deficiency are infrequent, often mild, result from injury or trauma, and very rarely affect critical organs (Salomon *et al.* (2011)).

[0006] Antibodies that bind Factor XI and/or Factor XIa have been studied. For example, WO 2016/207858 describes one such anti-Factor XI and/or Factor XIa antibody, disclosed in Table 1 as Antibody 1. The present disclosure adds to these developments and provides further clinical methods, including dosage regimens, to treat patients with specific thromboembolic disorders with desired safety and efficacy. Furthermore, the present disclosure adds to the earlier developments in the field by providing formulations comprising such FXI and/or FXIa antibodies that are sufficiently stable and suitable for administration to patients.

SUMMARY

[0007] The present disclosure relates to pharmaceutical formulations for anti-Factor XI and/or activated Factor XI (Factor XIa) antibodies, or antigen-binding fragments thereof. Also provided are dosage regimens for such antibodies or antigen-binding fragments thereof, and pharmaceutical formulations for use in the treatment of thromboembolic disorders or related conditions.

[0007a] In one aspect, the present disclosure provides a vial comprising a formulation comprising:

(a) a therapeutically effective amount of an isolated anti-Factor XI (FXI) and/or anti-activated Factor XI (FXIa) antibody or antigen-binding fragment thereof;

(b) a histidine buffer;

(c) a sugar or sugar alcohol; and

(d) a polysorbate,

at pH 5.0 to 6.0,

wherein the vial comprises an overfill for complete withdrawal of a therapeutically effective amount of the anti-FXI and/or anti-FXIa antibody or antigen-binding fragment thereof.

[0008] Accordingly, in one example, provided herein is a vial comprising a drug delivery formulation comprising: (a) a therapeutically effective amount of an isolated anti-Factor XI (FXI) and/or anti-activated Factor XI (FXIa) antibody, or antigen-binding fragment thereof; (b) a histidine buffer; (c) a sugar or sugar alcohol; and (d) a polysorbate, at pH 5.0 to 6.0,

wherein the vial comprises an overfill for complete withdrawal of a therapeutically effective amount of the anti-FXI and/or anti-FXIa antibody or the antigen-binding fragment thereof.

[0009] In certain examples, the vial comprises the therapeutically effective amount of the isolated anti-FXI and/or anti-FXIa antibody or antigen-binding fragment thereof at a concentration between 120 mg/ml and 180 mg/ml. In certain examples, the vial comprises the therapeutically effective amount of the isolated anti-FXI and/or anti-FXIa antibody or antigen-binding fragment thereof at a concentration of about 150 mg/ml.

[0010] In certain examples, the histidine buffer comprises a histidine and a histidine salt. In certain examples, the histidine is L-histidine. In certain examples, the histidine salt is histidine HCl monohydrate. In certain examples, the histidine buffer is at

a concentration between 10 mM and 30 mM. In certain examples, the histidine buffer is at a concentration of about 20 mM.

[0011] In certain examples, the sugar or sugar alcohol is a disaccharide. In certain examples, the disaccharide is sucrose. In certain examples, the sucrose is at a concentration between 170 mM to 270 mM. In certain examples, the sucrose is at a concentration of about 220 mM.

[0012] In certain examples, the polysorbate is polysorbate 20. In certain examples, the polysorbate 20 is at a concentration between 0.02% (v/v) to 0.06% (v/v). In certain examples, the polysorbate 20 is at a concentration of about 0.04% (v/v).

[0013] In certain examples, the pH of the drug delivery formulation is 5.3 to 5.7. In certain examples, the pH of the drug delivery formulation is about 5.5.

[0014] In certain examples, the overfill comprises between 10% (v/v) and 30% (v/v) of the drug delivery formulation, optionally wherein the vial comprises 1.1 mL to 1.3 mL of the drug delivery formulation. In certain examples, the overfill comprises about 20% (v/v) of the drug delivery formulation, optionally wherein the vial comprises about 1.2 mL of the drug delivery formulation.

[0014a] In another aspect, the present disclosure provides a vial comprising a formulation comprising:

(a) a therapeutically effective amount of an isolated anti-FXI and/or anti-FXIa antibody or antigen-binding fragment thereof at a concentration of about 150 mg;

(b) a histidine buffer at a concentration of about 20 mM;

(c) sucrose at a concentration of about 220 mM; and

(d) polysorbate 20 at a concentration of about 0.04% (v/v),

at pH 5.5,

wherein the vial comprises an overfill for complete withdrawal of a therapeutically effective amount of the anti-FXI and/or anti-FXIa antibody or antigen-binding fragment thereof.

