: administering to the patient a dose chosen from 400 mg once daily (QD), 300 mg twice daily (BID), and 400 mg BID of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (PRN1008).

2. The method according to Embodiment 1, wherein PRN1008 comprises a mixture of (E) and (Z) isomers of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile.

3. The method according to Embodiment 1, wherein PRN1008 is formulated as a pharmaceutical composition.

4. The method according to Embodiment 3, wherein the pharmaceutical composition comprises one or more pharmaceutical acceptable carriers or excipients.

5. The method according to Embodiment 4, wherein the pharmaceutical composition comprises microcrystalline cellulose, crospovidone, and sodium stearyl fumarate with a film coating.

6. The method according to Embodiment 1, further comprising repeating the administration of PRN1008 to the patient over a treatment period.

7. The method according to Embodiment 1, wherein the dose is 400 mg BID of PRN1008.

8. The method according to Embodiment 1, wherein the patient is administered an initial dose of 400 mg QD of PRN1008, and after 28 days, the dose is escalated to a higher dose of 300 mg BID or 400 mg BID of PRN1008.

9. The method according to Embodiment 1, wherein the patient is administered an initial dose of 300 mg BID of PRN1008, and after 28 days, the dose is escalated to 400 mg BID of PRN1008.

10. The method according to Embodiment 6, wherein the treatment period is for a period of up to 168 days.

11. The method according to Embodiment 6, wherein the treatment period ranges from 28 days to 168 days.

12. The method according to Embodiment 6, wherein the treatment period is for a minimum of 8 days.

13. The method according to Embodiment 6, wherein the treatment period ranges from 8 days to 28 days.

14. The method according to Embodiment 1, wherein before administration, the patient's platelet count is less than 30,000/μL for two or more consecutive platelet counts.

15. The method according to Embodiment 1, wherein after administration over a treatment period, the patient obtains two or more consecutive platelet counts, separated by at least 5 days, of ≥ 50,000/μL.

16. The method according to Embodiment 15, wherein the treatment period ranges from 28 days to 168 days.

17. The method according to Embodiment 6, wherein after administration over a treatment period, the patient has a stable response of a platelet count of greater than or equal to 50,000/μL during the treatment period and an increase of platelet count of ≥ 20,000/μL from baseline.

18. The method according to Embodiment 15, wherein the patient has a rapid onset of response within one to two weeks (7-14 days) corresponding to an increased platelet count of about 50,000/μL to 100,000/μL.

19. The method according to Embodiment 15, wherein the patient has a rapid onset of response within one to two weeks (7-14 days) corresponding to an increased platelet count of 60,000/μL to 90,000/μL

20. The method according to Embodiment 16, wherein the rapid onset of response is within 1 week (7 days).

21. The method according to Embodiment 16, wherein the patient is administered an initial dose of 300 mg BID or 400 mg BID of PRN1008.

22. The method according to Embodiment 1, wherein before administration, the patient has relapsed or refractory idiopathic thrombocytopenia, which is primary or secondary to other diseases afflicting the patient.

23. The method according to Embodiment 1, wherein in the patient has secondary ITP.

24. The method according to Embodiment 21, wherein the patient is administered a dose of 400 mg BID.

25. The method according to Embodiment 1, wherein the patient is also taking one or more concomitant medications.

26. The method according to Embodiment 25, wherein the one or more concomitant medication is chosen from corticosteroids, eltrombopag, and romiplostim.

27. A method for treating immune thrombocytopenia in a human patient comprising: administering to the patient a dose chosen from 400 mg once daily (QD), 300 mg twice daily (BID), and 400 mg BID of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]-pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (PRN1008), wherein before administration, the patient's platelet count is less than 30,000/μL for two or more consecutive platelet counts, and wherein after administration, the patient has a stable response of a platelet count of greater than or equal to 50,000/μL during the treatment period.

28. The method according to Embodiment 27, wherein the dose is 400 mg BID of PRN1008.

29. A method for treating immune thrombocytopenia in a human patient comprising: administering to the patient a dose chosen from 400 mg once daily (QD), 300 mg twice daily (BID), and 400 mg BID of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]-pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (PRN1008), wherein before administration, the patient's platelet count is less than 30,000/μL for two or more consecutive platelet counts, and after administration over a treatment period, the patient obtains two or more consecutive platelet counts, separated by at least 5 days, of $\geq$ 50,000/μL and an increase of platelet count of $\geq$ 20,000/μL from baseline.

30. The method according to Embodiment 29, wherein the dose is 400 mg BID of PRN1008.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1A illustrates PRN1008's reversible covalent binding mechanism, which enables optimized clinical activity with minimal drug exposure and benefits associated with reversibility.

FIG. 1B depicts PK exposure (ng/mL) and % BTK inhibition over 25 h for PRN1008.

FIG. 2 depicts the dose-escalation rules for the dose-finding portion of an adaptive, open-label, dose-finding, phase 1/2 study investigating PRN1008 in ITP patients.

FIG. 3A depicts the effects of 1 μM PRN1008 on platelet function as assessed *in vitro* in normal healthy volunteer blood platelets using a standard panel of platelet agonists.

FIG. 3B depicts the effects of 1 μM PRN1008 on platelet function as assessed *in vitro* in ITP patient blood platelets using a standard panel of platelet agonists.

FIG. 4 depicts the effects of 1 μM ibrutinib on platelet function as assessed *in vitro* in normal healthy volunteer blood platelets using a standard panel of platelet agonists.

FIG. 5 depicts the platelet count response over time for a patient with secondary ITP enrolled in a phase 1/2 study investigating PRN1008 in ITP patients.

FIG. 6 depicts the platelet count response over time for phase 1/2 ITP dose-finding study patients who started on a low starting dose of PRN1008 (QD dosing) (n = 10) (data cut-off: November 13, 2019).

FIG. 7 depicts the platelet count response over time for phase 1/2 ITP dose-finding study patients who started on a high starting dose of PRN1008 (BID dosing) (n = 21) (data cut-off: November 13, 2019).

FIG. 8 depicts summary statistics for platelet response in phase 1/2 ITP patients (data cut-off: November 13, 2019).

FIG. 9 depicts the platelet count response over time for phase 1/2 ITP patients who started on 400 mg PRN1008 bid (n = 32) (data cut-off: April 22, 2020).

FIG. 10 depicts summary statistics for platelet response in phase 1/2 ITP patients (data cut-off: April 22, 2020).

Definitions:

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meanings. All undefined technical and scientific terms used in this Application have the meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

As used herein, "a" or "an" entity refers to one or more of that entity; for example, a compound refers to one or more compounds or at least one compound unless stated otherwise. As such, the terms "a" (or "an"), "one or more", and "at least one" can be used interchangeably herein.

As used herein, the term "about" is used herein to mean approximately, in the region of, roughly, or around. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" is used herein to modify a numerical value above and below the stated value by a variance of 5%. With regard to specific values, it should be understood that specific values described herein for subject populations (e.g., the subject of the described clinical trial) represent median, mean, or statistical numbers, unless otherwise provided. Accordingly, aspects of the present disclosure requiring a particular value in a subject are supported herein by population data in which the relevant value is assessed to be a meaningful delimitation on the subject population.

As used herein, the term "active pharmaceutical ingredient" or "therapeutic agent" ("API") refers to a biologically active compound.

As used herein, the terms "administer," "administering," or "administration" herein refer to providing, giving, dosing, and/or prescribing by either a health practitioner or an authorized agent and/or putting into, taking or consuming by the patient or person himself or

herself. For example, "administration" of an API to a patient refers to any route (e.g., oral delivery) of introducing or delivering the API to the patient. Administration includes self administration and administration by another.

As used herein, "BID" and "bid" are used interchangeably to refer to twice a day.

As used herein, "immune thrombocytopenia" (ITP) encompasses or at least also refers to other terms commonly used such as idiopathic thrombocytopenia and idiopathic thrombocytopenic purpura. There are two main types of ITP: short (acute) and chronic (long term). Acute ITP typically lasts less than six months, whereas chronic ITP can last six months or longer. ITP affects multiple age groups and can be seen in children, teenagers, and adults.

As used herein, the term "in combination with," when referring to two or more compounds, agents, or additional active pharmaceutical ingredients, means the administration of two or more compounds, agents, or active pharmaceutical ingredients to the patient prior to, concurrent with, or subsequent to each other during a treatment period. Unless specified otherwise, the two or more compounds, agents, or active pharmaceutical ingredients may be administered on different schedules during the treatment period, such as, e.g., with one or more compounds, agents, or active pharmaceutical ingredients being administered once a day and one or more other compounds, agents, or active pharmaceutical ingredients being administered twice a day.

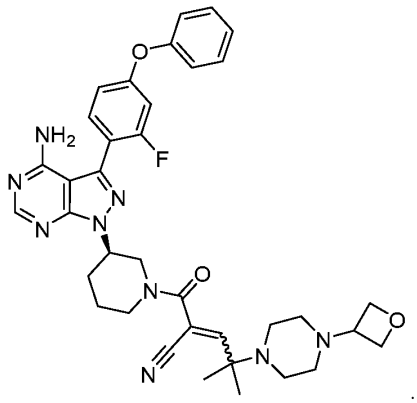
As used herein, an amount expressed in terms of "mg of [X]" refers to the total amount in milligrams of [X], i.e., the free base. In some embodiments, PRN1008 may be administered as a pharmaceutically acceptable salt of PRN1008, in which case an amount expressed in terms of "mg of PRN1008" refers to the total amount in milligrams of PRN1008, i.e., the free base, plus the equivalent amount of one or more pharmaceutically acceptable salts of PRN1008 based on the weight of free base therein. For example, "400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof" includes 400 mg of PRN1008 and a concentration of one or more pharmaceutically acceptable salts of PRN1008 equivalent to 400 mg of PRN1008.

As used herein, a "pharmaceutically acceptable carrier or excipient" means a carrier or an excipient that is useful in preparing a pharmaceutical composition that is generally safe, and neither biologically nor otherwise undesirable, such as, e.g., a carrier or an excipient that is acceptable for mammalian pharmaceutical use.

As used herein, the term "pharmaceutically acceptable salt" refers to a salt form, e.g., an acid addition salt, of an active pharmaceutical agent that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the API of which the salt is made.

Pharmaceutically acceptable salts are well known in the art and include those derived from suitable inorganic and organic acids. Such salts include, but are not limited to, salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, and the like; or formed with organic acids such as formic acid, acetic acid, propionic acid, hexanoic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, benzenesulfonic acid, 4-toluenesulfonic acid, and the like. S. M. Berge et al. describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19.

As used herein, the terms "PRN1008," "rilzabrutinib," "(R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile" and "2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]-pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile" are used interchangeably to refer to a compound having the structure:



A dose of PRN1008 may contain the corresponding (S) enantiomer as an impurity in less than about 5% by weight, such as, e.g., as an impurity in less than about 1% by weight. Similarly, a dose of the (E) isomer of PRN1008 may contain the corresponding (Z) isomer as an impurity in less than about 1% by weight; a dose of the (Z) isomer of PRN1008 may contain the corresponding (E) isomer as an impurity in less than about 1% by weight. When PRN1008 is denoted as a mixture of (E) and (Z) isomers of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, it means that the amount of (E) or (Z) isomer in the mixture is greater than about 1% by weight. In some embodiments, the molar ratio of (E) to (Z) isomer

is 9:1. PRN1008 or a pharmaceutically acceptable salt thereof may also be referred to herein as a "drug," "active agent," "a therapeutically active agent," or "API."

As used herein, "QD" and "qd" are used interchangeably to refer to once a day.

As used herein, the term "therapeutically effective amount" refers to that an of a compound that produces the desired effect for which it is administered (e.g., improvement in ITP or a symptom of ITP, or lessening the severity of ITP or a symptom of ITP). The exact amount of an effective dose will depend on the purpose of the treatment and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lloyd (1999) The Art, Science and Technology of Pharmaceutical Compounding).

As used herein, the term "treat," "treating," or "treatment," when used in connection with a disorder or condition, includes any effect, e.g., lessening, reducing, modulating, ameliorating, or eliminating, that results in the improvement of the disorder or condition. Improvements in or lessening the severity of any symptom of the disorder or condition can be readily assessed according to standard methods and techniques known in the art.

Some embodiments of the present disclosure relate to methods for treating immune thrombocytopenia (ITP) in a human patient in need thereof comprising administering to the human patient a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (PRN1008) and pharmaceutically acceptable salts thereof once a day or twice a day for a treatment period.

