METHODS OF TREATMENT OF IMMUNE THROMBOCYTOPENIA USING SOVLEPLENIB

TECHNICAL FIELD

The present disclosure relates to methods of treating immune thrombocytopenia (ITP).

BACKGROUND

Primary immune thrombocytopenia (ITP) is a complex bleeding disorder caused by autoimmune destruction and insufficient production of platelets, leading to a reduced platelet level in the peripheral blood ($<100\times10^9$/L). The development of autoantibodies against platelets and subsequent platelet phagocytosis are considered the central mechanisms responsible for the pathogenesis of ITP, although the exact cause behind the loss of tolerance remains unclear. The prevalence of ITP is 9.5 per 100,000 adults and its incidence is 2–5 per 100,000 adults per year. Although some patients with ITP are asymptomatic or experience minor bleeding, serious mucosal bleeding may occur. In addition, ITP has a negative impact on patients' quality of life due to fatigue, restrictions on activities, anxiety, and other affects.

For newly diagnosed ITP adults who have a platelet count of $<30\times10^9$/L and are asymptomatic or have minor mucocutaneous bleeding, oral corticosteroids are the recommended first-line treatment. The majority of patients initially responds to the treatment of glucocorticoids; however, a notable proportion of patients do not respond or they experience relapse. The assessment of health-related quality of life (HRQoL) during corticosteroid treatment is suggested for its negative impact on mental health. Second-line treatments include rituximab, thrombopoietin receptor agonists (TPO-RAs), and splenectomy; but the potential side effects of infection, thrombosis, and operative complications with these second-line treatments are concerned risks. (Blood Adv 2019; 3: 3829-66; and Blood Res 2022; 57: 112-9.) Fostamatinib is the only Syk inhibitor currently approved by the US Food and Drug Administration for ITP patients who have an insufficient response to a previous treatment. However, the overall response rate (ORR) to fostamatinib is low, and "the stable platelet response" rate is only 18% and 16% in 2 placebo-controlled studies. In these 2 studies, the incidences of treatment-emergent hypertension and diarrhea were significantly higher in the fostamatinib group (28% and 31%, respectively) compared to the placebo group (13% and 15%, respectively) during treatment (Am J Hematol. 2018 Jul;93(7):921-930.).

Thus, there remains a large population of subjects with ITP who have limited sensitivity to currently available agents or carry a higher risk of treatment-related toxicities. There is an unmet medical need in this field.

SUMMARY

Provided herein are the following embodiments:

E1. A method of treating immune thrombocytopenia (ITP) in a subject in need thereof comprising administering to the subject sovleplenib or a pharmaceutically acceptable salt thereof at a daily dosage of about 100-600 mg, or at a dosage sufficient to achieve an $AUC_{tau,ss}$ value of about 600-5000 h × ng/mL.

E2. The method of E1, wherein the daily dosage is about 100-400 mg, about 100-300 mg, about 300-500 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, or about 600 mg.

E3. The method of E1, wherein the daily dosage is about 300-500 mg, about 300 mg, about 400 mg or about 500mg.

E4. The method of E1, wherein the daily dosage is about 300 mg.

E5. The method of E1, wherein the daily dosage is about 500 mg.

E6. The method of any one of the preceding Embodiments, wherein the dosage is administered once per day (QD), or in divided doses, e.g., twice per day (BID) or three times per day (TID).

E7. The method of any one of the preceding Embodiments, wherein the dosage is administered once per day (QD).

E8. The method of E1, wherein $AUC_{tau,ss}$ value is about 600-4890 h ×ng/mL; optionally about 600-800, about 1000-1300, about 1900-2200, or about 2900-3200 h ×ng/mL; optionally about 600-700, about 1100-1200, about 2000-2100, or about 3000-3100 h ×ng/mL; optionally about 640-680, about 1135-1175, about 2045-2185, or about 3045-3085 h ×ng/mL; optionally about 650-670, about 1145-1165, about 2055-2175, or about 3055-3075 h ×ng/mL; optionally about 661 h ×ng/mL, about 1156 h ×ng/mL, about 2067 h ×ng/mL, about 3065 h ×ng/mL.

E9. The method of E1, wherein $AUC_{tau,ss}$ value is about 1900-2200, about 2000-2100, about 2045-2185, about 2055-2175, or about 2067 h ×ng/mL.

E10. The method of any one of the preceding Embodiments, wherein the ITP is primary ITP.

E11. The method of any one of the preceding Embodiments, wherein the ITP is newly diagnosed ITP, persistent ITP, or chronic ITP.

E12. The method of any one of the preceding Embodiments, wherein the ITP is chronic ITP or chronic primary ITP.

E13. The method of any one of the preceding Embodiments, wherein the subject has relapsed or refractory ITP.

E14. The method of any one of the preceding Embodiments, wherein the subject has previously received at least one prior anti-ITP treatment.

E15. The method of any one of the preceding Embodiments, wherein the subject has had an insufficient response or intolerance to at least one prior anti-ITP treatment.

E16. The method of any one of the preceding Embodiments, wherein the subject has chronic ITP and has had an insufficient response or intolerance to at least one prior anti-ITP treatment, or has chronic primary ITP and has had an insufficient response or intolerance to at least one prior anti-ITP treatment.

E17. The method of any one of the preceding Embodiments, wherein the subject has persistent ITP and has had an insufficient response or intolerance to at least one prior anti-ITP treatment, or has persistent primary ITP and has had an insufficient response or intolerance to at least one prior anti-ITP treatment.

E18. The method of any one of the preceding Embodiments, wherein the subject has relapsed after at least one prior anti-ITP treatment.

E19. The method of any one of E14-E18, wherein the at least one prior anti-ITP treatment is one, two, three, four, five, six, seven, eight or more prior anti-ITP treatments.

E20. The method of any one of E14-E19, wherein the at least one prior anti-ITP treatment is two, three, four, five, six, seven, eight or more prior anti-ITP treatments.

E21. The method of any one of E14-E20, wherein the at least one prior anti-ITP treatment is four, five, six, seven, eight or more prior anti-ITP treatments.

E22. The method of any one of E14-E21, wherein the at least one prior anti-ITP treatment comprises at least one treatment of first-line anti-ITP treatment, second-line anti-ITP treatment, third-line anti-ITP treatment and further treatment, e.g. comprises first-line anti-ITP treatment, second-line anti-ITP treatment and third-line anti-ITP treatment and optionally a further treatment.

E23. The method of any one of E14-E22, wherein the at least one prior anti-ITP treatment comprises at least one treatment of first-line anti-ITP treatment and second-line anti-ITP treatment.

E24. The method of any one of E14-E23, wherein the at least one prior anti-ITP treatment comprises one or more (e.g., one, two, three, four, five, six, seven, eight or more, e.g., four, five, six, seven or more) treatments selected from corticosteroids (including glucocorticoid, including prednisone, prednisolone, methylprednisolone, dexamethasone and/or betamethasone), an intravenous immunoglobulin treatment (IVIg), anti-D immunoglobulin, thrombopoietin (TPO) treatment (including rhTPO), thrombopoietin receptor agonist (TPO-RA) treatment (including thrombopoietin, eltrombopag, hetrombopag, avatrombopag and/or romiplostim), anti-CD20 antibody treatment (including rituximab), immunosuppressants (including cyclosporine A, azathioprine, mycophenolate mofetilb, cyclophosphamide), vinca alkaloids, alemtuzumab, danazol, dapsone, platelet transfusion, danazol/stanozolol, caffeic acid, IL-11, Traditional Chinese medicine and splenectomy; optionally, the at least one prior anti-ITP treatment does not comprise a Syk inhibitor (including fostamatinib).

E25. The method of any one of E14-E24, wherein the at least one prior anti-ITP treatment comprises one or more (e.g., one, two, three, four, five, six, seven, eight or more, e.g., four, five, six, seven or more) treatments selected from corticosteroids (including glucocorticoid, including prednisone, prednisolone, methylprednisolone, dexamethasone and betamethasone), an intravenous immunoglobulin treatment (IVIg), thrombopoietin (TPO) treatment (including rhTPO), thrombopoietin receptor agonist (TPO-RA) treatment (including thrombopoietin, eltrombopag, hetrombopag, avatrombopag and/or romiplostim), anti-CD20 antibody treatment (including rituximab) and splenectomy; optionally, the at least one prior anti-ITP treatment does not comprise a Syk inhibitor (including fostamatinib).

