

## CLAIMS

## WHAT IS CLAIMED IS:

1. 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.
2. The vial of claim 1, wherein the therapeutically effective amount of 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.
3. The vial of claim 1 or 2, wherein 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 150 mg/ml.
4. The vial of any one of claims 1-3, wherein the histidine buffer comprises a histidine and a histidine salt.
5. The vial of claim 4, wherein the histidine is L-histidine.
6. The vial of claim 4 or 5, wherein the histidine salt is histidine HCl monohydrate.
7. The vial of any one of claims 4-6, wherein the histidine buffer is at a concentration between 10 mM and 30 mM.
8. The vial of claim 7, wherein the histidine buffer is at a concentration of about 20 mM.

9. The vial of any one of claims 1-8, wherein the sugar or sugar alcohol is a disaccharide.
10. The vial of claim 9, wherein the disaccharide is sucrose.
11. The vial of claim 10, wherein the sucrose is at a concentration between 170 mM to 270 mM.
- 5 12. The vial of claim 11, wherein the sucrose is at a concentration of about 220 mM.
13. The vial of any one of claims 1-12, wherein the polysorbate is polysorbate 20.
14. The vial of claim 13, wherein the polysorbate 20 is at a concentration between 0.02% (v/v) to 0.06% (v/v).
15. The vial of claim 14, wherein the polysorbate 20 is at a concentration of about 0.04%  
10 (v/v).
16. The vial of any one of claims 1-15, wherein the pH is 5.3 to 5.7.
17. The vial of any one of claims 1-16, wherein the pH is about 5.5.
18. The vial of any one of claims 1-17, wherein 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  
15 1.3 mL of the drug delivery formulation.
19. The vial of claim 18, wherein 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.
20. The vial of any one of claims 1-19, wherein the antibody or antigen-binding fragment  
20 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.

21. The vial of any one of claims 1-20, wherein 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.

22. The vial of any one of claims 1-21, wherein 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.

23. The vial of any one of claims 1-22, wherein 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.

24. The vial of any one of claims 1-23, wherein the antibody 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.
25. The vial of any one of claims 1-24, wherein 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.
26. The vial of any one of claims 1-25, wherein the antibody is a human monoclonal antibody.
27. The vial of claim 26, wherein the antibody is a human IgG1 isotype.
28. The vial of claim 26 or 27, wherein 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.
29. 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.
30. 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

5 (e) a diluent

at pH 5.0 to 6.0,

wherein the diluent is a solution comprising a second sugar and water.

31. The intravenous drug delivery formulation of claim 30, wherein the  
therapeutically effective amount of the isolated anti-FXI and/or anti-FXIa antibody or antigen-  
10 binding fragment thereof is at a concentration between 1.20 mg/ml and 1.80 mg/ml.

32. The intravenous drug delivery formulation of claim 30 or 31, wherein 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.

33. The intravenous drug delivery formulation of any one of claims 30-32, wherein the  
15 histidine buffer comprises a histidine and a histidine salt.

34. The intravenous drug delivery formulation of claim 33, wherein the histidine is  
L-histidine.

35. The intravenous drug delivery formulation of claim 33 or 34, wherein the histidine salt is  
histidine HCl monohydrate.

20 36. The intravenous drug delivery formulation of any one of claims 30-35, wherein the  
histidine buffer is at a concentration between 0.10 mM and 0.30 mM.

37. The intravenous drug delivery formulation of any one of claims 30-36, wherein the  
histidine buffer is at a concentration of about 0.20 mM.

38. The intravenous drug delivery formulation of any one of claims 30-37, wherein the sugar  
25 or sugar alcohol is a disaccharide.

39. The intravenous drug delivery formulation of claim 38, wherein the disaccharide is sucrose.
40. The intravenous drug delivery formulation of claim 39, wherein the sucrose is at a concentration between 1.70 mM to 2.70 mM.
- 5 41. The intravenous drug delivery formulation of claim 40, wherein the sucrose is at a concentration of about 2.20 mM.
42. The intravenous drug delivery formulation of any one of claims 30-41, wherein the polysorbate is polysorbate 20.
43. The intravenous drug delivery formulation of claim 42, wherein the polysorbate  
10 20 is at a concentration of less than 0.001% (v/v).
44. The intravenous drug delivery formulation of claim 43, wherein the polysorbate 20 is at a concentration of about 0.0004% (v/v).
45. The intravenous drug delivery formulation of any one of claims 30-44, wherein the pH is 5.3 to 5.7.
- 15 46. The intravenous drug delivery formulation of any one of claims 30-45, wherein the pH is about 5.5.
47. The intravenous drug delivery formulation of any one of claims 30-46, wherein the second sugar in the diluent is a monosaccharide.
48. The intravenous drug delivery formulation of claim 47, wherein the monosaccharide is  
20 dextrose.
49. The intravenous drug delivery formulation of claim 48, wherein the dextrose is at a concentration between 2.5% (v/v) and 7.5% (v/v).
50. The intravenous drug delivery formulation of claim 48 or 49, wherein the dextrose is at a concentration of about 5% (v/v).
- 25 51. The intravenous drug delivery formulation of any one of claims 30-50, wherein 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.