[0015] In another example, disclosed herein is a vial comprising a drug delivery formulation comprising:

(a) a therapeutically effective amount of an isolated anti-Factor XI (FXI) and/or anti-activated Factor XI (FXIa) antibody, or antigen-binding fragment thereof at a concentration of about 150 mg;

(b) a histidine buffer at a concentration of about 20 mM;

(c) sucrose at a concentration of about 220 mM; and

(d) polysorbate-20 at a concentration of about 0.04% (v/v),

at pH 5.5,

wherein the vial comprises an overfill for complete withdrawal of a therapeutically effective amount of the anti-FXI and/or anti-FXIa antibody or the antigen-binding fragment thereof.

[0015a] In another aspect, the present disclosure provides an intravenous formulation comprising:

(a) a therapeutically effective amount of an isolated anti-FXI and/or anti-FXIa antibody or antigen-binding fragment thereof;

(b) a histidine buffer;

(c) a sugar or sugar alcohol;

(d) a polysorbate, and

(e) a diluent solution comprising a second sugar and water,

at pH 5.0 to 6.0.

[0016] In another example, provided herein is an intravenous drug delivery formulation comprising: (a) a therapeutically effective amount of an isolated anti-FXI and/or anti-FXIa antibody or antigen-binding fragment thereof; (b) a histidine buffer; (c) a sugar or sugar

alcohol; (d) a polysorbate, and (e) a diluent, at pH 5.0 to 6.0, wherein the diluent is a solution comprising a second sugar and water.

[0017] In certain examples, the therapeutically effective amount of the isolated anti-FXI and/or anti-FXIa antibody or antigen-binding fragment thereof is at a concentration between 1.20 mg/ml and 1.80 mg/ml. In certain examples, the therapeutically effective amount of the isolated anti-FXI and/or anti-FXIa antibody or antigen-binding fragment thereof is at a concentration of about 1.50 mg/ml.

[0018] In certain examples, the histidine buffer comprises a histidine and a histidine salt. In certain examples, the histidine is L-histidine. In certain examples, the histidine salt is histidine HCl monohydrate. In certain examples, the histidine buffer is at a concentration between 0.10 mM and 0.30 mM. In certain examples, the histidine buffer is at a concentration of about 0.20 mM.

[0019] In certain examples, the sugar or sugar alcohol is a disaccharide. In certain examples, the disaccharide is sucrose. In certain examples, the sucrose is at a concentration between 1.70 mM to 2.70 mM. In certain examples, the sucrose is at a concentration of about 2.20 mM.

[0020] In certain examples, the polysorbate is polysorbate 20. In certain examples, the polysorbate 20 is at a concentration of less than 0.001% (v/v). In certain examples, the polysorbate 20 is at a concentration of about 0.0004% (v/v).

[0021] In certain examples, the pH of the intravenous drug delivery formulation is 5.3 to 5.7. In certain examples, the pH of the intravenous drug delivery formulation is about 5.5.

[0022] In certain examples, the second sugar in the diluent is a monosaccharide. In certain examples, the monosaccharide is dextrose. In certain examples, the dextrose is at a concentration between 2.5% (v/v) and 7.5% (v/v). In certain examples, the dextrose is at a concentration of about 5% (v/v).

[0023] In another example, disclosed herein is an intravenous drug delivery formulation comprising:

(a) a therapeutically effective amount of an isolated anti-FXI and/or anti-FXIa antibody or antigen-binding fragment thereof at a concentration of about 1.5 mg;

(b) a histidine buffer at a concentration of about 0.20 mM;

(c) sucrose at a concentration of about 2.20 mM;

(d) a polysorbate-20 at a concentration of about 0.0004% (v/v), and

(e) a diluent at pH 5.5, wherein the diluent is dextrose 5% in water (D5W).

[0024] The following features can be incorporated into any of the examples recited above:

[0025] In certain examples, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (VH) comprising complementary determining regions HCDR1, HCDR2, and HCDR3 in SEQ ID NO: 9 or 29; and a light chain variable region (VL) comprising complementary determining regions LCDR1, LCDR2, LCDR3 in SEQ ID NO: 19 or 39.

[0026] In certain examples, the antibody or antigen-binding fragment thereof comprises: i. a heavy chain variable region CDR1 of SEQ ID NO: 23; a heavy chain variable region CDR2 of SEQ ID NO: 24; a heavy chain variable region CDR3 of SEQ ID NO: 25; a light chain variable region CDR1 of SEQ ID NO: 33; a light chain variable region CDR2 of SEQ ID NO: 34; and a light chain variable region CDR3 of SEQ ID NO: 35; ii. a heavy chain variable region CDR1 of SEQ ID NO: 26; a heavy chain variable region CDR2 of SEQ ID NO: 27; a heavy chain variable region CDR3 of SEQ ID NO: 28; a light chain variable region CDR1 of SEQ ID NO: 36; a light chain variable region CDR2 of SEQ ID NO: 37; and a light chain variable region CDR3 of SEQ ID NO: 38; iii. a heavy chain variable region CDR1 of SEQ ID NO: 43; a heavy chain variable region CDR2 of SEQ ID NO: 44; a heavy chain variable region CDR3 of SEQ ID NO: 45; a light chain variable region CDR1 of SEQ ID NO: 47; a light chain variable region CDR2 of SEQ ID NO: 37; and a light chain variable region CDR3 of SEQ ID NO: 15; or iv. a heavy chain variable region CDR1 of SEQ ID NO: 46; a heavy chain variable region CDR2 of SEQ ID NO: 4; a heavy chain variable region CDR3 of SEQ ID NO: 5; a light chain variable region CDR1 of SEQ ID NO: 33; a light chain variable region CDR2 of SEQ ID NO: 14; and a light chain variable region CDR3 of SEQ ID NO: 15.