E26. The method of any one of E14-E25, wherein the at least one prior anti-ITP treatment comprises TPO treatment and/or TPO-RA treatment.

E27. The method of any one of E14-E26, wherein the at least one prior anti-ITP treatment comprises either TPO treatment or TPO-RA treatment.

E28. The method of any one of E14-E26, wherein the at least one prior anti-ITP treatment comprises both TPO treatment and TPO-RA treatment.

E29. The method of any one of E14-E26, wherein the at least one prior anti-ITP treatment comprises only one medication of TPO/TPO-RA treatment.

E30. The method of any one of E14-E26, wherein the at least one prior anti-ITP treatment comprises at least two medications of TPO/TPO-RA treatment.

E31. The method of any one of E14-E26, wherein the at least one prior anti-ITP treatment comprises 2, 3, 4, 5 or more medications of TPO/TPO-RA treatment.

E32. The method of any one of E14-E26, wherein the at least one prior anti-ITP treatment comprises one or more agents selected from a recombinant human thrombopoietin, eltrombopag, hetrombopag, avatrombopag and romiplostim.

E33. The method of any one of E26-E31, wherein the medication of TPO/TPO-RA treatment comprises one or more agents selected from a recombinant human thrombopoietin, eltrombopag, hetrombopag, avatrombopag and romiplostim.

E34. The method of any one of E14-E33, wherein the at least one prior anti-ITP treatment comprises an anti-CD20 antibody treatment.

E35. The method of any one of E14-E34, wherein the at least one prior anti-ITP treatment comprises rituximab.

E36. The method of any one of E14-E35, wherein the at least one prior anti-ITP treatment comprises splenectomy.

E37. The method of any one of E14-E36, wherein the at least one prior anti-ITP treatment comprises a rescue anti-ITP treatment.

E38. The method of any one of the preceding Embodiments, wherein the subject has a platelet count of less than 30×10^9 per liter prior to the treatment of sovleplenib or a pharmaceutically acceptable salt thereof.

E39. The method of any one of the preceding Embodiments, wherein the subject has a platelet count of less than 15×10^9 per liter prior to the treatment of sovleplenib or a pharmaceutically acceptable salt thereof.

E40. The method of any one of the preceding Embodiments, wherein the subject has a platelet count of more than 15×10^9 per liter and less than 30×10^9 per liter prior to the treatment of sovleplenib or a pharmaceutically acceptable salt thereof.

E41. The method of any one of the preceding Embodiments, wherein the subject has a hemoglobin ≥100 g/L and neutrophil count $>1.5\times10^9$ per liter prior to the treatment of sovleplenib or a pharmaceutically acceptable salt thereof.

E42. The method of any one of the preceding Embodiments, wherein the subject has persistent ITP for ≥3, 4, 5, 6 or more months and less than 1 year, or has persistent ITP for ≥3 months and less than 1 year, or has chronic ITP for ≥1 year, prior to the treatment of sovleplenib or a pharmaceutically acceptable salt thereof.

E43. The method of any one of the preceding Embodiments, wherein the subject has an ITP Bleeding Scale (IBLS) score of 0 or 1, and/or has chronic ITP for ≥3 years, prior to the treatment of sovleplenib or a pharmaceutically acceptable salt thereof.

E44. The method of any one of the preceding Embodiments, wherein the subject has an WHO Bleeding Scale score of 0 or 1, and/or has chronic ITP for ≥3 years, prior to the treatment of sovleplenib or a pharmaceutically acceptable salt thereof.

E45. The method of any one of the preceding Embodiments, wherein the subject has a WHO Bleeding Scale score of 0 or 1, prior to the treatment of sovleplenib or a pharmaceutically acceptable salt thereof.

E46. The method of any one of the preceding Embodiments, wherein the subject has not responded to sovleplenib or a pharmaceutically acceptable salt thereof during the first 12 weeks treatment.

E47. The method of any one of the preceding Embodiments, wherein the subject is human adult.

E48. The method of any one of the preceding Embodiments, wherein the subject is Asian population.

E49. The method of any one of E1-E47, wherein the subject is non-Asian population, e.g., Western population, American population, European population, Caucasian population, Oceanian population (Australoid), and/or African population.

E50. The method of any one of the preceding Embodiments, wherein sovleplenib or a pharmaceutically acceptable salt thereof is administered at a dosage sufficient to achieve an $AUC_{tau,ss}$ value is about 2067 h × ng/mL.

E51. The method of any one of E1-E49, wherein sovleplenib or a pharmaceutically acceptable salt thereof is administered at a daily dosage of about 100-300 mg, e.g, about 100 mg, about 200 mg or about 300 mg, or at a dosage sufficient to achieve an $AUC_{tau,ss}$ value of about 2055-2175 h ×ng/mL (e.g. 2067 h × ng/mL).

E52. The method of any one of E1-E49, wherein sovleplenib or a pharmaceutically acceptable salt thereof is administered at a daily dosage of about 300mg, or at a dosage sufficient to achieve an $AUC_{tau,ss}$ value of about 2055-2175 h ×ng/mL (e.g. 2067 h ×ng/mL).

E53. The method of any one of E1-E49, wherein sovleplenib or a pharmaceutically acceptable salt thereof is administered at a daily dosage of about 100-300 mg, e.g, about 100 mg, about 200 mg or about 300 mg, or at a dosage sufficient to achieve an $AUC_{tau,ss}$ value of about 2055-2175 h ×ng/mL (e.g. 2067 h × ng/mL), and wherein the subject is Asian population.

E54. The method of any one of E1-E49, wherein sovleplenib or a pharmaceutically acceptable salt thereof is administered at a daily dosage of about 300 mg, or at a dosage sufficient to achieve an $AUC_{tau,ss}$ value of about 2055-2175 h ×ng/mL (e.g. 2067 h ×ng/mL), and wherein the subject is Asian population.

E55. The method of any one of E1-E49, wherein sovleplenib or a pharmaceutically acceptable salt thereof is administered at a daily dosage of about 300-500 mg, e.g, about 300 mg, about 400 mg or about 500 mg, or at a dosage sufficient to achieve an $AUC_{tau,ss}$ value of about 2055-2175 h ×ng/mL (e.g. 2067 h × ng/mL).

E56. The method of any one of E1-E49, wherein sovleplenib or a pharmaceutically acceptable salt thereof is administered at a daily dosage of about 500 mg, or at a dosage sufficient to achieve an $AUC_{tau,ss}$ value of about 2055-2175 h ×ng/mL (e.g. 2067 h ×ng/mL).

E57. The method of any one of E1-E49, wherein sovleplenib or a pharmaceutically acceptable salt thereof is administered at a daily dosage of about 300-500 mg, e.g, about 300 mg, about 400 mg or about 500 mg, or at a dosage sufficient to achieve an $AUC_{tau,ss}$ value of about 2055-2175 h ×ng/mL (e.g. 2067 h × ng/mL), and wherein the subject is non-Asian population, e.g., Western population, American population, European population, Caucasian population, Oceanian population (Australoid), and/or African population.

E58. The method of any one of E1-E49, wherein sovleplenib or a pharmaceutically acceptable salt thereof is administered at a daily dosage of about 500mg, or at a dosage sufficient to achieve an $AUC_{tau,ss}$ value of about 2055-2175 h ×ng/mL (e.g. 2067 h ×ng/mL), and wherein the subject is non-Asian population, e.g., Western population, American population, European population, Caucasian population, Oceanian population (Australoid), and/or African population.

E59. The method of any one of the preceding Embodiments, wherein the dosage of sovleplenib or a pharmaceutically acceptable salt thereof is reduced during the treatment, when

(1) the subject has a platelet count of ≥250 $\times 10^9$ platelets for about two weeks or a platelet count of ≥400$\times 10^9$/L for any time in a treatment period;

(2) the subject is in combination with a concomitant anti-ITP treatment and has a platelet count of ≥100$\times 10^9$/L lasting for about 4 weeks, or platelet count of ≥250$\times 10^9$/L lasting for about 2 weeks in a treatment period; or

(3) the subject experiences drug related adverse event.

E60. The method of any one of E4, E52 and E54, wherein the daily dosage of sovleplenib or a pharmaceutically acceptable salt thereof is reduced to 200 mg and optionally further to 100 mg daily during the treatment, when

(1) the subject has a platelet count of ≥250 $\times 10^9$ platelets for about two weeks or a platelet count of ≥400$\times 10^9$/L for any time in a treatment period;

(2) the subject is concurrently with a concomitant anti-ITP treatment and has a platelet count of ≥100$\times 10^9$/L lasting for about 4 weeks, or platelet count of ≥250$\times 10^9$/L lasting for about 2 weeks in a treatment period; or

(3) the subject experiences drug related adverse event.