5 52. The intravenous drug delivery formulation of any one of claims 30-51, wherein 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;

15 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

20 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.

53. The intravenous drug delivery formulation of any one of claims 30-52, wherein 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.

54. The intravenous drug delivery formulation of any one of claims 30-53, wherein 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.
- 5 55. The intravenous drug delivery formulation of any one of claims 30-54, wherein the antibody 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.
- 10 56. The intravenous drug delivery formulation of any one of claims 30-55, wherein 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.
57. The intravenous drug delivery formulation of any one of claims 30-56, wherein the antibody is a human monoclonal antibody.
- 15 58. The intravenous drug delivery formulation of claim 57, wherein the antibody is a human IgG1 isotype.
59. The intravenous drug delivery formulation of claim 57 or 58, wherein 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
- 20 subject.
60. 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;
- 25 (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).

61. 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 of any one of claims 1-28 or the intravenous drug delivery formulation of any one of claims 30-59 to the subject in need thereof.
62. The method of claim 61, wherein 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.
63. The method of claim 61 or 62, wherein the drug delivery formulation present in the vial or the intravenous drug delivery formulation is administered monthly.
64. The method of any one of claims 61-63, wherein 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.
65. The method of any one of claims 61-64, wherein the drug delivery formulation present in the vial is administered at a dose of about 120 mg.
66. The method of any one of claims 61-64, wherein the drug delivery formulation present in the vial is administered at a dose of about 150 mg.
67. The method of any one of claims 61-66, wherein the drug delivery formulation present in the vial is administered subcutaneously.
68. The method of any one of claims 61-67, wherein the thromboembolic disorder is atrial fibrillation or atrial flutter.

69. The method of claim 68, wherein the atrial fibrillation or atrial flutter is paroxysmal atrial fibrillation (PAF).
70. The method of any one of claims 61-69, wherein the drug delivery formulation present in the vial is administered once a month for a period of three months.
- 5 71. The method of any one of claims 61-70, wherein the subject is at low risk of stroke.
72. The method of claim 71, wherein the subject has a CHA<sub>2</sub>DS<sub>2</sub>VASc risk score of 0 to 1.
73. The method of any one of claims 61-70, wherein the subject is at moderate risk of stroke.
74. The method of any one of claims 61-70, wherein the subject is at high risk  
10 of stroke.
75. The method of claim 74, wherein the subject has a CHA<sub>2</sub>DS<sub>2</sub>VASc risk score of  $\geq 2$  for male subjects and  $\geq 3$  for female subjects.
76. The method of any one of claims 61-75, the method further comprising evaluating efficacy of the drug delivery formulation present in the vial by measuring inhibition  
15 of Factor XI at the trough after the third dose of the drug delivery formulation.
77. The method of any one of claims 61-76, the method further comprising 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.
- 20 78. The method of any one of claims 61-77, the method further comprising evaluating adverse events to the drug delivery formulation present in the vial by measuring bleeding events or the presence of anti-drug antibodies.
79. The method of claim 78, the method further comprising applying one or more of the following to the patient experiencing an adverse event, wherein the adverse event is a  
25 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.

80. 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 of any one of claims 30-59 to a subject in need thereof, wherein the subject is administered the intravenous drug delivery formulation on the same day as the surgical procedure.

81. The method of claim 80, wherein the surgical procedure is selected from the group consisting of knee replacement surgery, hip replacement surgery, orthopedic surgery, pacemaker installation, catheter installation, thoracic surgery, and abdominal surgery.

82. The method of claim 80 or 81, wherein the intravenous drug delivery formulation is administered monthly.

83. The method of any one of claims 80-82, wherein 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.

84. The method of any one of claims 80-83, wherein the intravenous drug delivery formulation is administered at a dose of about 30 mg.

85. The method of any one of claims 80-83, wherein the intravenous drug delivery formulation is administered at a dose of about 60 mg.

86. The method of any one of claims 80-83, wherein the intravenous drug delivery formulation is administered at a dose of about 150 mg.

87. The method of any one of claims 80-82, wherein the intravenous drug delivery formulation is administered at a dose of about 75 mg.

88. The method of any one of claims 80-87, wherein the intravenous drug delivery formulation is administered approximately 4-8 hours after surgery.

89. 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 of any one of claims 1-28 or the intravenous drug delivery formulation of any one of claims 30-59 in combination with a proton-pump inhibitor to the subject in need thereof.
90. The method of claim 89, wherein the drug delivery formulation present in the vial or the intravenous drug delivery formulation is administered monthly.
91. The method of claim 89 or 90, wherein 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.
92. The method of claim 88 or 89, wherein the drug delivery formulation present in the vial or the intravenous drug delivery formulation is administered at a dose of about 75 mg.
93. The method of any one of claims 89-91, wherein the drug delivery formulation present in the vial is administered subcutaneously.