[0027] In certain examples, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (VH) selected from the group consisting of SEQ ID NO: 9, 29, and a VH with 90% identity thereto; and a light chain variable region (VL) selected from the group consisting of SEQ ID NO: 19, 39, and a VL with 90% identity thereto. In certain examples, the antibody or antigen-binding fragment thereof comprises

a heavy chain variable region (VH) selected from the group consisting of SEQ ID NO: 9 and 29; and a light chain variable region (VL) selected from the group consisting of SEQ ID NO: 19 and 39.

[0028] In certain examples, the antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 31, 11, and a heavy chain with 90% identity thereto; and a light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 41, 21, and a light chain with 90% identity thereto.

[0029] In certain examples, the antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 31 and a light chain comprising an amino acid sequence of SEQ ID NO: 41.

[0030] In certain examples, the antibody is a human monoclonal antibody. In certain examples, the antibody is a human IgG1 isotype. In certain examples, the antibody comprises D265A and P329A substitutions in the Fc domain, optionally wherein 120 mg to 180 mg is the therapeutically effective amount of the anti-Factor XI (FXI) and/or anti-activated Factor XI (FXIa) antibody or antigen-binding fragment thereof, for administration to a subject.

[0030a] In another aspect, the present disclosure provides the formulation as described herein or the intravenous formulation as described herein for use in treating a subject afflicted with or at risk of developing a thromboembolic disorder. In yet another aspect, the present disclosure provides a use of the formulation present in the vial as described herein or the intravenous formulation as described herein for the manufacture of a medicament for treating a subject afflicted with or at risk of developing a thromboembolic disorder.

[0031] In another example, provided herein is a method of treating a subject afflicted with or at risk of developing a thromboembolic disorder, the method comprising administering a therapeutically effective amount of the drug delivery formulation present in the vial or the intravenous drug delivery formulation to the subject in need thereof.

[0032] In certain examples, the thromboembolic disorder is selected from the group consisting of atrial fibrillation or atrial flutter, transient ischemic attack, ischemic stroke, thromboembolic stroke, hemorrhagic stroke, venous thromboembolism (VTE), pediatric VTE, systemic embolism, non-central nervous systemic embolism, myocardial infarction, deep vein thrombosis, Severe Protein S deficiency, cerebrovascular accident, and cancer.

[0033] In certain examples, the drug delivery formulation present in the vial or the intravenous drug delivery formulation is administered monthly.

[0034] In certain examples, the drug delivery formulation present in the vial or the intravenous drug delivery formulation is administered at a dose selected from the group consisting of about 30 mg, about 60 mg, about 90 mg, about 120 mg, about 150 mg, and

about 180 mg. In certain examples, the drug delivery formulation present in the vial is administered at a dose of about 90 mg. In certain examples, the drug delivery formulation present in the vial is administered at a dose of about 120 mg. In certain examples, the drug delivery formulation present in the vial is administered at a dose of about 150 mg.

[0035] In certain examples, the drug delivery formulation present in the vial is administered subcutaneously.

[0036] In certain examples, wherein the thromboembolic disorder is atrial fibrillation or atrial flutter. In certain examples, wherein the atrial fibrillation or atrial flutter is paroxysmal atrial fibrillation (PAF).

[0037] In certain examples, the drug delivery formulation present in the vial is administered once a month for a period of three months.

[0038] In certain examples, wherein the subject is at low risk of stroke. In certain examples, the subject has a CHA_2DS_2VASc risk score of 0 to 1.

[0039] In certain examples, the subject is at moderate risk of stroke.

[0040] In certain examples, the subject is at high risk of stroke. In certain examples, the subject has a CHA_2DS_2VASc risk score of ≥ 2 for male subjects and ≥ 3 for female subjects.

[0041] In certain examples, the method further comprises evaluating efficacy of the drug delivery formulation present in the vial by measuring inhibition of Factor XI at the trough after the third dose of the drug delivery formulation. In certain examples, the method further comprises evaluating efficacy of the drug delivery formulation present in the vial by assessing one or more biomarkers selected from the list consisting of free Factor XI, total Factor XI, Factor XI coagulation activity, activated partial thromboplastin time, and D-dimer.