E61. The method of any one of E4, E52 and E54, wherein the daily dosage of sovleplenib or a pharmaceutically acceptable salt thereof is reduced sequentially to 200 mg and 100 mg during the treatment, when

(1) the subject has a platelet count of ≥250 $\times 10^9$ platelets for two weeks or a platelet count of ≥400$\times 10^9$/L for any time in a treatment period;

(2) the subject is concurrently with a concomitant anti-ITP treatment and has a platelet count of ≥100$\times 10^9$/L lasting for 4 weeks, or platelet count of ≥250$\times 10^9$/L lasting for 2 weeks in a treatment period; or

(3) the subject experiences drug related adverse event.

E62. The method of any one of E5, E56 and E58, wherein the daily dosage of sovleplenib or a pharmaceutically acceptable salt thereof is reduced sequentially to 400 mg and optionally further to 300 mg during the treatment, when

(1) the subject has a platelet count of $\geq 250 \times 10^9$ platelets for about two weeks or a platelet count of $\geq 400 \times 10^9$/L for any time in a treatment period; or

(2) the subject is concurrently with a concomitant anti-ITP treatment and has a platelet count of $\geq 100 \times 10^9$/L lasting for about 4 weeks, or platelet count of $\geq 250 \times 10^9$/L lasting for about 2 weeks in a treatment period; or

(3) the subject experiences drug related adverse event.

E63. The method of any one of E5, E56 and E58, wherein the daily dosage of sovleplenib or a pharmaceutically acceptable salt thereof is reduced sequentially to 400 mg and 300 mg during the treatment, when

(1) the subject has a platelet count of $\geq 250 \times 10^9$ platelets for two weeks or a platelet count of $\geq 400 \times 10^9$/L for any time in a treatment period; or

(2) the subject is concurrently with a concomitant anti-ITP treatment and has a platelet count of $\geq 100 \times 10^9$/L lasting for 4 weeks, or platelet count of $\geq 250 \times 10^9$/L lasting for 2 weeks in a treatment period; or

(3) the subject experiences drug related adverse event.

E64. The method of any one of the preceding Embodiments, wherein sovleplenib or a pharmaceutically acceptable salt thereof is administered once per day (QD) or in divided doses twice per day (BID).

E65. The method of any one of the preceding Embodiments, wherein sovleplenib or a pharmaceutically acceptable salt thereof is administered orally.

E66. The method of any one of the preceding Embodiments, wherein sovleplenib or a pharmaceutically acceptable salt thereof is administered as a monotherapy, or in combination with one or more additional therapeutic agents.

E67. The method of any one of the preceding Embodiments, wherein sovleplenib or a pharmaceutically acceptable salt thereof is administered in combination with a concomitant anti-ITP treatment, e.g, concurrently with one concomitant anti-ITP treatment.

E68. The method of any one of the preceding Embodiments, wherein the subject has been receiving a stable dose of concomitant anti-ITP treatment.

E69. The method of any one of E66-E68, wherein the additional therapeutic agents or the concomitant anti-ITP treatment is one concomitant medication selected from corticosteroids, TPO-RAs, danazol, and immunosuppressants.

E70. The method of any one of E66-E68, wherein the additional therapeutic agents or the concomitant anti-ITP treatment is one concomitant medication selected from corticosteroids and TPO-RAs.

E71. The method of any one of E66-E68, wherein the additional therapeutic agents or the concomitant anti-ITP treatment is one concomitant medication selected from corticosteroids, danazol, and immunosuppressants.

E72. The method of any one of E66-E68, wherein the additional therapeutic agents or the concomitant anti-ITP treatment is not a rescue treatment.

E73. The method of any one of the preceding Embodiments, comprising administering to the subject sovleplenib or a pharmaceutically acceptable salt thereof for at least 2 or more weeks, e.g., at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more weeks, or for at least 1, 2, 3 or more years.

E74. The method of any one of the preceding Embodiments, comprising administering to the subject sovleplenib or a pharmaceutically acceptable salt thereof for at least 12 or more weeks, e.g., at least 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more weeks.

E75. The method of any one of the preceding Embodiments, comprising administering to the subject sovleplenib or a pharmaceutically acceptable salt thereof for at least 1, 2, 3 or more years.

E76. The method of any one of the preceding Embodiments, wherein the subject has (relative to prior to treatment) durable response (including an improved durable response rate (DRR)), improved overall response (including improved overall response rate (ORR)), improved platelet counts (e.g., improved median platelet counts), a fast onset of action or improved time to response (TTR), a reduction of bleeding incidence or severity, including reduction in the WHO bleeding scale, less frequency of hemorrhage of grade ≥3, improved hemoglobin level, long-term ITP remission, improved health-related quality of life (HRQoL) (e.g., in terms of physical functioning, energy/fatigue, role limitations due to physical health, role limitations due to emotional problems, emotional well-being, and/or general health), a reduction in the use of rescue treatment (e.g., a rescue medication) and/or reduction or interruption of baseline concomitant anti-ITP treatment, and/or is safe and tolerable over time, optionally with low risk gastrointestinal toxicity, after treatment with sovleplenib or a pharmaceutically acceptable salt thereof.

E77. The method of any one of the preceding Embodiments, wherein the subject has durable response (including an improved DRR), after treatment with sovleplenib or a pharmaceutically acceptable salt thereof.

E78. The method of any one of the preceding Embodiments, wherein the subject has improved overall response (including improved ORR), e.g., improved overall response rate in 0-12 weeks or in 0-24 weeks, after treatment with sovleplenib or a pharmaceutically acceptable salt thereof.

E79. The method of any one of the preceding Embodiments, wherein the subject has improved platelet counts (e.g., improved median platelet counts), including achieving an increase in platelet counts, e.g., by at least 10×10^9/L, 15×10^9/L, 20×10^9/L, 25×10^9/L, 30×10^9/L, 35×10^9/L, 40×10^9/L, 45×10^9/L, 50×10^9/L, 60×10^9/L, 70×10^9/L, 80×10^9/L, 90×10^9/L, or 100×10^9/L, e.g. by about 10×10^9/L to 100×10^9/L, or about 25×10^9/L to 75×10^9/L, or about 30×10^9/L to 60×10^9/L, relative to prior to treatment;

or achieving a platelet count of at least 30×10^9/L, 40×10^9/L, 50×10^9/L, 60×10^9/L, 70×10^9/L, 80×10^9/L, 90×10^9/L, 100×10^9/L, 110×10^9/L, 120×10^9/L, 130×10^9/L, 140×10^9/L, 150×10^9/L, 180×10^9/L, 200×10^9/L, or 250×10^9/L; and/or maintaining the improvedplatelet count for at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or more weeks, after treatment with sovleplenib or a pharmaceutically acceptable salt thereof.

E80. The method of any one of the preceding Embodiments, wherein the subject has an improved hemoglobin level, including achieving an increase in hemoglobin level, e.g., by at least 10g/L, 15g/L, 20g/L, 25g/L, 30g/L, 35g/L, 40g/L, 45g/L, or 50g/L, relative to prior to treatment; or achieving a hemoglobin level of at least 100g/L, 110g/L, 115g/L, 120g/L, 125g/L, 130g/L, 135g/L, 140g/L, 145g/L, or 150g/L, after treatment with sovleplenib or a pharmaceutically acceptable salt thereof.

E81. The method of any one of the preceding Embodiments, wherein the subject has a fast onset of action or improved TTR, a reduction of bleeding incidence or severity, including reduction in the WHO bleeding scale, and/or less frequency of hemorrhage of grade ≥3, after treatment with sovleplenib or a pharmaceutically acceptable salt thereof.

E82. The method of any one of the preceding Embodiments, wherein the subject has improved health-related quality of life (HRQoL), e.g., in terms of physical functioning, energy/fatigue, role limitations due to physical health, role limitations due to emotional problems, emotional well-being, and/or general health, after treatment with sovleplenib or a pharmaceutically acceptable salt thereof.

E83. The method of any one of the preceding Embodiments, wherein the subject has improved health-related quality of life (HRQoL) in terms of physical functioning and energy/fatigue, after treatment with sovleplenib or a pharmaceutically acceptable salt thereof.