In some embodiments, the treatment period is 8 days. In some embodiments, the treatment period is 28 days. In some embodiments, the treatment period is 84 days. In some embodiments, the treatment period is 168 days.

In some embodiments, the treatment period is at least 8 days. In some embodiments, the treatment period is at least 28 days. In some embodiments, the treatment period is at least 84 days. In some embodiments, the treatment period is at least 168 days.

In some embodiments, the treatment period is from 8 days to 28 days. In some embodiments, the treatment period is from 8 days to 84 days. In some embodiments, the treatment period is from 8 days to 168 days. In some embodiments, the treatment period is from 28 days to 84 days. In some embodiments, the treatment period is from 28 days to 168 days. In some embodiments, the treatment period is from 84 days to 168 days.

In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts

thereof once a day or twice a day. In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof once a day. In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof twice a day.

In some embodiments, the methods comprise administering to the human patient 300 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof twice a day.

In some embodiments, the methods comprise treating primary ITP. In some embodiments, the methods comprise treating secondary ITP. In some embodiments, the methods comprise treating chronic ITP. In some embodiments, the methods comprise treating relapsing ITP. In some embodiments, the methods comprise treating refractory ITP.

In some embodiments, the human patient has at least one characteristic prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has at least 2 characteristics prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has at least 3 characteristics prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has at least 4 characteristics prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has at least 5 characteristics prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has all of the following characteristics prior to the start of the treatment period:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient is from 21 to 74 years old prior to the start of the treatment period.

In some embodiments, the human patient has 2 platelet counts of less than 30,000/μL prior to the start of the treatment period. In some embodiments, the human patient has 2 platelet counts of less than 30,000/μL prior to the start of the treatment period, wherein the 2 counts are measured no sooner than 7 days apart. In some embodiments, the human patient has 2 platelet counts of less than 30,000/μL prior to the start of the treatment period, wherein the 2 counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period.

In some embodiments, the human patient has a platelet count of less than 30,000/μL for at least 2 consecutive platelet counts prior to the start of the treatment period. In some embodiments, the human patient has a platelet count of less than 30,000/μL for at least 2 consecutive platelet counts prior to the start of the treatment period, wherein the 2 counts are measured no sooner than 7 days apart. In some embodiments, the human patient has a platelet count of less than 30,000/μL for at least 2 consecutive platelet counts prior to the start of the treatment period, wherein the 2 counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 28,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 28,000/μL, wherein the two counts are measured no sooner than 7 days apart. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 28,000/μL, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 33,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 33,000/μL, wherein the two counts are measured no sooner than 7 days apart. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 33,000/μL, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 28,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 28,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 28,000/μL.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 15,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 15,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 15,000/μL.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 33,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 33,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 33,000/μL.

In some embodiments, the human patient had ITP for at least 2 months prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 3 months prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 4 months prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 5 months prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 6 months prior to the start of the treatment period.

In some embodiments, the human patient had ITP for at least 1 year prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 2 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 3 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 4 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 5 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 6 years prior to the start of the treatment

period. In some embodiments, the human patient had ITP for at least 7 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 8 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 9 years prior to the start of the treatment period.

In some embodiments, the human patient had ITP for at least 10 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 20 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 30 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 40 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 50 years prior to the start of the treatment period.

In some embodiments, the human patient has a history of taking from 1 to 41 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking from 1 to 54 prior ITP therapies prior to the start of the treatment period.

In some embodiments, the human patient has a history of taking at least one prior ITP therapy prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 2 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 3 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 4 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 5 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 6 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 7 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 8 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 9 prior ITP therapies prior to the start of the treatment period.

In some embodiments, the human patient has a history of taking at least 10 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 15 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 20 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 25 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 30 prior ITP therapies prior to

the start of the treatment period. In some embodiments, the human patient has a history of taking at least 35 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 40 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 45 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 50 prior ITP therapies prior to the start of the treatment period.

In some embodiments, the at least one prior ITP therapy is chosen from corticosteroids, thrombopoietin receptor agonists, intravenous immunoglobulin, anti-D immunoglobulin, and rituximab.

In some embodiments, the human patient had a splenectomy prior to the start of the treatment period.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof is administered as a monotherapy.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof is administered in combination with at least one concomitant ITP therapy.

In some embodiments, the at least one concomitant ITP therapy is chosen from corticosteroids and thrombopoietin receptor agonists. In some embodiments, the at least one concomitant ITP therapy is chosen from corticosteroids, eltrombopag, and romiplostim.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof comprises at least one compound chosen from the (E) isomer of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and pharmaceutically acceptable salts thereof.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof comprises at least one compound chosen from the (Z) isomer of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and pharmaceutically acceptable salts thereof.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof comprises a mixture of (E) and (Z) isomers of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-

carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile or a pharmaceutically acceptable salt of the foregoing.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof consists of at least one compound chosen from the (E) isomer of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and pharmaceutically acceptable salts thereof.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof consists of at least one compound chosen from the (Z) isomer of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and pharmaceutically acceptable salts thereof.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof consists of a mixture of (E) and (Z) isomers of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile or a pharmaceutically acceptable salt of the foregoing.

Some embodiments of the present disclosure relate to methods for increasing a platelet count in a human patient with immune thrombocytopenia (ITP) comprising administering to the human patient a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (PRN1008) and pharmaceutically acceptable salts thereof once a day or twice a day for a treatment period.

In some embodiments, the methods comprise increasing at least 2 consecutive platelet counts relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 2 consecutive platelet counts relative to a pre-administration baseline platelet count without requiring rescue medication.

In some embodiments, the methods comprise increasing a platelet count by at least 5,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing a platelet count by at least 10,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing a platelet count by at least 15,000/μL relative to a pre-administration baseline platelet count. In

some embodiments, the methods comprise increasing a platelet count by at least 20,000/μL relative to a pre-administration baseline platelet count.

In some embodiments, the methods comprise increasing at least 30% of platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 40% of platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 50% of platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 60% of platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 70% of platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count.

In some embodiments, the methods comprise increasing at least 2 of the final 8 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 3 of the final 8 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 4 of the final 8 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 5 of the final 8 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 6 of the final 8 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 7 of the final 8 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count.

In some embodiments, the methods comprise increasing at least 2 of the final 6 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 3 of the final 6 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 4 of the final 6 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In

some embodiments, the methods comprise increasing at least 5 of the final 6 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count.

In some embodiments, the pre-administration baseline platelet count is an average of the human patient's two most recent platelet counts prior to the start of the treatment period and the human patient's platelet count on the first day of the treatment period. In some embodiments, the pre-administration baseline platelet count is an average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart, and the human patient's platelet count on the first day of the treatment period. In some embodiments, the pre-administration baseline platelet count is an average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period, and the human patient's platelet count on the first day of the treatment period.

In some embodiments, consecutive platelet counts are measured at least 5 days apart.

In some embodiments, the treatment period is 8 days. In some embodiments, the treatment period is 28 days. In some embodiments, the treatment period is 84 days. In some embodiments, the treatment period is 168 days.

In some embodiments, the treatment period is at least 8 days. In some embodiments, the treatment period is at least 28 days. In some embodiments, the treatment period is at least 84 days. In some embodiments, the treatment period is at least 168 days.

In some embodiments, the treatment period is from 8 days to 28 days. In some embodiments, the treatment period is from 8 days to 84 days. In some embodiments, the treatment period is from 8 days to 168 days. In some embodiments, the treatment period is from 28 days to 84 days. In some embodiments, the treatment period is from 28 days to 168 days. In some embodiments, the treatment period is from 84 days to 168 days.

In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof once a day or twice a day. In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof once a day. In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof twice a day.

In some embodiments, the methods comprise administering to the human patient 300 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof twice a day.

In some embodiments, the human patient has primary ITP. In some embodiments, the human patient has secondary ITP. In some embodiments, the human patient has chronic ITP. In some embodiments, the human patient has relapsing ITP. In some embodiments, the human patient has refractory ITP.

In some embodiments, the human patient has at least one characteristic prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has at least 2 characteristics prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has at least 3 characteristics prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has at least 4 characteristics prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has at least 5 characteristics prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has all of the following characteristics prior to the start of the treatment period:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient is from 21 to 74 years old prior to the start of the treatment period.

In some embodiments, the human patient has 2 platelet counts of less than 30,000/μL prior to the start of the treatment period. In some embodiments, the human patient has 2 platelet counts of less than 30,000/μL prior to the start of the treatment period, wherein the 2 counts are measured no sooner than 7 days apart. In some embodiments, the human patient has 2 platelet counts of less than 30,000/μL prior to the start of the treatment period, wherein the 2 counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period.

In some embodiments, the human patient has a platelet count of less than 30,000/μL for at least 2 consecutive platelet counts prior to the start of the treatment period. In some embodiments, the human patient has a platelet count of less than 30,000/μL for at least 2 consecutive platelet counts prior to the start of the treatment period, wherein the 2 counts are measured no sooner than 7 days apart. In some embodiments, the human patient has a platelet

count of less than 30,000/μL for at least 2 consecutive platelet counts prior to the start of the treatment period, wherein the 2 counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 28,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 28,000/μL, wherein the two counts are measured no sooner than 7 days apart. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 28,000/μL, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 33,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 33,000/μL, wherein the two counts are measured no sooner than 7 days apart. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 33,000/μL, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 28,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 28,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 28,000/μL.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 15,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart, and the human

patient's platelet count on the first day of the treatment period is from 3,000/μL to 15,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 15,000/μL.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 33,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 33,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 33,000/μL.

In some embodiments, the human patient had ITP for at least 2 months prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 3 months prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 4 months prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 5 months prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 6 months prior to the start of the treatment period.

In some embodiments, the human patient had ITP for at least 1 year prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 2 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 3 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 4 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 5 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 6 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 7 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 8 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 9 years prior to the start of the treatment period.

In some embodiments, the human patient had ITP for at least 10 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 20 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 30 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 40 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 50 years prior to the start of the treatment period.

In some embodiments, the human patient has a history of taking from 1 to 41 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking from 1 to 54 prior ITP therapies prior to the start of the treatment period.

In some embodiments, the human patient has a history of taking at least one prior ITP therapy prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 2 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 3 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 4 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 5 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 6 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 7 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 8 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 9 prior ITP therapies prior to the start of the treatment period.

In some embodiments, the human patient has a history of taking at least 10 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 15 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 20 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 25 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 30 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 35 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 40 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of

taking at least 45 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 50 prior ITP therapies prior to the start of the treatment period.

In some embodiments, the at least one prior ITP therapy is chosen from corticosteroids, thrombopoietin receptor agonists, intravenous immunoglobulin, anti-D immunoglobulin, and rituximab.

In some embodiments, the human patient had a splenectomy prior to the start of the treatment period.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof is administered as a monotherapy.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof is administered in combination with at least one concomitant ITP therapy.

In some embodiments, the at least one concomitant ITP therapy is chosen from corticosteroids and thrombopoietin receptor agonists. In some embodiments, the at least one concomitant ITP therapy is chosen from corticosteroids, eltrombopag, and romiplostim.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof comprises at least one compound chosen from the (E) isomer of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and pharmaceutically acceptable salts thereof.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof comprises at least one compound chosen from the (Z) isomer of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and pharmaceutically acceptable salts thereof.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof comprises a mixture of (E) and (Z) isomers of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile or a pharmaceutically acceptable salt of the foregoing.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof consists of at least one compound chosen from the (E) isomer of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-

yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and pharmaceutically acceptable salts thereof.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof consists of at least one compound chosen from the (Z) isomer of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and pharmaceutically acceptable salts thereof.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof consists of a mixture of (E) and (Z) isomers of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile or a pharmaceutically acceptable salt of the foregoing.

Some embodiments of the present disclosure relate to methods for achieving a platelet count of at least 50,000/μL in a human patient with immune thrombocytopenia (ITP) comprising administering to the human patient a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (PRN1008) and pharmaceutically acceptable salts thereof once a day or twice a day for a treatment period.

In some embodiments, the methods comprise achieving at least 2 platelet counts of at least 50,000/μL. In some embodiments, the methods comprise achieving at least 2 platelet counts of at least 50,000/μL without requiring rescue medication.

In some embodiments, the methods comprise achieving at least 2 consecutive platelet counts of at least 50,000/μL. In some embodiments, the methods comprise achieving at least 2 consecutive platelet counts of at least 50,000/μL without requiring rescue medication.

In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 30% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 35% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 40% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 45% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet

count of at least 50,000/μL in at least 50% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 55% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 60% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 65% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 70% of platelet counts measured during the treatment period.