[0042] In certain examples, the method further comprises evaluating adverse events to the drug delivery formulation present in the vial by measuring bleeding events or the presence of anti-drug antibodies. In certain examples, the method further comprises applying one or more of the following to the patient experiencing an adverse event, wherein the adverse event is a bleeding event: (i) fluid replacement using colloids, crystalloids, human plasma or plasma proteins such as albumin; (ii) transfusion with packed red blood or whole

blood; or (iii) administration of fresh frozen plasma (FFP), prothrombin complex concentrates (PCC), activated PCC (APCC), such as, factor VIII inhibitor, and/or recombinant, activated factor VII.

[0042a] In another aspect, the present disclosure provides the formulation present in the vial as described herein or the intravenous formulation as described herein for use in treating a subject afflicted with or at risk of developing a thromboembolic disorder and who is undergoing a surgical procedure, wherein the subject is to be administered the intravenous formulation on the same day as the surgical procedure. In yet another aspect, the present disclosure provides a use of the intravenous formulation as described herein in the manufacture of a medicament for treating a subject afflicted with or at risk of developing a thromboembolic disorder and who is undergoing a surgical procedure, wherein the subject is to be administered the intravenous formulation on the same day as the surgical procedure.

[0043] In another example, provided herein is a method of treating a subject afflicted with or at risk of developing a thromboembolic disorder and who is undergoing a surgical procedure, the method comprising administering the intravenous drug delivery formulation as described herein to a subject in need thereof, wherein the subject is administered the intravenous drug delivery formulation on the same day as the surgical procedure.

[0044] In certain examples, the surgical procedure is selected from the group consisting of knee replacement surgery, *e.g.,* unilateral total knee arthroplasty (TKA), hip replacement surgery, orthopedic surgery, pacemaker installation, catheter installation, thoracic surgery, and abdominal surgery. In certain examples, the surgical procedure is unilateral total knee arthroplasty (TKA).

[0045] In certain examples, the intravenous drug delivery formulation is administered monthly.

[0046] In certain examples, the intravenous drug delivery formulation is administered at a dose selected from the group consisting of about 30 mg, about 60 mg, about 90 mg, about 120 mg, about 150 mg, and about 180 mg. In certain examples, the intravenous drug delivery formulation is administered at a dose of about 30 mg. In certain examples, the intravenous drug delivery formulation is administered at a dose of about 60 mg. In certain examples, the intravenous drug delivery formulation is administered at a dose of about 75 mg. In certain examples, the intravenous drug delivery formulation is administered at a dose of about 150 mg.

[0047] In certain examples, the intravenous drug delivery is administered approximately 4-8 hours after surgery.

[0047a] In another aspect, the present disclosure provides the formulation present in the vial as described herein or the intravenous formulation as described herein for use in treating a subject afflicted with or at risk of developing a thromboembolic disorder, wherein the subject is receiving NSAIDs, and wherein the subject is to be administered a therapeutically effective amount of the formulation in combination with a proton-pump inhibitor. In yet another aspect, the present disclosure provides a use of the formulation present in the vial vial as described herein or the intravenous formulation vial as described herein for the manufacture of a medicament for treating a subject afflicted with or at risk of developing a thromboembolic disorder, wherein the subject is receiving non-steroidal anti-inflammatory drugs (NSAIDs), and wherein the subject is to be administered a therapeutically effective amount of the formulation in combination with a proton-pump inhibitor.

[0048] In another example, provided herein is a method of treating a subject afflicted with or at risk of developing a thromboembolic disorder, wherein the subject is receiving non-steroidal anti-inflammatory drugs (NSAIDs), the method comprising administering a therapeutically effective amount of the drug delivery formulation present in the vial or the intravenous drug delivery in combination with a proton-pump inhibitor to the subject in need thereof.

[0049] In certain examples, the drug delivery formulation present in the vial or the intravenous drug delivery formulation is administered monthly.

[0050] In certain examples, the drug delivery formulation present in the vial or the intravenous drug delivery formulation is administered at a dose selected from the group consisting of about 30 mg, about 60 mg, about 90 mg, about 120 mg, about 150 mg, and about 180 mg.

[0051] In certain examples, the drug delivery formulation present in the vial is administered subcutaneously.

[0052] Other examples and details of the disclosure are presented herein below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0053] **FIG. 1A – FIG. 1B** show linearity analysis of size exclusion high-performance liquid chromatography (SE-HPLC) for drug product containing antibody 1 diluted in dextrose (D5W, shown in **FIG. 1A**) or aprotinin (APN, shown in **FIG. 1B**).

[0054] **FIG. 2A – FIG. 2C** show the temporal duration of the effects of Antibody 1 on various biomarkers. **FIG. 2A** shows the concentration of Antibody 1 in plasma for subjects with atrial fibrillation (AF). **FIG. 2B** shows free Factor XI in plasma for AF subjects treated with Antibody 1. **FIG. 2C** demonstrates the effect of multiple doses of Antibody 1 on free Factor XI.