E84. The method of any one of the preceding Embodiments, wherein the subject has a reduction in the use of rescue treatment (e.g., rescue medication) and/or reduction or interruption of baseline concomitant anti-ITP treatment, after treatment with sovleplenib or a pharmaceutically acceptable salt thereof.

E85. The method of any one of the preceding Embodiments, wherein the pharmaceutically acceptable salt of sovleplenib is sovleplenib acetate.

E86. An article of manufacture comprising:

a sovleplenib or a pharmaceutically acceptable salt thereof, and

a package insert comprising instructions for using sovleplenib or a pharmaceutically acceptable salt thereof to treat immune thrombocytopenia (ITP) in a subject in need thereof, wherein the instructions indicate that sovleplenib or a pharmaceutically acceptable salt thereof is administrated as defined in any one of the preceding Embodiments.

E87. Sovleplenib or a pharmaceutically acceptable salt thereof for use in a method as defined in any one of E1-E85.

E88. Sovleplenib or a pharmaceutically acceptable salt thereof for use for the treatment of immune thrombocytopenia (ITP) in a subject in need thereof at a daily dosage of about 100-600 mg, or at a dosage sufficient to achieve an $AUC_{tau,ss}$ value about 600-5000 h × ng/mL, wherein the treatment is according to the method of any one of E1-E85.

E89. A pharmaceutical composition comprising sovleplenib or a pharmaceutically acceptable salt thereof, for treating immune thrombocytopenia (ITP) in a subject in need thereof as defined in any one of E1-E85.

E90. A pharmaceutical composition comprising sovleplenib or a pharmaceutically acceptable salt thereof, for the treatment of immune thrombocytopenia (ITP) in a subject in need thereof at a daily dosage of about 100-600 mg, or at a dosage sufficient to achieve an $AUC_{tau,ss}$ value about 600-5000 h × ng/mL, wherein the treatment is according to the method of any one of E1-E85.

E91. Use of sovleplenib or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of immune thrombocytopenia (ITP) in a subject in need thereof at a daily dosage of about 100-600 mg, or at a dosage sufficient to achieve an $AUC_{tau,ss}$ value about 600-5000 h × ng/mL, wherein the treatment is according to the method of any one of E1-E85.

E92. Use of sovleplenib or a pharmaceutically acceptable salt thereof for the treatment of immune thrombocytopenia (ITP) in a subject in need thereof at a daily dosage of about 100-600 mg, or at a dosage sufficient to achieve an $AUC_{tau,ss}$ value about 600-5000 h × ng/mL, wherein the treatment is according to the method of any one of E1-E85.

Each embodiment described in the present disclosure and the features in each embodiment should be understood as being capable of combining with each other in any manner, and those technical solutions obtained by such combination(s) are all included in the scope of the present disclosure the same as if each and every technical solution obtained by such combination(s) were specifically and individually listed, unless the context clearly shows otherwise.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows median platelet count over time during 24-week double-blind treatment period.

DETAILED DESCRIPTION

Definitions

The following terms, unless otherwise indicated, shall be understood to have the following meanings:

As used herein, including the claims, the singular forms of words, such as "a", "an" and "the", include their corresponding plural references unless the context clearly dictates otherwise.

As used herein, the term "about" means approximately, in the region of, roughly, or around. When the term "about" is used in conjunction with a numerical range, it modifies that range or that numerical value 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 ≤ ± 20%, e.g., ± 10%, ± 5%, ± 1%, or ± 0.1%, as such variations are appropriate to perform the disclosed methods.

The term "comprise", "comprises" and "comprising" are to be interpreted inclusively rather than exclusively and are intended to mean "including, but not limited to". Likewise, the terms "include", "contain" and variations of them should all be construed to be inclusive, unless such a construction is clearly prohibited from the context. For example, a method "comprising" X may consist exclusively of X or may include something additional, e.g., X+Y.

The term "and/or" shall be construed to mean that one or more of the listed elements or conditions may be present individually or in combination, without necessarily requiring all elements or conditions to be present simultaneously.

As used herein, the term of "immune thrombocytopenia" or "ITP" refers to an autoimmune disease or disorder in which pathogenic IgGs destroy platelet-producing cells (megakaryocytes) and circulating blood platelets (thrombocytes). Pathogenic IgGs drive disease progression in a multimodal approach: they accelerate platelet clearance, inhibit platelet production, directly induce platelet killing, and interfere with platelets' ability to perform their clotting function. Primary ITP is idiopathic, not associated with any other conditions, whereas secondary ITP is associated with an underlying autoimmune condition or infection (e.g. HCV, or HIV infection). Affected patients generally are at risk for spontaneous bleeding at platelet counts $< 30 \times 10^9$/L, including life-threatening bleeding at platelet counts $< 10 \times 10^9$/L. ITP can be acute or chronic. ITP may be categorized as newly diagnosed ITP, persistent ITP, or chronic ITP. Newly diagnosed ITP is ITP within three months of initial diagnosis. Persistent ITP is ITP lasting 3 to 12 months from diagnosis. Chronic ITP is ITP lasting more than 12 months from diagnosis. Rodeghiero F et al., Blood 113(11): 2386-2393 (2009). ITP also comprises relapsed or refractory ITP and severe ITP; and persistent ITP, chronic ITP or severe ITP with insufficient response to at least one prior anti-ITP treatment (e.g. first line anti-ITP treatment, second line anti-ITP treatment, and/or or third line anti-ITP treatment), with a new relapse and/or with exacerbation.

As used herein, the terms "treat" or "treatment" refer to therapeutic treatment wherein the object is to slow down or lessen an undesired physiological change or disease, or provide a beneficial or desired clinical outcome during treatment. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, one or more of the following: decreasing one or more symptoms resulting from the disease, diminishing the extent of the disease, stabilizing the disease (e.g., preventing or delaying the worsening of the disease), delay or slowing the progression of the disease, ameliorating the disease state, decreasing the dose of one or more other medications required to treat the disease, and/or increasing the quality of life.

Treatment may involve a treatment agent, also referred to herein as a "medication" or "drug" that may be intended to help achieve the beneficial or desired clinical outcome of interest by its action. Treatment agents or medications may be administered to a subject by many routes, including at least intravenous and oral routes. The term "oral", in connection to the administration of treatment agents or medications, refers to the administration of said treatment agents or medications via an oral passage such as the mouth.

As used herein, the term of "anti-ITP treatment" or "ITP treatment" refers to any method of treatment generally recognized as being effective in the treatment of ITP. In certain embodiments, such anti-ITP treatment is in accordance with guidelines published by national or international authorities such as the American Society of Hematology. In some embodiments, "anti-ITP treatment" comprises taking a wait- and-see approach, i.e.,

monitoring clinical and laboratory parameters without treatment intervention while a subject has a platelet count > 30 x 10^9/L and/or has no evidence of bleeding. In some embodiments, "anti-ITP treatment" comprises treatment intervention with one or more anti-ITP drugs discussed herein and/or splenectomy. For anti-ITP drugs involving intervention with one or more anti-ITP drugs, the one or more anti-ITP drugs can be administered on one or more occasions, and in the case of multiple occasions, each compound independently on a scheduled basis or on an as-needed basis.

As used herein, the term "anti-ITP drug", "anti-ITP agent" or "anti-ITP medication" is used interchangeably and refers to any compound that is generally recognized as being effective in the treatment of ITP, including anti-ITP standard drug. In 2019 the American Society of Hematology issued Guidelines for the treatment of ITP (Blood Adv (2019) 3 (23): 3829–3866.). Any compound or class of compounds mentioned in these Guidelines is deemed as "anti-ITP standard drug" and within the definition of "anti-ITP drug". Similarly, the Updated International Consensus Report on the Investigation and Management of Primary Immune Thrombocytopenia of 2019 (Blood advances vol. 3, 22 (2019): 3780-3817.) and the Chinese guideline on the diagnosis and management of adult primary immune thrombocytopenia (version 2020) (Chin J Hematol, August 2020, Vol. 41, No.8) provide examples of compounds deemed to be within this definition. These include, without limitation, corticosteroids (including glucocorticoids, e.g. prednisone, prednisolone, dexamethasone, methylprednisolone and betamethasone), IV immunoglobulin, anti-D immunoglobulin, anti-CD20 antibody, including rituximab, platelet stimulating agents, including TPO treatment agents, e.g., recombinant human thrombopoietin (rhTPO), TPO-RAs (e.g., eltrombopag, hetrombopag, avatrombopag and romiplostim), immunosuppressants (e.g. cyclosporine A, azathioprine, mycophenolate mofetilb), vinca alkaloids, alemtuzumab, danazol, dapsone, platelet transfusion, danazol/stanozolol, caffeic acid, IL-11, Traditional Chinese medicine and any combination thereof. It will be understood that new compounds will be added to this definition as science progresses.