In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 2 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 3 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 4 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 5 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 6 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 7 of the final 8 platelet counts measured during the treatment period.

In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 2 of the final 6 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 3 of the final 6 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 4 of the final 6 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 5 of the final 6 platelet counts measured during the treatment period.

In some embodiments, the methods comprise increasing at least 30% of platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 40% of platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing

at least 50% of platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 60% of platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 70% of platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count.

In some embodiments, the methods comprise increasing at least 2 of the final 8 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 3 of the final 8 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 4 of the final 8 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 5 of the final 8 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 6 of the final 8 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 7 of the final 8 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count.

In some embodiments, the methods comprise increasing at least 2 of the final 6 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 3 of the final 6 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 4 of the final 6 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count. In some embodiments, the methods comprise increasing at least 5 of the final 6 platelet counts measured during the treatment period by at least 20,000/μL relative to a pre-administration baseline platelet count.

In some embodiments, the pre-administration baseline platelet count is an average of the human patient's two most recent platelet counts prior to the start of the treatment period and the human patient's platelet count on the first day of the treatment period. In some embodiments, the pre-administration baseline platelet count is an average of the human patient's two most

recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart, and the human patient's platelet count on the first day of the treatment period. In some embodiments, the pre-administration baseline platelet count is an average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period, and the human patient's platelet count on the first day of the treatment period.

In some embodiments, consecutive platelet counts are measured at least 5 days apart.

In some embodiments, the treatment period is 8 days. In some embodiments, the treatment period is 28 days. In some embodiments, the treatment period is 84 days. In some embodiments, the treatment period is 168 days.

In some embodiments, the treatment period is at least 8 days. In some embodiments, the treatment period is at least 28 days. In some embodiments, the treatment period is at least 84 days. In some embodiments, the treatment period is at least 168 days.

In some embodiments, the treatment period is from 8 days to 28 days. In some embodiments, the treatment period is from 8 days to 84 days. In some embodiments, the treatment period is from 8 days to 168 days. In some embodiments, the treatment period is from 28 days to 84 days. In some embodiments, the treatment period is from 28 days to 168 days. In some embodiments, the treatment period is from 84 days to 168 days.

In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof once a day or twice a day. In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof once a day. In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof twice a day.

In some embodiments, the methods comprise administering to the human patient 300 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof twice a day.

In some embodiments, the human patient has primary ITP. In some embodiments, the human patient has secondary ITP. In some embodiments, the human patient has chronic ITP. In some embodiments, the human patient has relapsing ITP. In some embodiments, the human patient has refractory ITP.

In some embodiments, the human patient has at least one characteristic prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has at least 2 characteristics prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has at least 3 characteristics prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has at least 4 characteristics prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has at least 5 characteristics prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has all of the following characteristics prior to the start of the treatment period:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient is from 21 to 74 years old prior to the start of the treatment period.

In some embodiments, the human patient has 2 platelet counts of less than 30,000/μL prior to the start of the treatment period. In some embodiments, the human patient has 2 platelet counts of less than 30,000/μL prior to the start of the treatment period, wherein the 2 counts are measured no sooner than 7 days apart. In some embodiments, the human patient has 2 platelet counts of less than 30,000/μL prior to the start of the treatment period, wherein the 2 counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period.

In some embodiments, the human patient has a platelet count of less than 30,000/μL for at least 2 consecutive platelet counts prior to the start of the treatment period. In some embodiments, the human patient has a platelet count of less than 30,000/μL for at least 2 consecutive platelet counts prior to the start of the treatment period, wherein the 2 counts are measured no sooner than 7 days apart. In some embodiments, the human patient has a platelet count of less than 30,000/μL for at least 2 consecutive platelet counts prior to the start of the treatment period, wherein the 2 counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 28,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 28,000/μL, wherein the two counts are

measured no sooner than 7 days apart. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 28,000/μL, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 33,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 33,000/μL, wherein the two counts are measured no sooner than 7 days apart. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 33,000/μL, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 28,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 28,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 28,000/μL.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 15,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 15,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 15,000/μL.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period and the human patient's platelet count on the

first day of the treatment period is from 3,000/μL to 33,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 33,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 33,000/μL.

In some embodiments, the human patient had ITP for at least 2 months prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 3 months prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 4 months prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 5 months prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 6 months prior to the start of the treatment period.

In some embodiments, the human patient had ITP for at least 1 year prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 2 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 3 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 4 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 5 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 6 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 7 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 8 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 9 years prior to the start of the treatment period.

In some embodiments, the human patient had ITP for at least 10 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 20 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 30 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 40 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 50 years prior to the start of the treatment period.

In some embodiments, the human patient has a history of taking from 1 to 41 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking from 1 to 54 prior ITP therapies prior to the start of the treatment period.

In some embodiments, the human patient has a history of taking at least one prior ITP therapy prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 2 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 3 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 4 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 5 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 6 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 7 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 8 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 9 prior ITP therapies prior to the start of the treatment period.

In some embodiments, the human patient has a history of taking at least 10 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 15 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 20 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 25 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 30 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 35 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 40 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 45 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 50 prior ITP therapies prior to the start of the treatment period.

In some embodiments, the at least one prior ITP therapy is chosen from corticosteroids, thrombopoietin receptor agonists, intravenous immunoglobulin, anti-D immunoglobulin, and rituximab.

In some embodiments, the human patient had a splenectomy prior to the start of the treatment period.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof is administered as a monotherapy.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof is administered in combination with at least one concomitant ITP therapy.

In some embodiments, the at least one concomitant ITP therapy is chosen from corticosteroids and thrombopoietin receptor agonists. In some embodiments, the at least one concomitant ITP therapy is chosen from corticosteroids, eltrombopag, and romiplostim.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof comprises at least one compound chosen from the (E) isomer of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and pharmaceutically acceptable salts thereof.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof comprises at least one compound chosen from the (Z) isomer of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and pharmaceutically acceptable salts thereof.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof comprises a mixture of (E) and (Z) isomers of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile or a pharmaceutically acceptable salt of the foregoing.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof consists of at least one compound chosen from the (E) isomer of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and pharmaceutically acceptable salts thereof.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof consists of at least one compound chosen from the (Z) isomer of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-

yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and pharmaceutically acceptable salts thereof.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof consists of a mixture of (E) and (Z) isomers of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile or a pharmaceutically acceptable salt of the foregoing.

Some embodiments of the present disclosure relate to methods for achieving at least one platelet count of at least 50,000/μL and increasing at least one platelet count by at least 20,000/μL in a human patient with immune thrombocytopenia (ITP) comprising administering to the human patient a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (PRN1008) and pharmaceutically acceptable salts thereof once a day or twice a day for a treatment period.

In some embodiments, the methods comprise achieving at least 2 platelet counts of at least 50,000/μL. In some embodiments, the methods comprise achieving at least 2 platelet counts of at least 50,000/μL without requiring rescue medication.

In some embodiments, the methods comprise achieving at least 2 consecutive platelet counts of at least 50,000/μL. In some embodiments, the methods comprise achieving at least 2 consecutive platelet counts of at least 50,000/μL without requiring rescue medication.

In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 30% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 35% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 40% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 45% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 50% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 55% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 60% of platelet counts measured during the treatment period. In some embodiments, the

methods comprise achieving a platelet count of at least 50,000/μL in at least 65% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 70% of platelet counts measured during the treatment period.

In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 2 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 3 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 4 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 5 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 6 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 7 of the final 8 platelet counts measured during the treatment period.

In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 2 of the final 6 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 3 of the final 6 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 4 of the final 6 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 50,000/μL in at least 5 of the final 6 platelet counts measured during the treatment period.

In some embodiments, consecutive platelet counts are measured at least 5 days apart.

In some embodiments, the treatment period is 8 days. In some embodiments, the treatment period is 28 days. In some embodiments, the treatment period is 84 days. In some embodiments, the treatment period is 168 days.

In some embodiments, the treatment period is at least 8 days. In some embodiments, the treatment period is at least 28 days. In some embodiments, the treatment period is at least 84 days. In some embodiments, the treatment period is at least 168 days.

In some embodiments, the treatment period is from 8 days to 28 days. In some embodiments, the treatment period is from 8 days to 84 days. In some embodiments, the treatment period is from 8 days to 168 days. In some embodiments, the treatment period is from

28 days to 84 days. In some embodiments, the treatment period is from 28 days to 168 days. In some embodiments, the treatment period is from 84 days to 168 days.

In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof once a day or twice a day. In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof once a day. In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof twice a day.

In some embodiments, the methods comprise administering to the human patient 300 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof twice a day.

In some embodiments, the human patient has primary ITP. In some embodiments, the human patient has secondary ITP. In some embodiments, the human patient has chronic ITP. In some embodiments, the human patient has relapsing ITP. In some embodiments, the human patient has refractory ITP.

In some embodiments, the human patient has at least one characteristic prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has at least 2 characteristics prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has at least 3 characteristics prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has at least 4 characteristics prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has at least 5 characteristics prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has all of the following characteristics prior to the start of the treatment period:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient is from 21 to 74 years old prior to the start of the treatment period.

In some embodiments, the human patient has 2 platelet counts of less than 30,000/μL prior to the start of the treatment period. In some embodiments, the human patient has 2 platelet

counts of less than 30,000/μL prior to the start of the treatment period, wherein the 2 counts are measured no sooner than 7 days apart. In some embodiments, the human patient has 2 platelet counts of less than 30,000/μL prior to the start of the treatment period, wherein the 2 counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period.

In some embodiments, the human patient has a platelet count of less than 30,000/μL for at least 2 consecutive platelet counts prior to the start of the treatment period. In some embodiments, the human patient has a platelet count of less than 30,000/μL for at least 2 consecutive platelet counts prior to the start of the treatment period, wherein the 2 counts are measured no sooner than 7 days apart. In some embodiments, the human patient has a platelet count of less than 30,000/μL for at least 2 consecutive platelet counts prior to the start of the treatment period, wherein the 2 counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 28,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 28,000/μL, wherein the two counts are measured no sooner than 7 days apart. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 28,000/μL, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 33,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 33,000/μL, wherein the two counts are measured no sooner than 7 days apart. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 33,000/μL, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 28,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 28,000/μL.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 28,000/μL.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 15,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 15,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 15,000/μL.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 33,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 33,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 33,000/μL.

In some embodiments, the human patient had ITP for at least 2 months prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 3 months prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 4 months prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 5 months prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 6 months prior to the start of the treatment period.

In some embodiments, the human patient had ITP for at least 1 year prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 2 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at

least 3 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 4 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 5 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 6 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 7 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 8 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 9 years prior to the start of the treatment period.

In some embodiments, the human patient had ITP for at least 10 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 20 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 30 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 40 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 50 years prior to the start of the treatment period.

In some embodiments, the human patient has a history of taking from 1 to 41 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking from 1 to 54 prior ITP therapies prior to the start of the treatment period.

In some embodiments, the human patient has a history of taking at least one prior ITP therapy prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 2 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 3 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 4 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 5 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 6 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 7 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 8 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 9 prior ITP therapies prior to the start of the treatment period.

In some embodiments, the human patient has a history of taking at least 10 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 15 prior ITP therapies prior to the start of the treatment period. In

some embodiments, the human patient has a history of taking at least 20 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 25 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 30 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 35 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 40 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 45 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 50 prior ITP therapies prior to the start of the treatment period.

In some embodiments, the at least one prior ITP therapy is chosen from corticosteroids, thrombopoietin receptor agonists, intravenous immunoglobulin, anti-D immunoglobulin, and rituximab.

In some embodiments, the human patient had a splenectomy prior to the start of the treatment period.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof is administered as a monotherapy.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof is administered in combination with at least one concomitant ITP therapy.

In some embodiments, the at least one concomitant ITP therapy is chosen from corticosteroids and thrombopoietin receptor agonists. In some embodiments, the at least one concomitant ITP therapy is chosen from corticosteroids, eltrombopag, and romiplostim.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof comprises at least one compound chosen from the (E) isomer of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and pharmaceutically acceptable salts thereof.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof comprises at least one compound chosen from the (Z) isomer of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and pharmaceutically acceptable salts thereof.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof comprises a mixture of (E) and (Z) isomers of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile or a pharmaceutically acceptable salt of the foregoing.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof consists of at least one compound chosen from the (E) isomer of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and pharmaceutically acceptable salts thereof.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof consists of at least one compound chosen from the (Z) isomer of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and pharmaceutically acceptable salts thereof.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof consists of a mixture of (E) and (Z) isomers of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile or a pharmaceutically acceptable salt of the foregoing.