[0055] **FIG. 3A – FIG. 3C** show safety analysis of experimental antithrombotic treatments based on number of patients experiencing any venous thromboembolism (VTE) event for Antibody 1 (**FIG. 3A**), and published clinical trials with Factor XI antisense oligonucleotide (FXI-ASO) (**FIG. 3B**), and FOXTROT (**FIG. 3C**); each experimental treatment shows comparison to enoxaparin as a control.

[0056] **FIG. 4A – FIG. 4B** show the temporal duration of the effects of Antibody 1 on various biomarkers. **FIG. 4A** shows the concentration of Antibody 1 in plasma for subjects undergoing total knee arthroplasty (TKA). **FIG. 4B** shows free Factor XI in plasma for TKA subjects treated with Antibody 1.

CLAIMS

WHAT IS CLAIMED IS:

1. A vial comprising a formulation comprising:

(a) a therapeutically effective amount of an isolated anti-Factor XI (FXI) and/or anti-activated Factor XI (FXIa) antibody or antigen-binding fragment thereof;

(b) a histidine buffer;

(c) a sugar or sugar alcohol; and

(d) a polysorbate,

at pH 5.0 to 6.0,

wherein the vial comprises an overfill for complete withdrawal of a therapeutically effective amount of the anti-FXI and/or anti-FXIa antibody or antigen-binding fragment thereof.

2. The vial of claim 1, wherein:

(a) the isolated anti-FXI and/or anti-FXIa antibody or antigen-binding fragment thereof is at a concentration between 120 mg/mL and 180 mg/mL, optionally about 150 mg/mL;

(b) the histidine buffer comprises a histidine and a histidine salt;

(c) the sugar or sugar alcohol is a disaccharide;

(d) the polysorbate is polysorbate 20;

(e) the pH is 5.3 to 5.7, optionally about 5.5;

(f) the overfill comprises between 10% (v/v) and 30% (v/v) of the formulation;

(g) the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (VH) comprising complementary determining regions HCDR1, HCDR2, and HCDR3 in SEQ ID NOs: 9 or 29; and a light chain variable region (VL) comprising complementary determining regions LCDR1, LCDR2, LCDR3 in SEQ ID NOs: 19 or 39;

(h) the antibody or antigen-binding fragment thereof comprises:

i. a heavy chain variable region CDR1 of SEQ ID NO: 23; a heavy chain variable region CDR2 of SEQ ID NO: 24; a heavy chain variable region CDR3 of SEQ ID NO: 25; a light chain variable region CDR1 of SEQ ID NO: 33; a light chain variable region CDR2 of SEQ ID NO: 34; and a light chain variable region CDR3 of SEQ ID NO: 35;

ii. a heavy chain variable region CDR1 of SEQ ID NO: 26; a heavy chain variable region CDR2 of SEQ ID NO: 27; a heavy chain variable region CDR3 of SEQ ID NO: 28; a light chain variable region CDR1 of SEQ ID NO: 36; a light chain variable region CDR2 of SEQ ID NO: 37; and a light chain variable region CDR3 of SEQ ID NO: 38;

iii. a heavy chain variable region CDR1 of SEQ ID NO: 43; a heavy chain variable region CDR2 of SEQ ID NO: 44; a heavy chain variable region CDR3 of SEQ ID NO: 45; a light chain variable region CDR1 of SEQ ID NO: 47; a light chain variable region CDR2 of SEQ ID NO: 37; and a light chain variable region CDR3 of SEQ ID NO: 15; or

iv. a heavy chain variable region CDR1 of SEQ ID NO: 46; a heavy chain variable region CDR2 of SEQ ID NO: 4; a heavy chain variable region CDR3 of SEQ ID NO: 5; a light chain variable region CDR1 of SEQ ID NO: 33; a light chain variable region CDR2 of SEQ ID NO: 14; and a light chain variable region CDR3 of SEQ ID NO: 15;

(i) the antibody or antigen-binding fragment thereof comprises a VH selected from the group consisting of SEQ ID NOs: 9, 29, and a VH with 90% identity thereto; and a VL selected from the group consisting of SEQ ID NOs: 19, 39, and a VL with 90% identity thereto;

(j) the antibody or antigen-binding fragment thereof comprises a VH selected from the group consisting of SEQ ID NOs: 9 and 29; and a VL selected from the group consisting of SEQ ID NOs: 19 and 39;

(k) the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 31, 11, and a heavy chain with 90% identity thereto; and a light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 41, 21, and a light chain with 90% identity thereto;

(l) the antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 31 and a light chain comprising an amino acid sequence of SEQ ID NO: 41; and/or

(m) the antibody is a human monoclonal antibody.