The term "lines of treatment" or "lines of therapy" as used in connection with methods of treatment herein, refers to one or more cycles of a planned treatment program, which may have consisted of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. A new line of therapy is considered to have started when a planned course of therapy has been modified to include other treatment agents or medications (alone or in combination) as a result of disease progression, relapse, or toxicity. A new line of therapy is also considered to have started when a planned period of observation off therapy had been interrupted by a need for additional treatment for the disease.

"First-line" as in first-line treatment or first-line therapy for a disease or condition refers to the first or initial treatment or therapy administered for said disease or condition. "Second-line" as in second-line treatment or second-line therapy for a disease or condition refers to a treatment or therapy administered after an initial treatment for said disease or condition (first-line treatment), usually because the initial treatment is ineffective or insufficiently effective, has stopped being effective, or has side effects. For example, "first-line treatment" for ITP includes, but not limited to corticosteroids (including glucocorticoid, e.g. prednisone, prednisolone, dexamethasone, methylprednisolone, and betamethasone), and/or IV immunoglobulin, "second-

line treatment" for ITP includes one or more of TPO-RAs (e.g., romiplostim, eltrombopag, and avatrombopag), anti-CD20 antibody, including rituximab, splenectomy, immunosuppressants (e.g. cyclosporine A, azathioprine, mycophenolate mofetilb, cyclophosphamide), and/or TPO treatment agents, e.g., rhTPO.

As used herein, the term "thrombopoietin treatment" or "TPO treatment" refers to any treatment intervention with an agent having the similar biological functions as endogenous TPO. For example, the agent can be recombinant human thrombopoietin (rhTPO), a full-length glycosylated-TPO produced by Chinese hamster ovary cells.

As used herein, the term "TPO receptor agonist treatment" or "TPO-RA treatment" refers to any treatment intervention with one or more TPO receptor agonists. In some embodiments, "TPO receptor agonist" or "TPO-RA" is an agent that promotes, to some extent, a biological function of TPO receptor, generally through binding to TPO receptor and promoting its activity. Examples of TPO receptor agonists specifically contemplated herein are, eltrombopag, hetrombopag, avatrombopag and romiplostim.

As used herein, the term "TPO/TPO-RA treatment" refers to TPO treatment and/or TPO-RA treatment.

As used herein, "corticosteroid" refers to any one of several synthetic or naturally occurring substances with the general chemical structure of steroids that mimic or augment the effects of the naturally occurring corticosteroids (e.g., glucocorticoids). Examples of glucocorticoids include, including prednisone, prednisolone, methylprednisolone, dexamethasone and betamethasone.

As used herein, the term "CD20 antibody" or "anti-CD20 antibody" as used herein refers to an antibody which binds specifically to the antigen CD20, in particular to human CD20. In some embodiments, the previously received anti-CD20 antibody comprises rituximab.

As used herein, the term "relapsed or refractory" or "R/R" disease, unless specified otherwise, is intended to refer to relapsed and/or refractory disease. "Refractory" disease refers to disease which either progressed during therapy, failed to achieve an objective response to prior therapy, or progressed after completion of therapy. "Relapsed" or "recurrence" disease refers to disease which previously responded to therapy but progressed after completion of therapy. For example, "recurrence" or "relapsed" ITP may include the following clinical outcomes: the platelet count is again $<30 \times 10^9$/L, or a platelet count <2 times the baseline value, or bleeding after a post-effective anti-ITP treatment. "Refractory" ITP includes a disease of a subject with the presence of severe ITP occurring after splenectomy.

As used herein, the term "response" refers to an outcome that can be assessed using any endpoint indicating a benefit to the subject, including, without limitation, (1) increasing platelet counts of patient; (2) improving onset of action; (3) reduction of bleeding incidence or severity (e.g. decrease WHO bleeding scale, less frequency of hemorrhage of grade ≥3); (4) achieving long-term ITP remission; (5) reduction of incidence of patients receiving rescue treatment; (6) reduction or interruption of baseline concomitant anti-ITP treatment; (7) relief, to some extent, of one or more symptoms associated with the previously untreated ITP; and/or (8) increasing quality of life, including health-related quality of life (HRQoL).

As used herein, the term "insufficient response" refers to signs and/or symptoms of persistently active disease (e.g., ITP) despite a history of treatment with one or more therapeutics, for example, prior anti-ITP treatment(s), such as corticosteroids (e.g., glucocorticoids), anti-CD20 antibody treatment, TPOs and/or TPO-

RAs. Insufficient response may be defined by specific clinical or other endpoints such as those described in the Examples provided herein. An insufficient response as provided herein includes outcomes where no discernable response to treatment is observed (e.g., no response), and outcomes where a response to treatment is observable but considered insufficient or suboptimal to meaningfully alleviate symptoms or treat the disease. An insufficient response includes a refractory response and recurrence. In some embodiments, "insufficient response" or "no response" to a prior anti-ITP treatment may be defined by the following clinical outcomes: the platelet count of a subject does not increase to a level sufficient to avoid clinically important bleeding after the prior anti-ITP treatment, e.g., platelet count $<30 \times 10^9$/L, or a platelet count <2 times the baseline value.

As used herein, the term "intolerance" or "intolerant" to treatment refers to the situation where a patient experiences excessive side effect(s), etc. from at least one line of therapy, or even all available therapies for ITP, leading to an inappropriate benefit/risk ratio. Intolerance may require cessation of therapy for a period of time, or indefinitely.

As used herein, the term "overall response rate" refers to the percentage of patients, n (%), who experience platelet counts $\geq 50 \times 10^9$/L at least once during the treatment period in the absence of rescue therapy.

As used herein, the term "durable response rate" refers to the percentage of patients, n (%), who experience platelet counts $\geq 50 \times 10^9$/L in at least 4 visits of 6 biweekly visits between Weeks 14 and 24 (inclusive) during the treatment period

As used herein, the term "health-related quality of life (HRQoL)" is generally accepted as a multidimensional assessment of how disease and treatment affect a patient's sense of overall function and wellbeing. The US Food and Drug Administration (FDA) officially defines HRQoL as "a multi-domain concept that represents the patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of life".

As used herein, "SF-36" refers to the widely-used medical outcomes health survey "Short Form-36", which is used as a tool for monitoring the results of medical care in patients. See Tarlov A.R., et al, JAMA 1989, 262(7): 925-30; Linde, L., et al., J Rheumatol, 35 (2008), pp. 1528-1537.

The term "concomitant anti-ITP treatment" refers to one or more anti-ITP treatments administrated concomitantly with primary therapeutic agent (such as sovleplenib or pharmaceutically acceptable salts for the present disclosure). In some embodiments, the concomitant anti-ITP treatment is one selected from corticosteroids (including glucocorticoid), danazol, immunosuppressants (including azathioprine, ciclosporin A, or mycophenolate mofetil), or TPO-RAs. In some embodiments, the concomitant anti-ITP treatment is one selected from corticosteroids (including glucocorticoid), danazol or immunosuppressants (including azathioprine, ciclosporin A, or mycophenolate mofetil). In some embodiments, the concomitant anti-ITP treatment is one selected from corticosteroids (including glucocorticoid) or TPO-RAs. In some embodiments, the concomitant anti-ITP treatment is one rescue treatment.

As used herein, the term "concomitantly" refers to administration of two or more therapeutic agents, give in close enough temporal proximity where their individual therapeutic effects overlap in time. Accordingly, concurrent administration includes a dosing regimen when the administration of one or more agent(s) continues after discontinuing the administration of one or more other agent(s). In some embodiments, the concomitantly

administration is concurrently, sequentially, and/or simultaneously.

As used herein, the term "patient" or "subject" refers to a warm-blooded animal. In an embodiment, the patient is human. It may be a human who has been diagnosed and is in the need of treatment for a disease or disorder, as disclosed herein. For the purposes herein, such patient or subject is one who is experiencing, has experienced, or is likely to experience, one or more signs, symptoms or other indicators of ITP; or has newly diagnosed ITP, persistent ITP, chronic ITP; or has relapsed ITP, refractory ITP or severe ITP; or has persistent ITP, chronic ITP or severe ITP with insufficient response to at least one prior anti-ITP treatment (e.g. first line anti-ITP treatment, second line anti-ITP treatment, and/or or third line anti-ITP treatment), a new relapse and/or exacerbation.