Some embodiments of the present disclosure relate to methods for achieving a platelet count of at least 30,000/μL in a human patient with immune thrombocytopenia (ITP) comprising administering to the human patient a therapeutically effective amount of at least one compound chosen from (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (PRN1008) and pharmaceutically acceptable salts thereof once a day or twice a day for a treatment period.

In some embodiments, the methods comprise achieving a platelet count of at least 30,000/μL in at least 30% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 30,000/μL in at least 35% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 30,000/μL in at least 40% of platelet counts measured during the treatment period. In some embodiments, the methods comprise

achieving a platelet count of at least 30,000/μL in at least 45% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 30,000/μL in at least 50% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 30,000/μL in at least 55% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 30,000/μL in at least 60% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 30,000/μL in at least 65% of platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 30,000/μL in at least 70% of platelet counts measured during the treatment period.

In some embodiments, the methods comprise achieving a platelet count of at least 30,000/μL in at least 2 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 30,000/μL in at least 3 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 30,000/μL in at least 4 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 30,000/μL in at least 5 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 30,000/μL in at least 6 of the final 8 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 30,000/μL in at least 7 of the final 8 platelet counts measured during the treatment period.

In some embodiments, the methods comprise achieving a platelet count of at least 30,000/μL in at least 2 of the final 6 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 30,000/μL in at least 3 of the final 6 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 30,000/μL in at least 4 of the final 6 platelet counts measured during the treatment period. In some embodiments, the methods comprise achieving a platelet count of at least 30,000/μL in at least 5 of the final 6 platelet counts measured during the treatment period.

In some embodiments, the treatment period is 8 days. In some embodiments, the treatment period is 28 days. In some embodiments, the treatment period is 84 days. In some embodiments, the treatment period is 168 days.

In some embodiments, the treatment period is at least 8 days. In some embodiments, the treatment period is at least 28 days. In some embodiments, the treatment period is at least 84 days. In some embodiments, the treatment period is at least 168 days.

In some embodiments, the treatment period is from 8 days to 28 days. In some embodiments, the treatment period is from 8 days to 84 days. In some embodiments, the treatment period is from 8 days to 168 days. In some embodiments, the treatment period is from 28 days to 84 days. In some embodiments, the treatment period is from 28 days to 168 days. In some embodiments, the treatment period is from 84 days to 168 days.

In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof once a day or twice a day. In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof once a day. In some embodiments, the methods comprise administering to the human patient 400 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof twice a day.

In some embodiments, the methods comprise administering to the human patient 300 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof twice a day.

In some embodiments, the human patient has primary ITP. In some embodiments, the human patient has secondary ITP. In some embodiments, the human patient has chronic ITP. In some embodiments, the human patient has relapsing ITP. In some embodiments, the human patient has refractory ITP.

In some embodiments, the human patient has at least one characteristic prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has at least 2 characteristics prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has at least 3 characteristics prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has at least 4 characteristics prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has at least 5 characteristics prior to the start of the treatment period chosen from:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient has all of the following characteristics prior to the start of the treatment period:

an age of from 18 years to 80 years;

no available and approved therapeutic options;

a platelet count of less than 30,000/μL;

an ITP duration of at least one month;

a history of taking at least one prior ITP therapy; and

splenectomy.

In some embodiments, the human patient is from 21 to 74 years old prior to the start of the treatment period.

In some embodiments, the human patient has 2 platelet counts of less than 30,000/μL prior to the start of the treatment period. In some embodiments, the human patient has 2 platelet counts of less than 30,000/μL prior to the start of the treatment period, wherein the 2 counts are measured no sooner than 7 days apart. In some embodiments, the human patient has 2 platelet counts of less than 30,000/μL prior to the start of the treatment period, wherein the 2 counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period.

In some embodiments, the human patient has a platelet count of less than 30,000/μL for at least 2 consecutive platelet counts prior to the start of the treatment period. In some embodiments, the human patient has a platelet count of less than 30,000/μL for at least 2 consecutive platelet counts prior to the start of the treatment period, wherein the 2 counts are measured no sooner than 7 days apart. In some embodiments, the human patient has a platelet count of less than 30,000/μL for at least 2 consecutive platelet counts prior to the start of the treatment period, wherein the 2 counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 28,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 28,000/μL, wherein the two counts are measured no sooner than 7 days apart. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 28,000/μL, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 33,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 33,000/μL, wherein the two counts are measured no sooner than 7 days apart. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period is from 3,000/μL to 33,000/μL, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 28,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 28,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 28,000/μL.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 15,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 15,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 15,000/μL.

In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 33,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 33,000/μL. In some embodiments, the average of the human patient's two most recent platelet counts prior to the start of the treatment period, wherein the two counts are measured no sooner than 7 days apart in the 15 days prior to the start of the treatment period, and the human patient's platelet count on the first day of the treatment period is from 3,000/μL to 33,000/μL.

In some embodiments, the human patient had ITP for at least 2 months prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 3 months prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 4 months prior to the start of the treatment period. In some embodiments, the human

patient had ITP for at least 5 months prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 6 months prior to the start of the treatment period.

In some embodiments, the human patient had ITP for at least 1 year prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 2 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 3 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 4 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 5 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 6 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 7 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 8 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 9 years prior to the start of the treatment period.

In some embodiments, the human patient had ITP for at least 10 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 20 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 30 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 40 years prior to the start of the treatment period. In some embodiments, the human patient had ITP for at least 50 years prior to the start of the treatment period.

In some embodiments, the human patient has a history of taking from 1 to 41 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking from 1 to 54 prior ITP therapies prior to the start of the treatment period.

In some embodiments, the human patient has a history of taking at least one prior ITP therapy prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 2 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 3 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 4 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 5 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 6 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 7 prior ITP therapies prior to the start of the treatment

period. In some embodiments, the human patient has a history of taking at least 8 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 9 prior ITP therapies prior to the start of the treatment period.

In some embodiments, the human patient has a history of taking at least 10 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 15 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 20 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 25 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 30 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 35 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 40 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 45 prior ITP therapies prior to the start of the treatment period. In some embodiments, the human patient has a history of taking at least 50 prior ITP therapies prior to the start of the treatment period.

In some embodiments, the at least one prior ITP therapy is chosen from corticosteroids, thrombopoietin receptor agonists, intravenous immunoglobulin, anti-D immunoglobulin, and rituximab.

In some embodiments, the human patient had a splenectomy prior to the start of the treatment period.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof is administered as a monotherapy.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof is administered in combination with at least one concomitant ITP therapy.

In some embodiments, the at least one concomitant ITP therapy is chosen from corticosteroids and thrombopoietin receptor agonists. In some embodiments, the at least one concomitant ITP therapy is chosen from corticosteroids, eltrombopag, and romiplostim.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof comprises at least one compound chosen from the (E) isomer of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-

yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and pharmaceutically acceptable salts thereof.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof comprises at least one compound chosen from the (Z) isomer of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and pharmaceutically acceptable salts thereof.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof comprises a mixture of (E) and (Z) isomers of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile or a pharmaceutically acceptable salt of the foregoing.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof consists of at least one compound chosen from the (E) isomer of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and pharmaceutically acceptable salts thereof.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof consists of at least one compound chosen from the (Z) isomer of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile and pharmaceutically acceptable salts thereof.

In some embodiments, the at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof consists of a mixture of (E) and (Z) isomers of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile or a pharmaceutically acceptable salt of the foregoing.

In some embodiments, the present disclosure is directed to a method for treating immune thrombocytopenia in a human patient comprising: administering to the patient a dose chosen from 400 mg once daily (QD), 300 mg twice daily (BID), and 400 mg BID of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]-pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (PRN1008).

In some embodiments, PRN1008 comprises a mixture of (E) and (Z) isomers of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]-pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile. Further, in some embodiments, PRN1008 is formulated as a pharmaceutical composition and the pharmaceutical composition comprises one or more pharmaceutical acceptable carriers or excipients. For example, in some embodiments, the pharmaceutical composition comprises microcrystalline cellulose, crospovidone, and sodium stearyl fumarate with a film coating.

In some embodiments of the present disclosure, the method further comprises repeating the administration of PRN1008 to the patient over a treatment period. Additionally, in some embodiments, the treatment period ranges from 28 days to 168 days, for a minimum of 8 days or from 8 days to 28 days.

In some embodiments, the present disclosure provides that before administration, the patient's platelet count is less than 30,000/μL for two or more consecutive platelet counts. Further, in some embodiments, after administration over a treatment period, the patient obtains two or more consecutive platelet counts, separated by at least 5 days, of ≥ 50,000/μL; the treatment period ranges from 28 days to 168 days. Additionally, in some embodiments, after administration over a treatment period, the patient has a stable response of a platelet count of greater than or equal to 50,000/μL during the treatment period and an increase of platelet count of ≥ 20,000/μL from baseline.

In some embodiments, the present disclosure provides that before administration, the patient has relapsed or refractory idiopathic thrombocytopenia, which is primary or secondary to other diseases afflicting the patient. For example, in some embodiments, the patient has secondary ITP. In some embodiments, the patient is administered a dose of 400 mg QD.

In some embodiments, the present disclosure is directed to the occurrence where the patient is also taking one or more concomitant medications. For example, in some embodiments, the one or more concomitant medication is chosen from corticosteroids, eltrombopag, and romiplostim.

In some embodiments, the present disclosure is directed to a method for treating immune thrombocytopenia in a human patient comprising: administering to the patient a dose chosen from 400 mg once daily (QD), 300 mg twice daily (BID), and 400 mg BID of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (PRN1008), wherein before administration, the patient's platelet count is less than 30,000/μL for two or more consecutive

platelet counts, and wherein after administration, the patient has a stable response of a platelet count of greater than or equal to 50,000/μL during the treatment period.

In some embodiments, the present disclosure is directed to a method for treating immune thrombocytopenia in a human patient comprising: administering to the patient a dose chosen from 400 mg once daily (QD), 300 mg twice daily (BID), and 400 mg BID of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (PRN1008), wherein before administration, the patient's platelet count is less than 30,000/μL for two or more consecutive platelet counts, and after administration over a treatment period, the patient obtains two or more consecutive platelet counts, separated by at least 5 days, of ≥ 50,000/μL and an increase of platelet count of ≥ 20,000/μL from baseline.

Pharmaceutical Compositions:

In some embodiments of the present disclosure, PRN1008 is administered as part of a pharmaceutical composition comprising: at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof; and at least one pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is in the form of at least one tablet.

In some embodiments of the present disclosure, PRN1008 is orally administered as part of a pharmaceutical composition comprising: at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof; and at least one pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is in the form of at least one tablet. In some embodiments, the pharmaceutical composition is in the form of at least one tablet comprising 100 mg or 300 mg of PRN1008. In some embodiments, the pharmaceutical composition is in the form of at least one tablet comprising 100 mg of PRN1008. In some embodiments, the pharmaceutical composition is in the form of at least one tablet comprising 300 mg of PRN1008.

In some embodiments, PRN1008 is administered in the form of a film-coated tablet.

In some embodiments of the present disclosure, PRN1008 is administered in the form of at least one tablet comprising: at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof; and at least one pharmaceutically acceptable excipient. In some embodiments, PRN1008 is administered in the form of at least one tablet comprising: at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof; at least one filler; at least one disintegrant; at least one lubricant; and at least one

film coating. In some embodiments, the at least one filler is microcrystalline cellulose. In some embodiments, the at least one disintegrant is crospovidone. In some embodiments, the at least one lubricant is sodium stearyl fumarate.

In some embodiments of the present disclosure, PRN1008 is administered in the form of at least one tablet comprising: 100 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof; and at least one pharmaceutically acceptable excipient. In some embodiments, PRN1008 is administered in the form of at least one tablet comprising: 100 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof; at least one filler; at least one disintegrant; at least one lubricant; and at least one film coating. In some embodiments, the at least one filler is microcrystalline cellulose. In some embodiments, the at least one disintegrant is crospovidone. In some embodiments, the at least one lubricant is sodium stearyl fumarate.

In some embodiments of the present disclosure, PRN1008 is administered in the form of at least one tablet comprising: 300 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof; and at least one pharmaceutically acceptable excipient. In some embodiments, PRN1008 is administered in the form of at least one tablet comprising: 300 mg of at least one compound chosen from PRN1008 and pharmaceutically acceptable salts thereof; at least one filler; at least one disintegrant; at least one lubricant; and at least one film coating. In some embodiments, the at least one filler is microcrystalline cellulose. In some embodiments, the at least one disintegrant is crospovidone. In some embodiments, the at least one lubricant is sodium stearyl fumarate.