3. The vial of claim 2, wherein:

(a) the histidine is L-histidine;

(b) the histidine salt is histidine HCl monohydrate;

(c) the histidine buffer is at a concentration between 10 mM and 30 mM, optionally about 20 mM;

(d) the disaccharide is sucrose;

(e) the polysorbate 20 is at a concentration between 0.02% (v/v) to 0.06% (v/v), optionally about 0.04% (v/v);

(f) the vial comprises 1.1 mL to 1.3 mL, optionally 1.2 mL, of the formulation;

(g) the overfill comprises about 20% (v/v) of the formulation;

(h) the antibody is a human IgG1 isotype; and/or

(i) the antibody comprises D265A and P329A substitutions in the Fc domain.

4. The vial of claim 3, wherein:

(a) the sucrose is at a concentration between 170 mM to 270 mM, optionally about 220 mM; and/or

(b) 120 mg to 180 mg is the therapeutically effective amount of the anti-FXI and/or anti-FXIa antibody or antigen-binding fragment thereofto be administered to a subject in need thereof.

5. The vial of claim 4, wherein:

(a) the subject is (i) obese, (ii) severely obese, and/or (ii) has a body mass index of ≥ 35 kg/m^2; and/or

(b) the subject has a body weight between 50 kg and 130 kg.

6. A vial comprising a formulation comprising:

(a) a therapeutically effective amount of an isolated anti-FXI and/or anti-FXIa antibody or antigen-binding fragment thereof at a concentration of about 150 mg;

(b) a histidine buffer at a concentration of about 20 mM;

(c) sucrose at a concentration of about 220 mM; and

(d) polysorbate 20 at a concentration of about 0.04% (v/v),

at pH 5.5,

wherein the vial comprises an overfill for complete withdrawal of a therapeutically effective amount of the anti-FXI and/or anti-FXIa antibody or antigen-binding fragment thereof.

7. An intravenous formulation comprising:

(a) a therapeutically effective amount of an isolated anti-FXI and/or anti-FXIa antibody or antigen-binding fragment thereof;

(b) a histidine buffer;

(c) a sugar or sugar alcohol;

(d) a polysorbate, and

(e) a diluent solution comprising a second sugar and water,

at pH 5.0 to 6.0.

8. The intravenous formulation of claim 7, wherein:

(a) the isolated anti-FXI and/or anti-FXIa antibody or antigen-binding fragment thereof is at a concentration between 1.20 mg/mL and 1.80 mg/mL, optionally about 1.50 mg/mL;

(b) the histidine buffer comprises a histidine and a histidine salt;

(c) the histidine buffer is at a concentration between 0.10 mM and 0.30 mM, optionally about 0.20 mM;

(d) the sugar or sugar alcohol is a disaccharide;

(e) the polysorbate is polysorbate 20;

(f) the pH is 5.3 to 5.7, optionally about 5.5;

(g) the second sugar in the diluent is a monosaccharide;

(h) the isolated anti-FXI and/or anti-FXIa antibody or antigen-binding fragment thereof comprises a VH comprising complementary determining regions HCDR1, HCDR2, and HCDR3 in SEQ ID NOs: 9 or 29; and a VL comprising complementary determining regions LCDR1, LCDR2, LCDR3 in SEQ ID NOs: 19 or 39;

(i) the isolated anti-FXI and/or anti-FXIa antibody or antigen-binding fragment thereof comprises:

i. a heavy chain variable region CDR1 of SEQ ID NO: 23; a heavy chain variable region CDR2 of SEQ ID NO: 24; a heavy chain variable region CDR3 of SEQ ID NO: 25; a light chain variable region CDR1 of SEQ ID NO: 33; a light chain variable region CDR2 of SEQ ID NO: 34; and a light chain variable region CDR3 of SEQ ID NO: 35;

ii. a heavy chain variable region CDR1 of SEQ ID NO: 26; a heavy chain variable region CDR2 of SEQ ID NO: 27; a heavy chain variable region CDR3 of SEQ ID NO:

28; a light chain variable region CDR1 of SEQ ID NO: 36; a light chain variable region CDR2 of SEQ ID NO: 37; and a light chain variable region CDR3 of SEQ ID NO: 38;

iii. a heavy chain variable region CDR1 of SEQ ID NO: 43; a heavy chain variable region CDR2 of SEQ ID NO: 44; a heavy chain variable region CDR3 of SEQ ID NO: 45; a light chain variable region CDR1 of SEQ ID NO: 47; a light chain variable region CDR2 of SEQ ID NO: 37; and a light chain variable region CDR3 of SEQ ID NO: 15; or

iv. a heavy chain variable region CDR1 of SEQ ID NO: 46; a heavy chain variable region CDR2 of SEQ ID NO: 4; a heavy chain variable region CDR3 of SEQ ID NO: 5; a light chain variable region CDR1 of SEQ ID NO: 33; a light chain variable region CDR2 of SEQ ID NO: 14; and a light chain variable region CDR3 of SEQ ID NO: 15;