As used herein, a subject is "in need of" a treatment if such subject would benefit biologically, medically or in quality of life from such treatment.

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

An "effective amount", "therapeutically effective amount", or "pharmaceutically effective amount" are used interchangeably herein, and encompass an amount of a compound, formulation, material or composition, sufficient to treat or inhibit a symptom, sign or other indicators of the medical condition to be treated. An effective amount for a particular patient may vary depending on factors, such as the condition being treated, the overall health of the patient, the method route and dose of administration and the severity of side effects. An effective amount can be the maximal dose or dosing protocol that avoids significant side effects or toxic effects. The effect will result in an improvement of a diagnostic measure or parameter by at least 5%, such as by at least 10%, further such as at least 20%, further such as at least 30%, further such as at least 40%, further such as at least 50%, further such as at least 60%, further such as at least 70%, further such as at least 80%, and even further such as at least 90%, wherein 100% is defined as the diagnostic parameter shown by a normal subject.

The term "$AUC_{tau,ss}$" refers to area under the plasma concentration-time curve at steady state within dosing interval.

The term "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The term "pharmaceutically acceptable salts" can be formed, for example, as acid addition salts, preferably with organic or inorganic acids. Suitable inorganic acids are, for example, halogen acids, such as hydrochloric acid. Suitable organic acids are, e.g., carboxylic acids or sulfonic acids, such as acetic acid, p-toluenesulfonic acid, malic acid, fumaric acid or methanesulfonic acid, preferably acetic acid, more preferably monoacetic acid. For isolation or purification purposes, it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. For therapeutic use, only pharmaceutically acceptable salts or free compounds are employed (where applicable in the form of pharmaceutical preparations), and these are

therefore preferred. Any reference to the free compound herein is to be understood as referring also to the corresponding salt, as appropriate and expedient.

The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, combination therapy, contraindications and/or warnings concerning the use of such therapeutic products.

As used herein, "in combination with" refers to administration of one treatment modality (e.g., a drug therapy) in addition to another treatment modality. As such, this term refers to administration of one treatment modality before, during, or after administration of the other treatment modality to a patient.

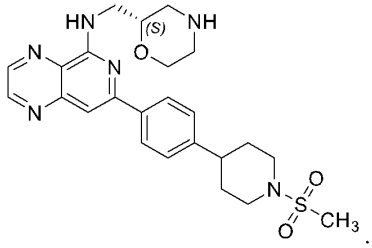
As used herein, "one or more" or "at least one" refers to the presence of at least one instance of the specified element or parameter, for example 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more. Similarly, "two or more" refers to 2, 3, 4, 5, 6, 7, 8, 9, 10 or more.

It will be appreciated that reference to an amount of a compound herein (e.g., sovleplenib or a pharmaceutically acceptable salt thereof) means the amount of that compound in free base form.

All numerical ranges herein should be understood as disclosing each and every value within the range and each and every subset of values within the range, regardless of whether they are specifically disclosed otherwise. For example, when referring to any numerical range, it should be regarded as referring to each and every numerical value in the numerical range, for example, each and every integer in the numerical range. The present disclosure includes all values falling within these ranges, all smaller ranges, and the upper or lower limit of the range.

Sovleplenib (HMPL-523)

Sovleplenib (also known as HMPL-523) is a highly effective and selective small molecular Syk inhibitor, which can inhibit B cells on the production of antiplatelet antibody and inhibit phagocytosis of autoantibody coated platelets by macrophages. Sovleplenib namely (S)-7-(4-(1-(methylsulfonyl)piperidin-4-yl) phenyl)-N-(morpholin-2-ylmethyl)pyrido[3,4-b]pyrazin-5-amine has the following structure:



In some embodiments, sovleplenib is provided and/or utilized as a salt form (e.g., as a pharmaceutically acceptable salt form). Pharmaceutically acceptable salts are known in the art. See, e.g., S. M. Berge et al., J. Pharmaceutical Sciences, 1977, 66, 1–19.

In some embodiments, sovleplenib is provided and/or utilized as a salt form, such as acetate, as described in the patent application WO 2019/037737 A1, which is incorporated herein by reference in its entirety.

Methods and Uses

The present disclosure provides methods of treating immune thrombocytopenia (ITP) in a subject in need thereof comprising administering to the subject an effective amount of sovleplenib or a pharmaceutically acceptable salt thereof.

In some embodiments, the ITP is primary ITP. In some embodiments, the ITP is newly diagnosed ITP. In some embodiments, the ITP is persistent ITP. In some embodiments, the subject has persistent ITP for ≥3 months and less than 1 year. In some embodiments, the ITP is chronic ITP. In some embodiments, the subject has chronic ITP for ≥1 year. In some embodiments, the subject has chronic ITP for 1 to 2 years. In some embodiments, the subject has chronic ITP for 1 to 3 years. In some embodiments, the subject has chronic ITP for ≥3 years.

In some embodiments, the subject has received at least one prior anti-ITP treatment, optionally at least one prior line (e.g. one prior line, two prior lines, three prior lines, four prior lines, five prior lines, or more prior lines) of anti-ITP treatment. In some embodiments, the subject has received at least one, two, three, four, five, six, seven, eight or more prior anti-ITP treatments. In some embodiments, the subject has received at least two, three, four, five, six, seven or more prior anti-ITP treatments. In some embodiments, the subject has received at least three, four, five, six, seven or more prior anti-ITP treatments. In some embodiments, the subject has received at least four, five, six or more prior anti-ITP treatments. In some embodiments, the subject has received four, five or more prior anti-ITP treatment. In some embodiments, the subject has received at least four or more prior anti-ITP treatment. In some embodiments, the subject has had an insufficient response to or intolerance to or has relapsed after at least one prior anti-ITP treatment, e.g., the at least one prior line (e.g. one prior line, two prior lines, three prior lines, four prior lines, five prior lines, or more prior lines) of anti-ITP treatment.

In some embodiments, the at least one prior anti-ITP treatment comprises splenectomy, anti-ITP drug treatment, or any combination of such treatments. In some embodiments, the at least one prior anti-ITP treatment comprises splenectomy. In some embodiments, the at least one prior anti-ITP treatment comprises an anti-ITP drug treatment (e.g. anti-ITP standard drug treatment, or anti-ITP non-standard drug treatment). In some embodiments, the prior anti-ITP treatment comprises one or more (e.g., 2, 3, 4, 5 or 6) treatments with corticosteroid, IV immunoglobulin, anti-D immunoglobulin, TPO treatment, TPO-RA treatment, anti-CD20 antibody treatment, immunosuppressant, vinca alkaloids, Traditional Chinese medicine, platelet transfusion, danazol/stanozolol, ciclosporin, caffeic acid, IL-11 and/or other agents. In some embodiments, the at least one prior anti-ITP treatment comprises a treatment with corticosteroid (e.g. glucocorticoid selected from prednisone, prednisolone, dexamethasone, methylprednisolone, and betamethasone). In some embodiments, the at least one prior anti-ITP treatment comprises a platelet stimulating agent. In some embodiments, the at least one prior anti-ITP treatment comprises a treatment with a TPO treatment agent (e.g. rhTPO). In some embodiments, the at least one prior anti-ITP treatment comprises a treatment with a TPO-RA (e.g., at least one of eltrombopag, hetrombopag, avatrombopag and romiplostim). In some embodiments, the at least one prior anti-ITP treatment comprises a treatment with an anti-CD20 antibody (e.g. rituximab). In some embodiments, the at least one prior anti-ITP treatment comprises a treatment with an immunosuppressant (e.g. at least one of cyclosporine A, azathioprine, mycophenolate mofetilb). In some embodiments, the at least one prior anti-ITP

treatment comprises a treatment with IVIG. In some embodiments, the at least one prior anti-ITP treatment comprises a treatment with anti-D immunoglobulin. In some embodiments, the at least one prior anti-ITP treatment comprises a treatment with other agents, e.g., alemtuzumab, danazol and/or dapsone, vinca alkaloids.