In some embodiments, PRN1008 is administered with a glass of water.

In some embodiments, PRN1008 is administered with food.

In some embodiments, PRN1008 is administered without food.

The proportion and nature of any pharmaceutically acceptable excipient may be determined by the chosen route of administration and standard pharmaceutical practice. Except insofar as any conventional pharmaceutically acceptable excipient is incompatible with PRN1008, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically composition, its use is contemplated to be within the scope of this disclosure.

Some non-limiting examples of materials which may serve as pharmaceutically acceptable excipients include: (1) sugars, such as, e.g., lactose, glucose, and sucrose; (2) starches, such as, e.g., corn starch and potato starch; (3) cellulose and its derivatives, such as, e.g., sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; (4) powdered

tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as, e.g., cocoa butter and suppository waxes; (9) oils, such as, e.g., peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil, and soybean oil; (10) glycols, such as, e.g., propylene glycol; (11) polyols, such as, e.g., glycerin, sorbitol, mannitol, and polyethylene glycol; (12) esters, such as, e.g., ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as, e.g., magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

Remington: The Science and Practice of Pharmacy, 21st edition, 2005, ed. D.B. Troy, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York also discloses additional non-limiting examples of pharmaceutically acceptable excipients, as well as known techniques for preparing and using the same.

One skilled in the art can readily select the proper form and route of administration depending upon the disorder or condition to be treated, the stage of the disorder or condition, and other relevant circumstances.

EXAMPLES

The following example is intended to be illustrative and is not meant in any way to limit the scope of the disclosure.

Abbreviations:

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
bid/BID	Twice daily (morning and evening)
BP	Blood pressure
BTK	Bruton's Tyrosine Kinase
CA	Competent Authority

CBC	Complete blood count
CI	Confidence Interval
CL/F	Apparent total clearance of the drug from plasma after oral administration
CLL	Chronic lymphocytic leukemia
Cmax	Maximum observed plasma concentration
CPK	Creatine phosphokinase
CRF	Case report form
CRO	Contract research organization
CTCAE	Common Terminology Criteria for AEs
CYP	Cytochrome P450
D	Day
DLT	Dose-limiting toxicity
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EQ-5D VAS	Euro-QoL 5-Dimension Visual Analog Scale
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
H2	Histamine two (receptor)
HCV	Hepatitis C Virus
HDPE	High-density polyethylene
HIV	Human Immunodeficiency Virus
HR	Heart rate
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDSM	Independent Data Safety Monitor
IR	Immediate release
IRB	Institutional Review Board (Human Research Ethics Committee)

ITP	Immune Thrombocytopenic Purpura
ITP-BAT	Idiopathic Thrombocytopenic Purpura Bleeding Assessment Tool
IVIG	Intravenous immunoglobulin
LPLV	Last participant last visit
LTE	Long term extension
MAD	Multiple ascending dose (trial)
MedDRA	Medical Dictionary for Regulatory Activities
NK	Natural killer (cell)
NSAID	Non-Steroidal Anti-Inflammatory Drug
OTC	Over the counter
PK	Pharmacokinetic
PT/INR	Prothrombin Time/International Normalized Ratio
PV	Pemphigus vulgaris
PVG	Pharmacovigilance
qd/QD	Once a day
QoL	Quality of Life
QTcF	QT interval corrected for heart rate (Fridiricia Correction)
RR	Resting Rate
SAE	Serious adverse event
SAP	Statistical Analytical Plan
SI	Système international d'unités (International system of units)
SMC	Safety Monitoring Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
Tmax	Time of observed maximum plasma concentration
TPO	Thrombopoietin
t½	Elimination half-life
ULN	Upper limit of normal
USUBJID	Unique subject identifier
VAS	Visual analog scale

WBC	White blood cell
WHODD	World Health Organization Drug Dictionary

Example 1: An Adaptive, Open-Label, Dose-Finding, Phase 1/2 Study Investigating the Safety, Pharmacokinetics, and Clinical Activity of PRN1008, an Oral BTK Inhibitor, in Patients with Relapsed/Refractory Immune Thrombocytopenia

An ongoing phase 1/2 clinical trial (NCT03395210) investigating the safety, pharmacokinetics, and clinical activity of PRN1008, an oral BTK inhibitor, in patients with relapsed/refractory immune thrombocytopenia (ITP) began enrolling patients on March 22, 2018. As of October 6, 2020, the estimated primary completion date for the study is September 2022, with an estimated study completion date of September 2023. To date, PRN1008 has been well-tolerated in ITP patients with no reported treatment-related bleeding or thrombotic events. Moreover, positive preliminary results have been observed in a highly treatment-resistant and refractory patient population.

The key inclusion criteria for the phase 1/2 study are: adults aged 18-80 years old with relapsed/refractory ITP; ITP primary or secondary to other diseases (e.g., systemic lupus erythematosus, chronic lymphocytic leukemia); no other available/approved treatment options; $\geq$ 2 platelet counts < 30,000/μL at study entry; and adequate hematologic, hepatic, and renal function. Key exclusion criteria included: pregnant or lactating women; current drug or alcohol abuse; history of solid organ transplant; and positive screening for HIV, hepatitis B, or hepatitis C. Enrolled patients have low platelet counts, having relapsed on or been refractory to prior therapies with no available and approved therapeutic options and may continue corticosteroids and/or thrombopoietin mimetics during the study. For example, stable concomitant corticosteroid (CS) or thrombopoietin receptor agonist (TPO-RA) treatment is permitted during the study.

The sample size employed in the study is based on clinical considerations with the intention of gaining a sufficiently high confidence level in the study results using normal approximation methods.

The completed PRN1008 intrapatient dose escalation portion of the study used a 3+3 design. Specifically, if response was observed in 1 of 3 patients, then 3 more patients were added to the dose level. However, if no response was observed in 3 patients for 28 days, the dose was dropped, and patients were escalated to higher doses and all subsequently enrolled patients started treatment at the higher dose. During the dose escalation portion, patients were orally dosed with PRN1008 for an active treatment period of 24 weeks at doses of 200 and 400

mg qd and 300 and 400 mg bid. If patients exhibited a response at an initial dose, the patient continued at that dose (**FIG. 2**). If the patient did not respond to the initial dose, the dose was escalated to a higher dose. Patients were monitored frequently by weekly platelet counts and complete blood counts (CBCs) throughout the active treatment period. PK samples were collected intensively on the first day of each new, higher dose level and at random times following dosing at each on-treatment follow up visit to assess dose response. Other standard clinical and laboratory assessments of patients with ITP were also employed in the dose escalation study, including a bleeding assessment (ITP-BAT; Rodeghiero 2013) that has been used in prior ITP trials.

The safety objective of the phase 1/2 study is to characterize the safety and tolerability of up to four dose levels of PRN1008 in patients with ITP. In the study, safety is assessed by the incidence, severity, and relationship of TEAEs, including clinically significant changes in physical examination, laboratory tests, and vital signs. Adverse events are categorized as treatment emergent after the first dose of PRN1008 has been received. TEAEs in the post-treatment follow-up period are also assessed and examined for possible relationship to the prior PRN1008 treatment. TEAEs include all AEs that start on or after the first dose of study medication, or AEs that are present prior to the first dose of study medication, but their severity or relationship increases after the first dose of study medication up to and including the final study medication dosing date. Within each preferred term, patients are counted only once if they had more than one event reported during the dosing period.

The pharmacokinetic objective of the study is to characterize the pharmacokinetics of PRN1008 in patients with ITP. Plasma PK parameters (C_{max}, T_{max}, AUC, $t_{1/2}$, V/F, CL/F) of PRN1008 in ITP patients are evaluated in each patient based on frequent sampling on Day 1 of a new, higher dosing level and reported by dose and, if relevant, overall. Non-compartmental analysis is employed to derive PK parameters for each individual. Results are reported by descriptive statistics, and exploratory analyses may pool these data with the data from other studies of PRN1008.

Efficacy objectives of the study include: (1) to explore the clinical activity of up to four dose levels of PRN1008 in relapsed/refractory patients with ITP (200 and 400 mg qd; 300 and 400 mg bid); and (2) to identify a potential dose regimen to use in future studies of PRN1008 in patients with ITP. The dose-finding/dose escalation portion of the study has been completed, and all enrolled patients are currently being treated with 400 mg bid.

In Part A of the study, the primary efficacy outcome measure is consecutive increased platelet counts, i.e., two or more consecutive platelet counts $\geq$ 50,000/μL without requiring

rescue medication. Specifically, Part A examines the proportion of patients able to achieve two or more consecutive platelet counts, separated by at least 5 days, of ≥ 50,000/μL and an increase of platelet count of ≥ 20,000/μL from baseline, without use of rescue medication in the 4 weeks prior to the latest elevated platelet count. The analysis of the primary efficacy endpoint is a weighted logistic regression, with the binary indicator of platelet response as the dependent variable, and dose level in total mg per day as a covariate, weighted by the number of days the patient was on the dose.

Additional efficacy endpoints include: any 2 platelet counts ≥ 50,000/μL; platelet responses over time, by duration of treatment, and clinical benefit (≥ 30,000/μL); stable response (platelet counts ≥ 50,000/μL at 50% of visits for 4 of the last 8 weeks of active treatment). For example, secondary efficacy endpoints of the study include: (1) proportion of patients able to achieve two or more platelet counts of ≥ 50,000/μL and increase of platelet count of ≥ 20,000/μL from baseline at any time (on treatment or during follow up) without use of rescue medication in the 4 weeks prior to the latest elevated platelet count; (2) proportion of patients able to achieve two or more platelet counts, separated by at least 5 days, representing an increase of platelet count of ≥ 20,000/μL from baseline, by dose level, without use of rescue medication in the 4 weeks prior to the latest elevated platelet count; (3) proportion of patients able to achieve two or more platelet counts, separated by at least 5 days, of ≥ 100,000/μL, by dose level, without use of rescue medication in the 4 weeks prior to the latest elevated platelet count; (4) change from baseline to the average of the last two platelet counts at each dosing level; (5) time to first platelet response (as defined in the primary endpoint); (6) proportion of patients receiving rescue medication at each dosing level and overall; (7) proportion of patients with a Grade 2 or higher bleeding event at each dosing level and overall; (8) bleeding scale (ITP-BAT scale) at the end of treatment period for each dosing level; and (9) proportion of patients that completed 24 weeks of treatment and demonstrated a platelet response defined as platelet counts ≥ 50,000/μL at ≥ 50% of the visits during the last 8 weeks of the active treatment period.

Exploratory objectives of the study include: the effect of PRN1008 on platelet autoantibody levels; the effect of PRN1008 on markers of hemolysis; the effect of PRN1008 on thrombopoietin (TPO) levels; the effect of PRN1008 on quality of life (QoL) using the Euro-QoL 5-Dimension Visual Analog Scale (EQ-5D VAS); and plasma metabolite analysis/identification for PRN1008.

Rationale for Doses Used and Duration of Study:

An adaptive, open-label, dose-finding study using rule-based intrapatient dose escalation is an appropriate phase 1/2 design to evaluate the safety and effect of PRN1008 in patients with ITP, a relatively rare autoimmune disease. The study design is similar to that used to study the initial efficacy and safety of the orally available tyrosine kinase inhibitor fostamatinib in ITP (Podolanczuk et al., 2009).

The dose and exposure explored in this study has been previously well-tolerated in human studies and their interrelationships well-characterized. Platelets express high levels of BTK; however, alternative signaling pathways exist which bypass BTK signaling to retain normal platelet functions. PRN1008 had no effect on the platelet aggregation from the blood of healthy volunteers or ITP patients tested *ex vivo* ($\leq$ 1 μM) using a standard panel of platelet agonists (**FIGs. 3A, 3B**). For example, *ex vivo* treatment with PRN1008 at clinically relevant concentrations did not impact collagen-induced platelet aggregation in either normal or ITP patient platelet samples, or interfere with responses to all other platelet agonists tested. In contrast, the BTK inhibitor ibrutinib has significant effects on platelet aggregation in healthy volunteers (**FIG. 4**).