(j) the isolated anti-FXI and/or anti-FXIa antibody or antigen-binding fragment thereof comprises a VH selected from the group consisting of SEQ ID NOs: 9, 29, and a VH with 90% identity thereto; and a VL selected from the group consisting of SEQ ID NOs: 19, 39, and a VL with 90% identity thereto;

(k) the isolated anti-FXI and/or anti-FXIa antibody or antigen-binding fragment thereof comprises a VH selected from the group consisting of SEQ ID NOs: 9 and 29; and a VL selected from the group consisting of SEQ ID NOs: 19 and 39;

(l) the isolated anti-FXI and/or anti-FXIa antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 31, 11, and a heavy chain with 90% identity thereto; and a light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 41, 21, and a light chain with 90% identity thereto;

(m) the isolated anti-FXI and/or anti-FXIa antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 31 and a light chain comprising an amino acid sequence of SEQ ID NO: 41; and/or

(n) the isolated anti-FXI and/or anti-FXIa antibody is a human monoclonal antibody.

9. The intravenous formulation of claim 8, wherein:

(a) the histidine is L-histidine;

(b) the histidine salt is histidine HCl monohydrate;

(c) the disaccharide is sucrose;

(d) the polysorbate 20 is at a concentration of less than 0.001% (v/v), optionally about 0.0004% (v/v);

(e) the monosaccharide is dextrose;

(f) the antibody is a human IgG1 isotype; and/or

(g) the antibody comprises D265A and P329A substitutions in the Fc domain.

10. The intravenous formulation of claim 9, wherein:

(a) the sucrose is at a concentration between 1.70 mM to 2.70 mM, optionally about 2.20 mM;

(b) the dextrose is at a concentration between 2.5% (v/v) and 7.5% (v/v), optionally about 5% (v/v); and/or

(c) 120 mg to 180 mg is the therapeutically effective amount of the anti-FXI and/or anti-FXIa antibody or antigen-binding fragment thereof to be administered to a subject in need thereof.

11. The intravenous formulation of claim 10, wherein the subject is obese.

12. The intravenous formulation of claim 10 wherein:

(a) the isolated anti-FXI and/or anti-FXIa antibody or antigen-binding fragment thereof is at a concentration of about 1.5 mg;

(b) the histidine buffer is at a concentration of about 0.20 mM;

(c) the sucrose is at a concentration of about 2.20 mM;

(d) the polysorbate 20 is at a concentration of about 0.0004% (v/v);

(e) the diluent is dextrose 5% in water (D5W); and

(f) the intravenous formulation is at pH 5.5.

13. The formulation present in the vial of any one of claims 1-6 or the intravenous formulation of any one of claims 7-12 for use in treating a subject afflicted with or at risk of developing a thromboembolic disorder.

14. Use of the formulation present in the vial of any one of claims 1-6 or the intravenous formulation of any one of claims 7-12 for the manufacture of a medicament for treating a subject afflicted with or at risk of developing a thromboembolic disorder.

15. The use of claim 14, wherein the thromboembolic disorder is selected from the group consisting of:

(a) atrial fibrillation or atrial flutter,

(b) transient ischemic attack,

(c) ischemic stroke,

(d) thromboembolic stroke,

(e) hemorrhagic stroke,

(f) venous thromboembolism (VTE),

(g) pediatric VTE,

(h) systemic embolism,

(i) non-central nervous systemic embolism,

(j) myocardial infarction,

(k) deep vein thrombosis,

(l) severe protein S deficiency,

(m) cerebrovascular accident, and

(n) cancer.

16. The use of claim 14 or 15, wherein the formulation present in the vial or the intravenous formulation is to be administered:

(a) monthly;

(b) once a month for a period of three months;

(c) at a dose of 1 mg to 600 mg;

(d) at a dose of 75 mg to 165 mg, 80 mg to 160 mg, 85 mg to 155 mg, or 90 mg to 160 mg;

(e) at a dose selected from the group consisting of about 30 mg, about 40 mg, about 60 mg, about 75 mg, about 90 mg, about 120 mg, about 150 mg, about 180 mg, and about 240 mg;

(f) at a dose of about 120 mg;

(g) at a dose of about 150 mg;

(h) at a dose of about 180 mg;

(i) subcutaneously or intravenously;

(j) subcutaneously, once a month for a period of three months at a dose of about 120 mg; and/or

(k) subcutaneously, once a month for a period of three months at a dose of about 180 mg.

17. The use of any one of claims 14-16, wherein the thromboembolic disorder is atrial fibrillation or atrial flutter and/or the subject is at low, moderate, or high risk of stroke.

18. The use of any one of claims 14-17, further comprising that one or more of the following is to be applied to the patient experiencing an adverse event, wherein the adverse event is a bleeding event:

(a) fluid replacement using colloids, crystalloids, human plasma or plasma proteins such as albumin;

(b) transfusion with packed red blood or whole blood; or

(c) administration of fresh frozen plasma (FFP), prothrombin complex concentrates (PCC), activated PCC (APCC), and/or recombinant, activated factor VII.