In some embodiments, the at least one prior anti-ITP treatment comprises a TPO treatment and/or TPO-RA treatment. In some embodiments, the at least one prior anti-ITP treatment comprises a TPO treatment or TPO-RA treatment. In some embodiments, the at least one prior anti-ITP treatment comprises both TPO treatment and TPO-RA treatment. In some embodiments, the at least one prior anti-ITP treatment comprises only one medication of TPO/TPO-RA treatment. In some embodiments, the at least one prior anti-ITP treatment comprises at least two medications of TPO/TPO-RA treatment (e.g., three, four, five, six or more medications of TPO/TPO-RA treatment), e.g. at least two medications (e.g., three, four, five, six or more medications) selected from a recombinant human thrombopoietin, eltrombopag, hetrombopag, avatrombopag and romiplostim.

In some embodiments, the medication of TPO treatment is recombinant human thrombopoietin. In some embodiments, the medication of TPO-RA treatment is selected form eltrombopag, hetrombopag, avatrombopag and romiplostim.

In some embodiments, the at least one prior anti-ITP treatment comprises at least one treatment of a first-line treatment, for example, comprises one or more medications selected from glucocorticoids including prednisone, prednisolone, dexamethasone, and betamethasone. In some embodiments, the at least one prior anti-ITP treatment comprises at least one treatment of a second-line treatment, for example, comprises one or more medications selected from rhTPO, romiplostim, eltrombopag, hetrombopag or avatrombopag, rituximab and splenectomy. In some embodiments, the at least one prior anti-ITP treatment comprises at least one treatment of a third-line, fourth-linen or further line treatment.

In some embodiments, the at least one prior anti-ITP treatment comprises an anti-CD20 antibody treatment. In some embodiments, the anti-CD20 antibody treatment is rituximab.

In some embodiments, the at least one prior anti-ITP treatment does not comprise a Syk inhibitor including fostamatinib.

In some embodiments, the subject has an ITP Bleeding Scale (IBLS) score (e.g., WHO Bleeding Scale) of 0 or 1 prior to the treatment. In some embodiments, wherein the subject has a platelet count of less than 30×10^9 per liter prior to the treatment. In some embodiments, the subject has a platelet count of less than 15×10^9 per liter prior to the treatment. In some embodiments, wherein the subject has a platelet count of more than 30×10^9 per liter and less than 30×10^9 per liter prior to the treatment. In some embodiments, the subject has a hemoglobin $\geq$100 g/L and neutrophil count $>1.5\times10^9$/L.

In some embodiments, the subject has not responded to sovleplenib during the first 12 weeks treatment. In some embodiments, the subject is human adult. In some embodiments, the subject is Asian population. In some embodiments, the subject is non-Asian population. In some embodiments, the subject is Western population.

Efficacy and Safety

The provided methods herein achieve (relative to prior to treatment) durable response, including an

improved durable response rate (DRR), improved overall response, including improved overall response rate(ORR), improved platelet counts, including improved median platelet counts, a fast onset of action or improved time to response (TTR), a reduction of bleeding incidence or severity, including reduction in the WHO bleeding scale, less frequency of hemorrhage of grade ≥3, improved hemoglobin level, long-term ITP remission, improved health-related quality of life (HRQoL) (e.g., in terms of physical functioning, energy/fatigue, role limitations due to physical health, role limitations due to emotional problems, emotional well-being, and/or general health), a reduction in the use of rescue treatment, including a rescue medication and/or reduction or interruption of baseline concomitant anti-ITP treatment, being safe and tolerable over a longer period, e.g., with low risk gastrointestinal toxicity.

The provided methods herein are advantageous over the prior art, e.g., not only reducing the risk of excessive bleeding, but also inducing long-term ITP remission, improving health-related quality of life (HRQoL) of a patient with ITP as defined in the present disclosure, while being safe and tolerable over a longer period.

In some embodiments, the administration in accord with the provided methods effectively treats the subject despite the subject having become insufficient response to another therapy. In some embodiments, criteria assessed for effective treatment includes durable response rate (DRR), overall response rate (ORR), proportion of patients who received rescue treatment, proportion of patients who reduced or interrupted baseline concomitant treatment, proportion of patients with two consecutive platelet count of $\geqslant 30\times10^9$/L and doubling from the baseline, improved platelet counts, time to response (TTR), WHO bleeding score, and/or health-related quality of life (HRQoL). In some embodiments, DRR of patients treated using the methods described herein is at least about 30% (e.g., at least 40% at least 50%, at least 60%, at least 70%, or at least 80%). In some embodiments, ORR of the patients treated using the methods described herein is at least about 40% (e.g., at least about 50%, at least about 60%, at least about 70%, at least 80%, or at least 90%). In some embodiments, at least 30% (e.g., at least 40% at least 50%, at least 60%, at least 70%, or at least 80%), of patients treated using the methods described herein achieve sustained efficacy. In some embodiments, less than about 35% ((e.g., less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, or less than about 5%), of the patients treated using the methods described herein receive in the use of rescue treatment. In some embodiments, at least 10%, (e.g., at least 15%, at least 20% at least 25%, at least 30%, at least 35%, or at least 40%), of the patients treated using the methods described herein achieve a significant reduction or interruption of baseline concomitant anti-ITP treatment. In some embodiments, at least 10% ((e.g., at least 20%, at least 30% at least 50%, at least 60%, at least 70%, at least 80% or at least 90%), of the patients treated using the methods described herein achieve two consecutive platelet count of $\geqslant 30\times10^9$/L and doubling from the baseline. In some embodiments, on average, patients treated using the methods described herein exhibit a median time to response of less than about 4 weeks, about 3 weeks, about 2 weeks, about 1 week, about 7 days, about 6 days, about 5 days, about 4 days, about 3 days, about 2 days, about 1 day. In some embodiments, on average, patients treated using the methods described herein exhibit a mean WHO bleeding score (least squares mean) of less than about 0.8, about 0.7, about 0.6, about 0.5, about 0.4, about 0.3, about 0.2, or about 0.1. In some embodiments, on average, patients treated

using the methods described herein achieve improved health-related quality of life (HRQoL), e.g. in terms of fatigue and/or physical functioning.

In some embodiments, less than about 25% (e.g., less than about 20%, less than about 15%, less than about 10%, or less than about 5%) of patients treated using the methods described herein experience Serious TEAEs.

In some embodiments, less than about 2% (e.g., less than 1.9%, less than 1.8%, less than 1.7%, less than 1.6%, less than 1.5%, less than 1.4%, less than 1.3%, less than 1.2%, less than 1.1% or less than 1.0%) of patients treated using the methods described herein experience treatment related serious TEAEs.

In some embodiments, less than about 15% (e.g., less than 14%, less than 13%, less than 12%, less than 11%, less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, or less than 1%) of patients treated using the methods described herein experience hypertension. In some embodiments, less than about 5% (e.g., less than 4%, less than 3%, less than 2%, or less than 1%,) of patients treated using the methods described herein experience Grade 3 hypertension.

In some embodiments, less than about 15% (e.g., less than 14%, less than 13%, less than 12%, less than 11%, less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, or less than 1%) of patients treated using the methods described herein experience hypertension. In some embodiments, less than about 5% (e.g., less than 4%, less than 3%, less than 2%, or less than 1%,) of patients treated using the methods described herein experience Grade 3 hypertension.

In some embodiments, less than about 10% (e.g., less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, or less than 1%) of patients treated using the methods described herein experience gastrointestinal related events (e.g., diarrhea, vomiting, nausea). In some embodiments, less than about 5% (e.g., less than 4%, less than 3%, less than 2%, or less than 1%,) of patients treated using the methods described herein experience diarrhea. In some embodiments, less than about 5% (e.g., less than 4%, less than 3%, less than 2%, or less than 1%,) of patients treated using the methods described herein experience vomiting. In some embodiments, less than about 5% (e.g., less than 4%, less than 3%, less than 2%, or less than 1%,) of patients treated using the methods described herein experience nausea.

Dosing

In some embodiments, provided methods comprise administering to a patient in need thereof a therapeutically effective amount of sovleplenib, or a pharmaceutically acceptable salt thereof.

It will be appreciated that reference to an amount of an agent herein (e.g., sovleplenib or a pharmaceutically acceptable salt thereof) means the amount of the corresponding compound in free base form. Accordingly, if a compound may be provided and/or utilized as, e.g., a salt form of the compound, any reference to an amount of the salt (or other forms) denotes an amount that corresponds to the "free base equivalent" of the salt (or other forms).