Based on BTK occupancies in a mouse model of anti-platelet driven immune thrombocytopenia, the 200 mg qd human starting dose was expected to result in minimal improvement in platelet counts. In that model, a 10 mg/kg/d dose was associated with mean 51% BTK occupancy 1 h post-dose, along with a slight increase in platelet count over vehicle control (mean 83.1% platelet decrease from baseline for vehicle with anti-platelet challenge, compared to a 71.9% platelet decrease for PRN1008 10 mg/kg/d). The top dose of 40 mg/kg/d in that model resulted in a maximum BTK occupancy of 91%, matching the expected peak occupancies with the maximum 400 mg QD and 400 mg BID doses. The 400 mg BID dose was expected to produce higher trough, or pre-dose BTK occupancies of approximately 70% vs. 50% for QD dosing, while having similar peak values. Dosing above 400 mg BID is thought unlikely to result in greater target inhibition.

In prior studies, no accumulation in exposure has been observed with multiple dosing of PRN1008 when administered once daily, with a small amount of accumulation observed with twice daily dosing.

The blistering disease pemphigus is an autoantibody-driven disease like ITP. In Study PRN1008-005, a rapid onset of clinical effect was seen in most pemphigus patients within 4 weeks, with continued improvement to very low levels of skin inflammation by the end of 12 weeks of therapy. Therefore, 28-day cycles to assess the initial platelet response and trigger

intrapatient dose-escalation were deemed appropriate for studying ITP. Additionally, a 24-week overall treatment period was preferred for the dose-finding study to enable all patients to potentially dose-escalate to the higher doses and be fully evaluated at those doses.

Dose Escalation Study Design:

Patients in the dose-escalation portion of the study were assigned to 4 cohorts, as shown in Table 1. The starting dose levels were 200 mg QD; 400 mg QD; 600 mg per day (300 mg BID); 800 mg per day (400 mg BID). Due to the study design, not all patients were necessarily dosed at all dose levels shown in Table 1. The "sentinel cohorts" at each dose level consisted of the first 3 patients, or 6, if 3 extra were added for a dose-limiting toxicity (DLT) event or platelet response (as defined in the primary endpoint and sustained for at least 3 of 4 consecutive platelet counts at any dose level). To be evaluable in a sentinel cohort, patients must have ≥ 75% compliance over the 28-day dosing period.

The following dose escalation rules applied in the study. Individual patients dose-escalate to successive dose levels unless they are withdrawn, have a platelet response at the current dose level, or the next dose level has been determined to be ineligible for further enrollment due to safety concerns. Patients experiencing a platelet response (as defined for the primary endpoint) will not have their dose escalated at the next cycle. If they do not experience a platelet response during the second cycle of the same dose level, then they may dose escalate for the following cycle. If they require rescue medication subsequently because the platelet response was only transient, these patients will be discontinued from the study. Patients experiencing a DLT will be discontinued from the study. Additionally, pregnant patients and patients with abnormal liver function tests suggestive of DILI, defined as: CTCAE ≥ Grade 3 elevation of ALT and/or AST (i.e. ALT or ALT >5xULN) or ALT or AST > 3xULN with total bilirubin > 2xULN without ALP > 2xULN in the absence of another cause will be discontinued.

The DLT evaluation period for any patient is defined as the duration of PRN1008 dosing. Dose-limiting toxicity in the phase 1/2 study, including the completed dose escalation study, is established as follows. Hematologic DLT is determined based on: ANC < 500 /μL for ≥ 5 days; Grade 3 or higher decreased hemoglobin in the absence of a pre-existing Grade 2 decreased hemoglobin; febrile neutropenia, with absolute neutrophil count (ANC) < 1000 /mm^3 and single temperature > 38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 °C (100.4 °F) for more than one hour (CTCAE, version 4.0); and ≥ Grade 3 or higher bleeding event requiring platelet transfusion. Non-hematologic DLT is considered any > Grade 3 non-hematologic toxicity per the NCI Common Terminology Criteria for Adverse Events

(CTCAE), version 4.0, with the following exceptions: laboratory TEAEs that are asymptomatic and return to baseline or to Grade 1 within 7 days; fatigue; nausea, vomiting or diarrhea that return to baseline or Grade 1 within 7 days; and systemic reactions (such as, e.g., fever, headache) that return to baseline or Grade 1 within 7 days. Any toxicity that, at the discretion of the Investigator, is thought to warrant withholding the study drug for more than 7 days is also considered a DLT.

In Table 1, n indicates the expected enrollment in each cohort unless a sustained platelet response was seen or a DLT, in which case 3 extra patients would be added to that group. A starting dose level could be dropped for futility after 3 or 6 patients were evaluated, or retained if efficacy is observed. Notably, individual patients in each cohort do not dose-escalate when there is a platelet response at a lower dose level or toxicity. If several dose levels are therapeutic, some or all patients would not reach the higher dose levels.

Table 1: Adaptive Cohort Dosing

Cohort	Starting dose level (n) 4 weeks	Next dose level 4 weeks	Next dose level** 4 weeks	Next dose level**	Next dose level**	Next dose level**
1	200 mg QD (3-6)	400 mg QD	300 mg BID	400 mg BID	400 mg BID	400 mg BID
2	400 mg QD (≤ 6)	300 mg BID	400 mg BID	400 mg BID	400 mg BID	400 mg BID
3	300 mg BID (≤ 6)	400 mg BID	400 mg BID	400 mg BID	400 mg BID	400 mg BID
4	400 mg BID (≤ 6)	400 mg BID	400 mg BID	400 mg BID	400 mg BID	400 mg BID

Each patient enrolled in the dose-escalation portion of the study was allowed to up-titrate their dose after 28 days of PRN1008 therapy at each dose level if they did not experience a platelet response (as defined in the primary endpoint) or a DLT at the last dose level. If they experienced a platelet response in the first cycle at any one dose level but did not have a platelet response in the second cycle at that dose, they could dose escalate at the end of the second cycle. Patients experiencing a platelet response (as defined for the primary endpoint) did not have their dose escalated at the next cycle.

Patients could receive PRN1008 treatment for up to 24 weeks, starting on Day 1 and ending on Study Day 169, followed by 4 weeks of post-treatment safety follow-up. However, patients who dose escalated to 400 mg BID could continue in the active treatment period until 24 weeks of treatment at the 400 mg BID dose were completed.

Patients were monitored with weekly platelet counts and CBCs throughout the dose-escalation study. Additionally, PK samples were collected intensively on the first day of each new, higher dose level and at random times following dosing at each on-treatment follow up visit.

Long Term Extension (LTE):

After completing an active treatment period in the phase 1/2 study (such as, e.g., the dose escalation study), patients demonstrating a platelet response defined as platelet counts ≥ 50,000/μL at ≥ 50% of the visits during the last 8 weeks of the active treatment period are allowed to enter the Long Term Extension (LTE) to receive study drug at the 400 mg BID dose. Patients may continue in the LTE until the patient is: no longer responding per the LTE-defined platelet response and/or experiences dose limiting toxicities; the drug is no longer being developed by the Sponsor; the program is stopped for safety reasons; or the drug becomes commercially available in the patient's country.

Patients who continue into the LTE will be monitored with weekly platelet counts and CBC's for the first 6 months, and then monthly for an additional 6 months, then once every 3 months.

Patients who previously completed the study, were responders per the LTE requirement, and did not experience a DLT were eligible to enroll in the LTE.

Concomitant Medications:

All patients can receive, but are not required to be taking, concomitant corticosteroids. The dose should be fixed (± 10%) for at least 2 weeks before Day 1 and remain unchanged throughout the study unless rescue criteria are triggered. If the patient requires rescue treatment or concomitant ITP drug increases of more than 10% of the Day 1 daily dose, the patient will be discontinued from the study and receive rescue treatment per standard of care. These drugs may not have their dose increased as part of "rescue" medication.

All patients may receive, but are not required to be taking, eltrombopag or romiplostim. The dose should be fixed for at least 2 weeks before Day 1 and remain constant (10% variation

from Day 1 daily dose is allowed) throughout the study unless there are safety concerns related to those drugs. These drugs may not have their dose increased as part of "rescue" medication.

In vitro, PRN1008 is a substrate of P-gp and CYP3A, and an inhibitor of CYP3A. When co-administered with midazolam in healthy volunteers, PRN1008 has been shown to act as a moderate CYP3A inhibitor, increasing midazolam exposure by approximately 3-fold. Moderate to strong inducers and inhibitors of cytochrome P450 3A (CYP3A) should be avoided during the study, as they may reduce or increase the exposure of PRN1008 when administered concomitantly. Additionally, clinically relevant CYP3A substrate drugs with a narrow therapeutic window are not permitted as PRN1008 is a weak to moderate CYP3A inhibitor. Other "sensitive substrates" if they are medically necessary for the patient should be monitored as concurrent use with PRN1008 will increase the blood levels of sensitive substrate drugs.

Proton pump inhibitors are not permitted during the phase 1/2 study as they may reduce the bioavailability of PRN1008 tablets. Co-administration of esomeprazole reduced exposure of the tablet formulation of PRN1008 by 48% in a prior study, demonstrating an impact of gastric pH on absorption. Patients could switch to H2 receptor blocking drugs as a substitute. PRN1008 should be administered 2 hours or more prior to permitted acid-reducing drugs.

Inclusion Criteria:

The following inclusion criteria are used to inform the enrollment of patients in the phase 1/2 study, including, e.g., the dose escalation study.

1. Male and female patients, aged 18 to 80 years old (Czech Republic and Norway only: aged 18 to 65 years old)
2. Immune-related ITP (both primary and secondary)
3. Refractory or relapsed patients with no available and approved therapeutic options with a platelet count of count <30,000/μL on two occasions no less than 7 days apart in the 15 days prior to beginning study treatment
4. A history of response (two or more platelet counts ≥ 50,000/μL with an increase of ≥ 20,000/μL) to at least one prior line of therapy (with splenectomy being considered a line of therapy)
5. Adequate hematologic, hepatic, and renal function (absolute neutrophil count ≥ 1.5 X 10^9/L, Hgb > 9 g/dL, AST/ALT ≤ 1.5 x ULN, albumin ≥ 3 g/dL, total bilirubin ≤ 1.5 x ULN, estimated GFR > 60 (Cockcroft and Gault method) (C1D1 pre dose may be checked up to Day -3 prior to C1D1)

6. Female patients who are of reproductive potential must agree for the duration of active treatment in the study to use a highly effective means of contraception (hormonal contraception methods that inhibits ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal ligation, vasectomized partner, sexual abstinence). Unless surgically sterile, postmenopausal females should have menopause confirmed by FSH testing.
7. Able to provide written informed consent and agreeable to the schedule of assessment

Additionally, participants cannot commence enrollment procedures until all entry criteria have been fulfilled. Where the clinical significance of an abnormal screening test result (lab or any other tests) is uncertain, the test may be repeated.

Exclusion Criteria:

The following exclusion criteria are used to inform the enrollment of patients in the phase 1/2 study, including, e.g., the dose escalation study.

1. Pregnant or lactating women
2. ECG findings of QTcF > 450 msec (males) or > 470 msec (females), poorly controlled atrial fibrillation (*i.e.,* symptomatic patients or a ventricular rate above 100 beats/min on ECG), or other clinically significant abnormalities
3. History or current, active malignancy requiring or likely to require chemotherapeutic or surgical treatment during the trial, with the exception of non-melanoma skin cancer
4. Transfusion with blood or blood products or plasmapheresis within 2 weeks before Day 1
5. Change in corticosteroid and/or TPO agonist dose within 2 weeks prior to Day 1 (more than 10% variation from Day 1 daily doses)
6. Use of rescue medications other than corticosteroids or TPO in exclusion #5 in the two weeks before Day 1
7. Immunosuppressant drugs other than corticosteroids – these drugs should be discontinued for at least 14 days before Day 1
8. Treatment with rituximab or splenectomy within the 3 months prior to Day 1
9. Ongoing need for the use of proton pump inhibitor drugs such as omeprazole and esomeprazole (it is acceptable to change patient to H2 receptor blocking drugs prior to Day 1)

10. Concomitant use of known strong-to-moderate inducers or inhibitors of CYP3A within 3 days or 5 half-lives (whichever is longer) of Day 1
11. Use of CYP3A-sensitive substrate drugs with a narrow therapeutic index within 3 days or 5 half-lives (whichever is longer) of study drug dosing including, but not limited to, alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or terfenadine
12. Planned or concomitant use of any anticoagulants and platelet aggregation inhibiting drugs such as aspirin, NSAIDs, thienopyridenes (within 14 days of planned dosing through end of follow-up)
13. Has received any investigational drug within the 30 days before receiving the first dose of study medication, or at least 5 times elimination half-life of the drug (whichever is longer); patient should not be using an investigational device at the time of dosing
14. Current drug or alcohol abuse
15. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude adequate study drug absorption
16. History of solid organ transplant
17. Positive for screening for HIV, hepatitis B (surface and core antibodies unrelated to vaccination), or hepatitis C (anti-HCV antibody confirmed with Hep C RNA)
18. History of serious infections requiring intravenous therapy within the last 3 months before Day 1
19. Clinically significant cognitive dysfunction ($\geq$ Grade 1) or medical history suggestive of increased risk for cognitive dysfunction during the study
20. Live vaccine within 28 days prior to Day 1 or plan to receive one during the study
21. Planned surgery in the time frame of the dosing period
22. Any other clinically significant disease, condition, or medical history that, in the opinion of the Investigator, would interfere with patient safety, study evaluations, and/or study procedures

Additionally, participants must fulfill all entry criteria to be enrolled into the study. Participants who fail to meet the entry criteria may be rescreened once at the discretion of the Investigator after informing the study Medical Monitor.