19. The use of any one of claims 14-18, wherein:

(a) the atrial fibrillation or atrial flutter is paroxysmal atrial fibrillation (PAF);

(b) the subject has a CHA_2DS_2VASc risk score of 0 to 1;

(c) the subject has a CHA_2DS_2VASc risk score of 0 to 1 for male subjects and 1 to 2 for female subjects;

(d) the subject has a CHA_2DS_2VASc risk score of ≥ 2 for male subjects and ≥ 3 for female subjects.

20. The use of claim 18, wherein APCC comprises a factor VIII inhibitor.

21. The use of any one of claims 14-20, the use further comprising a method of:

(a) evaluating efficacy of the formulation present in the vial by measuring inhibition of Factor XI at the trough after the third dose of the formulation;

(b) evaluating efficacy of the formulation present in the vial by assessing one or more biomarkers selected from the list consisting of free Factor XI, total Factor XI, Factor XI coagulation activity, activated partial thromboplastin time, and D-dimer; and/or

(c) evaluating adverse events to the formulation present in the vial by measuring bleeding events or the presence of anti-drug antibodies.

22. The formulation present in the vial of any one of claims 1-6 or the intravenous formulation of any one of claims 7-12 for use in treating a subject afflicted with or at risk of developing a thromboembolic disorder and who is undergoing a surgical procedure, wherein the subject is to be administered the intravenous formulation on the same day as the surgical procedure.

23. Use of the intravenous formulation of any one of claims 7-12 in the manufacture of a medicament for treating a subject afflicted with or at risk of developing a thromboembolic disorder and who is undergoing a surgical procedure, wherein the subject is to be administered the intravenous formulation on the same day as the surgical procedure.

24. The use of claim 23, wherein:

(a) the surgical procedure is selected from the group consisting of:

(i) knee replacement surgery,

(ii) hip replacement surgery,

(iii) orthopedic surgery,

(iv) pacemaker installation,

(v) catheter installation,

(vi) thoracic surgery, and

(vii) abdominal surgery; and/or

(b) the intravenous formulation is to be administered:

(i) monthly;

(ii) once a month for a period of three months;

(iii) at a dose of 1 mg to 600 mg;

(iv) at a dose of 75 mg to 165 mg, 80 mg to 160 mg, 85 mg to 155 mg, or 90 mg to 160 mg;

(v) at a dose selected from the group consisting of about 30 mg, about 40 mg, about 60 mg, about 75 mg, about 90 mg, about 120 mg, about 150 mg, about 180 mg, and about 240 mg;

(vi) at a dose of about 120 mg;

(vii) at a dose of about 150 mg;

(viii) at a dose of about 180 mg;

(ix) subcutaneously or intravenously;

(x) subcutaneously, once a month for a period of three months at a dose of about 120 mg;

(xi) subcutaneously, once a month for a period of three months at a dose of about 180 mg; and/or

(xii) approximately 4-8 hours after surgery.

25. The use of claim 24, wherein:

(a) the knee replacement surgery is unilateral total knee arthroplasty (TKA);

(b) the subject is (i) obese, (ii), severely obese, and/or (iii) has a body mass index of ≥ 35 kg/m^2; and/or

(c) the subject has a body weight between 50 kg and 130 kg.

26. The formulation present in the vial of any one of claims 1-6 or the intravenous formulation of any one of claims 7-12 for use in treating a subject afflicted with or at risk of developing a thromboembolic disorder, wherein the subject is receiving NSAIDs, and wherein the subject is to be administered a therapeutically effective amount of the formulation in combination with a proton-pump inhibitor.

27. Use of the formulation present in the vial of any one of claims 1-6 or the intravenous formulation of any one of claims 7-12 for the manufacture of a medicament for treating a subject afflicted with or at risk of developing a thromboembolic disorder, wherein the subject is receiving non-steroidal anti-inflammatory drugs (NSAIDs), and wherein the subject is to be administered a therapeutically effective amount of the formulation in combination with a proton-pump inhibitor.

28. The use of claim 27, wherein the formulation present in the vial or the intravenous formulation is to be administered:

(a) monthly;

(b) once a month for a period of three months;

(c) at a dose of 1 mg to 600 mg;

(d) at a dose of 75 mg to 165 mg, 80 mg to 160 mg, 85 mg to 155 mg, or 90 mg to 160 mg;

(e) at a dose selected from the group consisting of about 30 mg, about 40 mg, about 60 mg, about 75 mg, about 90 mg, about 120 mg, about 150 mg, about 180 mg, and about 240 mg;

(f) at a dose of about 120 mg;

(g) at a dose of about 150 mg;

(h) at a dose of about 180 mg;

(i) subcutaneously or intravenously;

(j) subcutaneously, once a month for a period of three months at a dose of about 120 mg; and/or

(k) subcutaneously, once a month for a period of three months at a dose of about 180 mg.