Assessments:

After providing informed written consent, subjects typically complete the following clinical assessments: physical examination; medical history; concomitant medications; weight; height; vital signs; ITP-BAT bleeding scale; QOL assessment EQ-5D VAS; online cognitive testing; and safety assessments.

Subjects typically complete the following laboratory and ECG assessments as part of the study:

1. Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen and leukocytes measured by dip stick or local requirement
2. Hepatitis B and C, HIV
3. Pregnancy test for women of childbearing potential only. Serum pregnancy tests at screening, urine pregnancy tests at other visits
4. FSH: To confirm postmenopausal status for women who are not surgically sterile and of reproductive potential
5. ABO and Rh blood type
6. Immature Platelet Fraction and Mean Platelet Volume (where available at local lab)
7. Serum chemistry: Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Total, direct, and indirect bilirubin levels, Alkaline phosphatase (ALP), Albumin, Creatinine, Urea, Total Protein, Sodium, Chloride, Calcium, Phosphate, Potassium, Glucose (random), and creatine phosphokinase (CPK)
8. Hematology (CBC) including differential and reticulocyte counts
9. T/B/NK/monocyte counts by flow cytometry
10. PT/INR PTT
11. TPO levels
12. Hemolysis panel consisting of Coombs test, haptoglobin levels
13. Platelet autoantibody panel (**Australia Only**: test excluded)
14. PK sampling at various times
15. 12-lead ECG (single and triplicate)

Laboratory assessments may be performed at both central and local laboratories, if required.

Safety assessments include the following: the frequency, severity and relationship of AEs; clinical laboratory test changes; physical examination, ECGs, vital signs, and cognitive function.

In the dose escalation study, patients remain under observation in the clinic for 6 hours after administration of the first dose at the beginning of each new, higher dosing level while having intensive PK sampling performed.

Dosage Forms:

In the study, PRN1008 is administered in the form a film-coated tablet. PRN1008 tablets are packaged in white high-density polyethylene (HDPE) bottles with child-resistant induction-sealed caps; these bottles are intended to be stored at 2–8 °C and can be transported without ice at room temperature. Additionally, the bottles can be kept at room temperature conditions for up to 2 weeks.

Each PRN1008 film-coated tablet contains either 100 mg or 300 mg of PRN1008 drug substance. In addition, the tablet contains Microcrystalline Cellulose (filler), Crospovidone (disintegrant), Sodium Stearyl Fumarate (lubricant), and a non-functional film coating. A 100 mg tablet is a round shape and orange in color. A 300 mg tablet is an oval shape and white in color.

Based on previous studies, food does not appear to impact the extent of PRN1008 absorption but reduces the rate (longer average T_{max} of ~2.5 hours). Accordingly, PRN1008 tablets should be taken with a glass (~8 oz) of water but may be taken with or without food, i.e., a period of fasting is not required.

Analysis Populations:

The Screening Population for this study includes all participants who provide informed consent and have screening assessments evaluated for study participation are included in the Screening Population.

The Safety Population includes all participants who have received at least one dose of PRN1008 will be included in the safety analysis. The Safety Population will be used for all safety analyses. For assessment of safety by the IDSM, with regard to dropping a dose level for futility, 3 evaluable patients, defined as compliance of ≥ 75% of doses for that dose level, are required. During the study, patients will be replaced if necessary, to fulfill this requirement.

The Intent-to-Treat Exposed (ITT-E) Population includes all participants who have received at least one dose of PRN1008.

The Pharmacokinetic Analysis Population includes all participants who have received at least one dose of PRN1008 and have at least one plasma concentration value will be included in the PK analysis. The Pharmacokinetic Analysis Population will be used for all PK analyses.

Participants prematurely discontinued from the study, for reasons other than TEAEs, may be replaced at the discretion of the Sponsor to ensure adequate numbers of evaluable participants.

A patient who withdraws from the study before the planned end of study visit is considered to have withdrawn from the study early. Participants in this study have the right to withdraw at any time for any reason. Additionally, investigators may withdraw participants from the study in the event of intercurrent illness, AEs, treatment failure after a prescribed procedure, lack of compliance with the study and/or study procedures, or any other reasons where they feel it is in the best interest of the participant to be terminated from the study.

Safety and Toxicity Management:

An Independent Data Safety Monitor (IDSM) chosen from expert clinicians in the ITP field provides independent monitoring of the phase 1/2 study. A Safety Monitoring Committee (SMC), comprised of the IDSM as Chairperson, lead Investigator, Study Medical Monitor, and Sponsor's Medical Monitor, also closely supervises the conduct of the study, meeting approximately quarterly and recommending study modification or termination to the Sponsor, based on review of safety and efficacy information. SMC findings that impact the safety of patients in this study are reported to the local Competent Authority (CA) and IRB/EC.

The IDSM made "sentinel cohort" safety evaluations. The "sentinel patients" for each dose level had their data reviewed by the IDSM, in order to choose the starting dose for additional, new patients. After review, the IDSM could determine that a starting dose for new patients should be dropped for futility (lack of platelet response), increased to the next planned dosing level, kept the same, or reduced. New patients entering the study commenced at the dose level determined by the IDSM based on: (1) f $\geq$2/3 or $\geq$2/6 of those sentinel patients have a DLT at any dose level, that level shall be determined the "Maximally Administered Dose" and starting doses (new patients) and continuing doses (patients already on study) set at lower dosing levels (or study suspended if the current sentinel dose cohort was 200 mg QD); (2) two or more sustained platelet responses (3 of 4 counts) in the sentinel patients are seen at the current starting dose level the starting dose will not be escalated.

Clinical Adverse Events

The AE Collection Period begins at the time of the first screening/eligibility assessment and ends at the end of the study for each patient. An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the intervention. An AE can

therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product. Investigators are instructed to record all AEs encountered during the clinical study in detail from the date of participant consent throughout the study follow-up period. Pre-existing conditions that worsen during a study are reported as AEs.

Adverse Event Relationship to Study Drug

Investigators are instructed to use their knowledge of the study participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an AE may be considered as related to the study drug, indicating "yes" or "no" accordingly. Investigators are asked to consider following information in assessing relatedness: (1) temporal relationship of event onset to the initiation of study drug; (2) course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (if applicable); (3) known association of the event with the study drug or with similar treatments; (4) known association of the event with the disease under study; (5) presence of risk factors in the study participant or use of concomitant medications known to increase the occurrence of the events; and (6) presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

Investigators are instructed to follow up AEs, especially those for which the severity is Grade 3 or higher, until stabilization or until 4 weeks post last dose (considered as the last follow up), based on the PK profile of the drug.

Laboratory and ECG Abnormalities

Investigators are instructed to record any treatment-emergent abnormal laboratory or ECG result that is clinically significant, i.e., meeting one or more of the following conditions, as a single diagnosis on the AE page in the CRF. As non-limiting examples, laboratory and ECG abnormalities accompanied by clinical symptoms, leading to a change in study drug (e.g., dose modification, interruption or permanent discontinuation), or requiring a change in concomitant therapy (*e.g.,* addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment) should be recorded as an AE, with any laboratory or ECG result abnormality fulfilling the criteria for a serious adverse event (SAE) reported as such, in addition to being recorded as an AE.

Adverse Event Intensity Grading

Investigators are instructed to report all clinical AEs encountered during the study. The intensity of AEs is graded based on the NCI CTCAE, Version 4.0 or higher. For any AEs not found in the CTCAE, a description of intensity grading can be found below:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

A serious adverse event (SAE) is any experience (clinical AE or abnormal laboratory test) that suggests a significant hazard, contraindication, side effect, or precaution. An SAE must fulfill at least one of the following criteria at any dose level: is fatal (results in the outcome death); is life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or is medically significant or requires intervention to prevent one or other of the outcomes listed above. Investigators are instructed to report life-threatening events or any event with an outcome of death should be reported as an SAE.

Pregnancy

Any female clinical trial participant who becomes pregnant during the study must be instructed to stop taking the study drug and immediately inform the Investigator. Pregnancies occurring up to 90 days after the completion of the study drug must also be reported to the Investigator.

Ethical Considerations:

Investigators are tasked with ensuring that the study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. Additionally, the study adheres to the principles outlined in current "Guideline for Good Clinical Practice" ICH Tripartite Guideline or with local law if it affords greater protection to the participant.

Signed and dated informed consent is obtained from each participant prior to participating in the study after adequate explanation of the aims, methods, objectives and potential hazards of the study. The Investigator or designee must explain that the participants are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

Physical Examination Procedures:

At screening and follow-up visits in the study, a complete physical examination consists of checking the normality or abnormality of the following body systems: general appearance, skin, eyes, ears, nose, throat, heart, chest/breast, abdomen, neurological system, lymph nodes, spine and extremities (skeletal) and the conduct of and online cognitive testing of learning and memory. An abbreviated physical examination consists of checking the normality or abnormality of the following body systems: general appearance, skin, abdomen, and cardiorespiratory examination. Height is recorded at screening only. Blood pressure (BP), pulse rate, body temperature and respiratory rate are recorded at specific time points.

Single 12-lead ECG assessments are also obtained at specific time points to confirm eligibility and to ensure real time safety evaluation of the participants in the study. For ECG evaluations, participants should be in a resting position for at least 10 minutes prior to any measurement. Body position should also be consistently maintained for each ECG evaluation. In particular, changes in heart rate should be avoided. There should be no environmental distractions (TV, radio, conversation) during the pre-ECG rest and the ECG recording time.

Heart rate (HR), QRS duration and respiratory rate (RR), and QT intervals are recorded. Changes of the T-wave and U-wave morphology and overall ECG interpretation are documented. All ECG recordings are performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. For triplicate ECG assessments, at least three interpretable ECG recordings (without artifacts) are collected per time point within a ± 10 minute period per time point.

Laboratory Test Procedures:

Laboratory assessments are performed at a central laboratory, with the provision for occasional local laboratory testing, if required. Laboratory safety tests are collected at specific time points. Additional blood or urine samples may be taken at an investigator's discretion if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor participant safety. Where the clinical significance of abnormal lab results is

considered uncertain, screening lab tests may be repeated before Day 1 to confirm eligibility. In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range, are considered to be clinically stable, and/or an adequate explanation of the abnormality is found.

Preliminary Results:

Positive preliminary data has been observed in the ongoing phase 1/2 trial of PRN1008 in the treatment of ITP. Illustratively, FIG. 5 shows platelet count response for an enrolled patient with secondary ITP, demonstrating responsiveness to treatment at 400 mg qd. During the completed dose-escalation study, PRN1008 was well-tolerated across all doses (200 and 400 mg qd, 300 and 400 mg bid) in a highly treatment-resistant and refractory patient population with immune thrombocytopenia (ITP). All TEAEs were mild to moderate with no thrombotic events.

Early study data was reported in October 2019. At the time of reporting, the phase 1/2 trial of PRN1008 had enrolled 26 adult patients who have had two platelet counts < 30,000/μL within 15 days prior to treatment. Oral PRN1008 starting doses were 200 mg qd, 400 mg qd, 300 mg bid, and 400 mg bid, with intra-patient dose escalation allowed every four weeks, with the trial having a median treatment duration of 12.7 weeks (range: 0.14 to 39.71) at reporting. In the early study data reported in October 2019, 39 percent (80% confidence interval (CI) 27.3, 51.0) of the 26 patients that had enrolled up to that point achieved the trial's primary endpoint of ≥ 2 consecutive platelet counts of ≥ 50,000/μL, separated by at least five days, and increased by ≥ 20,000/μL from baseline without requiring rescue medication (Tables 2 and 3). In addition, 46 percent (80% CI 34.2, 58.5) of enrolled patients achieved any 2 platelet counts ≥ 50,000/μL (Table 3). These results were observed despite the limited duration of therapy and patients at multiple escalating dose levels. In the preliminary data on 15 patients across all doses who had completed at least 12 weeks of therapy, the response rate was greater than 50 percent for both endpoints. PRN1008 was well-tolerated at all doses studied, whether given as a monotherapy or with allowed concomitant ITP therapy, with no reported treatment related bleeding or thrombotic events, at the time of early reporting.

In Table 2, percentages are based on the number of patients in each dose group and overall. Patients are classified into different dose levels according to the dose they received prior to the start of the platelet response. The 95% confidence interval is based on the Wilson Score method.

Table 2: Preliminary Efficacy Data (ITT-E Population, October 2019 Reporting)

	200 mg QD (N=9)	400 mg QD (N=8)	300 mg BID (N=12)	400 mg BID (N=19)	Overall (N=26)
Responder	1 (11.1)	2 (25.0)	4 (33.3)	6 (31.6)	10 (38.5)
95% CI	1.99, 43.5	7.15, 59.1	13.8, 60.9	15.4, 54.0	22.4, 54.5
Non-Responder	8 (88.9)	6 (75.0)	8 (66.7)	13 (68.4)	16 (61.5)

Table 3: Preliminary Efficacy Data (ITT-E Population, October 2019 Reporting)

Treatment duration and dose	Platelet counts $\geq 50\times 10^9$/L 80% (CI)				
	Primary Endpoint: 2 consecutive	Any 2	50% of all	4 out of final 8	4 out of final 6
All patients enrolled (N = 26)	38.5 (27.3 - 51)	46.2 (34.2 - 58.5)	26.9 (17.4 - 39.2)	19.2 (11.3 - 30.8)	19.2 (11.3 - 30.8)
≥ 4 weeks, all doses (N = 20)	45 (31.7 - 59.1)	55 (40.9 - 68.3)	25 (14.8 - 39)	25 (14.8 - 39)	25 (14.8 - 39)
≥ 12 weeks, all doses (N = 15)	53.3 (37.3 - 68.7)	66.7 (50.1 - 79.9)	26.7 (14.9 - 43.1)	33.3 (20.1 - 49.9)	33.3 (20.1 - 49.9)
≥ 12 weeks, 300 mg BID & 400 mg BID (N = 11)	63.6 (44.4 - 79.3)	72.7 (53.5 - 86.1)	27.3 (13.9 - 46.5)	36.4 (20.7 - 55.6)	36.4 (20.7 - 55.6)

As of November 13, 2019, the 31 enrolled patients in the phase 1/2 study were characterized by the demographic information provided in Tables 4 and 5. The median age of enrolled patients was 50, with 29 of 31 classified with primary ITP (94%) and 2 of 31 classified with secondary ITP (6%). At enrollment, patients had ITP for a median duration of 7.8 years, were heavily pretreated (median of 6 prior therapies), and 26% had undergone a prior splenectomy. During the study, 10 patients (32%) received PRN1008 monotherapy and 21 patients (68%) were on ≥ 1 concomitant ITP medication.

As of November 13, 2019, study data confirmed that the optimal safety and efficacy dose for PRN1008 in the treatment of ITP is 400 mg bid.

The primary endpoint defined as 2 consecutive platelet counts ≥ 50,000 μL without requiring rescue medication, was met in 39% of all patients independent of dose or time on treatment. This patient population was highly treatment-resistant and refractory, with patients characterized by a median of 6 prior therapies, including 55% receiving a prior TPO-RA. Rapid onset (platelet counts > 30k by the first week of treatment) was observed following the start of

PRN1008 treatment, and responses were durable in the majority of patients. Platelet response was further improved with longer treatment and at higher doses of PRN1008.

Table 4: Patient Demographics (Data Cut-off: Nov. 13, 2019)

Demographics	**N = 31**
Median age, y (range)	50 (21-74)
Female, n (%)	18 (58)
ITP classification, n (%)	
Primary ITP	29 (94)
Secondary ITP	2 (6)
Median duration of ITP, y (range)	7.8 (0.5-42.4)
Median baseline platelet count, $\times 10^9$/L (range)	13 (3-28)

Table 5: Prior ITP Therapy (Data Cut-off: Nov. 13, 2019)

Prior ITP Therapy	**N = 31**
Median number of prior ITP therapies (range)	6 (1-41)
Splenectomy, n (%)	8 (26)
Prior ITP therapies, n (%)	
Corticosteroids	26 (84)
TPO-RA	17 (55)
IVIG/Anti-D	11 (35)
Rituximab	10 (32)

Table 6 provides a summary of platelet response by treatment duration and dose (data cut-off: November 13, 2019). Individual platelet counts of dose levels over time for low starting dose (qd dosing, n = 10) and high starting dose (bid dosing) (n = 21) are depicted in FIGs. 6 and 7, respectively (data cut-off: November 13, 2019). In FIGs. 6 and 7, responders are people who achieved ≥ 50,000/μL platelet counts at least one.

Subset analyses of primary platelet responses are depicted in FIG. 8 (data cut-off: November 13, 2019). As of November 13, 2019, 10 of 25 (40%) of heavily pretreated (≥ 4 prior therapies) patients were responding to PRN1008 treatment. Similar responses were achieved in patients receiving PRN1008 monotherapy (4 of 10 patients) and concomitant therapy (8 of 21 patients).

Table 6: Summary of Platelet Response by Treatment Duration and Dose (Data Cut-off: November 13, 2019)

Treatment Duration and Dose	Patients Achieving Platelet Counts ≥ 50 × 10^9/L (80% CI)		
	Primary Endpoint 2 consecutive	Any 2	4 of Final 8
All patients enrolled (N = 31)	39% (28%-50%)	45% (34%-57%)	29% (20%-40%)
≥ 4 weeks, all doses (n = 26)	46% (34%-59%)	54% (41%-66%)	35% (24%-47%)
≥ 12 weeks, all doses (n = 17)	47% (33%-62%)	59% (43%-73%)	35% (22%-51%)
≥ 12 weeks at 300 and 400 mg bid (n = 13)	54% (37%-70%)	62% (44%-77%)	39% (23%-56%)

PRN1008 was well-tolerated in ITP patients across all doses as of November 13, 2019 (Table 7). The median treatment duration at the November 13, 2019, cut-off was 12.0 weeks (range: 0.1-41.9). Related TEAEs were reported in 11 patients (35%), with all reported TEAEs being grade 1 or 2 (mild to moderate). No treatment-related bleeding or thrombotic events were reported, nor were significant changes in the ITP-BAT bleeding scale from baseline to last visit. No dose-limiting toxicities were observed by data cut-off. The observed safety profile was consistent with the safety observed in pemphigus studies (Murrell D. et al., AAD 2018).

Table 7: Summary of Related TEAEs (Data Cut-off: November 13, 2019)

Related TEAEs (≥ 2 Patients), n (%)	Grade 1/2
All TEAEs	11 (35)
Nausea	8 (26)
Diarrhea	7 (23)
Abdominal distension	3 (10)
Fatigue	3 (10)

As of April 22, 2020, 47 patients had enrolled in the study, with 32 patients initiated on a 400 mg bid dose. Demographic information for enrolled patients as of April 22, 2020, is included in Table 8. ITP patient characteristics were similar across all treatment groups in a difficult-to-treat population. Similar to the November 13, 2019, cut-off data, patients had ITP for a median of 7+ years at enrollment, were heavily pretreated (median of 6 prior medications), and 28% had undergone a prior splenectomy. Additionally, 31 patients (66%) were on ≥ 1 concomitant ITP medication (CS and/or TPO) and were considered inadequate responders.

Table 8: Patient Demographics and Prior ITP Therapy (Data Cut-off: April 22, 2020)

	All Patients (N = 47)	**400 mg bid (n = 32)**
Median age, y (range)	50 (21-74)	50 (21-74)
Female, n (%)	27 (57)	20 (63)
ITP classification, n (%)		
Primary ITP	44 (94)	31 (97)
Secondary ITP	3 (6)	1 (3)
Median duration of ITP, y (range)	7.8 (0.4-52.5)	7.3 (0.4-52.5)
Median baseline platelet count, $\times 10^9$/L (range)	14 (3-33)	13 (4-33)
Median number of prior ITP therapies (range)	6 (1-54)	6 (1-54)
Splenectomy, n (%)	13 (28)	9 (28)
At least one prior ITP therapy	100%	100%

As of April 22, 2020, platelet responses had a fast onset and were maintained in the majority of patients who started on the PRN1008 400 mg bid dose (FIG. 9). By day 8 (the first platelet count taken after the start of treatment), platelets $\geq 30 \times 10^9$/L (a clinically significant platelet count) were observed in 53% of patients initiated at 400 mg bid and 79% of primary endpoint responders, where the primary endpoint was defined as 2 consecutive platelet counts 50,000/μL ≥ without requiring rescue medication. By week 4, 57% of responders achieved the primary endpoint. In addition, 50% of patients achieved the primary endpoint response when initiated on PRN1008 400 mg bid and treated for 12 weeks or more. Moreover, the response was durable, with responders maintaining platelet counts: 71% of time (weeks) at $\geq 50 \times 10^9$/L; and 88% of time (week) at $\geq 20 \times 10^9$/L above baseline.

Subset analyses of platelet responses are depicted in FIG. 10 (data cut-off: April 22, 2020). Overall, 43% of patients met the primary endpoint, which increased with ≥ 12 weeks of PRN1008. As of April 22, 2020, 15 of 38 (40%) of heavily pretreated (≥ 4 prior therapies) patients were responding to PRN1008 treatment. Similar responses were achieved in patients receiving PRN1008 monotherapy (7 of 16 patients) and inadequate responders on concomitant therapy (13 of 31 patients).

PRN1008 was well-tolerated in ITP patients across all doses as of April 22, 2020 (Table 9). The median treatment duration at the April 22, 2020, data cut-off was 17.7 weeks for all patients (range: 0.6-41.9) and 18 weeks for patients initiated on 400 mg bid (range: 1.4-24.6). Related TEAEs were reported in 21 patients (45%), with all reported TEAEs being transient and grade 1 or 2 (mild to moderate). No related serious adverse events were reported. Additionally, no treatment-related bleeding or thrombotic events were reported, nor were significant changes in the ITP-BAT bleeding scale from baseline to last visit. The observed

safety profile was consistent with the safety observed in pemphigus studies (Murrell D. et al., AAD 2018).

Table 9: Summary of Related TEAEs (Data Cut-off: April 22, 2020)

Related TEAEs (≥ 10%), n (%)	All Patients (N = 47)		400 mg bid (n = 32)	
	Grade 1	Grade 2	Grade 1	Grade 2
All related TEAEs	10 (21)	11 (23)	15 (47)	11 (34)
Diarrhea	14 (30)	2 (4)	11 (34)	2 (6)
Nausea	12 (26)	1 (2)	8 (25)	1 (3)
Fatigue	5 (11)	1 (2)	3 (9)	1 (3)

As of May 5, 2020, oral PRN1008 achieved primary endpoint in 50% of patients treated for ≥ 12 weeks (n = 26) and demonstrated fast onset and durable responses. PRN1008 treatment for ≥ 12 weeks further improved platelet responses. Similar to the November 13, 2019, cut-off data, the primary endpoint was defined as 2 consecutive platelet counts ≥ 50,000 μL without requiring rescue medication. Table 10 provides a summary of platelet response by treatment duration and dose (data cut-off: May 5, 2020).

Table 10: Summary of Platelet Response by Treatment Duration and Dose (Data Cut-off: May 5, 2020)

Treatment Duration and Dose	Patients Achieving Platelet Counts ≥ 50 × 10^9/L (80% CI)		
	Primary Endpoint 2 consecutive	50% of Counts	4 of Final 6
All patients enrolled (N = 47)	43% (34, 52)	34% (26, 43)	28% (20, 37)
≥ 12 week treatment, all doses (n = 36), *includes patients escalated to 400 mg bid*	50% (40, 60)	39% (29, 50)	33% (24, 44)
Initiated 400 mg bid (n = 32)	44% (33, 55)	38% (27, 49)	31% (22, 42)
≥ 12 week treatment (initial 400 mg bid) (n = 26)	50% (38, 62)	42% (31, 55)	35% (24, 47)

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Claims or descriptions that include "or" or "and/or" between at least one members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The disclosure includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The disclosure includes embodiments in which more than one, or all the group members are present in, employed in, or otherwise relevant to a given product or process.

Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the disclosure should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.