In some embodiments, therapeutically effective amount of sovleplenib or a pharmaceutically acceptable salt thereof is a dosage sufficient to achieve an $AUC_{tau,ss}$ to about 600-5000 or about 600-4890 h ×ng/mL, e.g., about 600-800, about 1000-1300, about 1900-2200, or about 2900-3200 h ×ng/mL, e.g., about 600-700,

about 1100-1200, about 2000-2100, or about 3000-3100 h ×ng/mL, e.g., about 640-680, about 1135-1175, about 2045-2185, or about 3045-3085 h ×ng/mL, e.g., about 650-670, about 1145-1165, about 2055-2175, or about 3055-3075 h ×ng/mL (e.g., about 661 h ×ng/mL, about 1156 h ×ng/mL, about 2067 h ×ng/mL, about 3065 h ×ng/mL) in a patient. In some embodiments, therapeutically effective amount of sovleplenib or a pharmaceutically acceptable salt thereof is a dosage sufficient to achieve $AUC_{tau,ss}$ = about 1900-2200, about 2000-2100, about 2045-2185, about 2055-2175, or about 2067 h ×ng/mL.

In some embodiments, provided methods comprise administering to a patient in need thereof about 100 mg to about 800 mg sovleplenib, or a pharmaceutically acceptable salt thereof daily. In some embodiments, provided methods comprise administering to a patient in need thereof about 100, 200, 300, 400, 500, 600, 700 or 800 mg sovleplenib or a pharmaceutically acceptable salt thereof daily. The daily dosage (i.e., total daily dosage) may be administered once per day (QD), or in divided doses, e.g., twice per day (BID) or three times per day (TID).

In some embodiments, provided methods comprise administering to a patient in need thereof about 100 mg to about 800 mg sovleplenib, or a pharmaceutically acceptable salt thereof, once per day (QD). In some embodiments, provided methods comprise administering to a patient in need thereof about 100 mg to about 400 mg sovleplenib, or a pharmaceutically acceptable salt thereof, once per day (QD). In some embodiments, provided methods comprise administering to a patient in need thereof about 300 mg to about 500 mg sovleplenib, or a pharmaceutically acceptable salt thereof, once per day (QD). In some embodiments, provided methods comprise administering to a patient in need thereof about 100 mg sovleplenib, or a pharmaceutically acceptable salt thereof, once per day (QD). In some embodiments, provided methods comprise administering to a patient in need thereof about 200 mg sovleplenib, or a pharmaceutically acceptable salt thereof, once per day (QD). In some embodiments, provided methods comprise administering to a patient in need thereof about 300 mg sovleplenib, or a pharmaceutically acceptable salt thereof, once per day (QD). In some embodiments, provided methods comprise administering to a patient in need thereof about 400 mg sovleplenib, or a pharmaceutically acceptable salt thereof, once per day (QD). In some embodiments, provided methods comprise administering to a patient in need thereof about 500 mg sovleplenib, or a pharmaceutically acceptable salt thereof, once per day (QD). In some embodiments, provided methods comprise administering to a patient in need thereof about 600 mg sovleplenib, or a pharmaceutically acceptable salt thereof, once per day (QD). In some embodiments, provided methods comprise administering to a patient in need thereof about 700 mg sovleplenib, or a pharmaceutically acceptable salt thereof, once per day (QD). In some embodiments, provided methods comprise administering to a patient in need thereof about 800 mg sovleplenib, or a pharmaceutically acceptable salt thereof, once per day (QD).

In some embodiments, provided methods comprise administering to a patient in need thereof about 50 mg to about 400 mg sovleplenib, or a pharmaceutically acceptable salt thereof, twice per day (BID). In some embodiments, provided methods comprise administering to a patient in need thereof about 50 mg sovleplenib, or a pharmaceutically acceptable salt thereof, twice per day (BID). In some embodiments, provided methods comprise administering to a patient in need thereof about 100 mg sovleplenib, or a pharmaceutically acceptable salt thereof, twice per day (BID). In some embodiments, provided methods comprise administering to a patient

in need thereof about 150 mg sovleplenib, or a pharmaceutically acceptable salt thereof, twice per day (BID). In some embodiments, provided methods comprise administering to a patient in need thereof about 200 mg sovleplenib, or a pharmaceutically acceptable salt thereof, twice per day (BID). In some embodiments, provided methods comprise administering to a patient in need thereof about 250 mg sovleplenib, or a pharmaceutically acceptable salt thereof, twice per day (BID). In some embodiments, provided methods comprise administering to a patient in need thereof about 300 mg sovleplenib, or a pharmaceutically acceptable salt thereof, twice per day (BID). In some embodiments, provided methods comprise administering to a patient in need thereof about 350 mg sovleplenib, or a pharmaceutically acceptable salt thereof, twice per day (BID). In some embodiments, provided methods comprise administering to a patient in need thereof about 400 mg sovleplenib, or a pharmaceutically acceptable salt thereof, twice per day (BID).

In some embodiments, the dosage of sovleplenib, or a pharmaceutically acceptable salt thereof is reduced during the treatment described herein. In some embodiments, the dosage of sovleplenib, or a pharmaceutically acceptable salt thereof is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95%. For example, a dose of sovleplenib, or a pharmaceutically acceptable salt thereof, about 300 mg QD can be reduced sequentially to a dosage, e.g., about 250 mg QD, about 200 mg QD, about 150 mg QD, or 100mg QD; or a dosage of sovleplenib, or a pharmaceutically acceptable salt thereof, about 500 mg QD can be reduced sequentially to a dosage, e.g., about 400 mg QD, about 300 mg QD, about 200 mg QD, or 100mg QD.

In some embodiments, provided methods of treating immune thrombocytopenia (ITP) in a subject in need thereof comprises administering to the subject sovleplenib or a pharmaceutically acceptable salt thereof at a daily dosage of about 300~500 mg (e.g. about 300mg, about 400mg, about 500mg), or at a dosage sufficient to achieve an $AUC_{tau,ss}$ value of about 2055-2175 h ×ng/mL (e.g. 2067 h ×ng/mL), wherein the subject is non-Asian population, (e.g., Western population, American population, European population, Caucasian population, Oceanian population (Australoid), and/or African population) and wherein the subject response to and/or tolerant to the treatment, e.g. the subject has durable response (including an improved durable response rate), improved overall response (including improved overall response rate), improved platelet counts, a fast onset of action or improved time to response, a reduction of bleeding incidence or severity, including reduction in the WHO bleeding scale score, less frequency of hemorrhage of grade ≥3, improved hemoglobin level, long-term ITP remission, improved health-related quality of life (HRQoL), and/or a reduction in the use of rescue treatment and/or reduction or interruption of baseline concomitant anti-ITP treatment, and/or is safe and tolerable over time, optionally with low risk gastrointestinal toxicity, after treatment with sovleplenib or a pharmaceutically acceptable salt thereof.

In some embodiments, sovleplenib is administered orally. In some embodiments, sovleplenib is administered with or without food.

Concomitant Treatment

In some embodiments, the subject has been optionally receiving a concomitant anti-ITP treatment. In

some embodiments, provided methods comprise administering to a patient in need thereof a therapeutically effective amount of sovleplenib, or a pharmaceutically acceptable salt thereof, and in combination with a concomitant anti-ITP treatment (e.g. concomitant medication, or rescue treatment).

In some embodiments, the concomitant anti-ITP treatment is no more than one concomitant medication selected from corticosteroid, danazol, and immunosuppressant. In some embodiments, the corticosteroid is glucocorticoid. In some embodiments, the immunosuppressant is azathioprine, ciclosporin A, and/or mycophenolate mofetil. In some embodiments, the concomitant anti-ITP treatment is one medication of a TPO-RA treatment. In some embodiments, the concomitant anti-ITP treatment is one rescue treatment (e.g., platelet transfusion, intravenous gamma globulin, high-dose glucocorticoid pulse).

In some embodiments, the concomitant medication has been administered at a stable dose (e.g., dose of glucocorticoid is equivalent to prednisone $\leqslant$ 20 mg/day for at least 2 weeks, or danazol or azathioprine is administered at a stable dose for at least 3 months) prior to the treatment provided herein. In some embodiments, the dose of the concomitant medication is reduced by at least about 10%, by at least about 20%, by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95% during the treatment provided herein. In some embodiments, the concomitant medication is discontinued during the treatment provided herein.

Unit Dosage Forms

In some embodiments, provided therapies are administered as one or more unit dosage forms. As used herein, a "unit dosage form" refers to a physically discrete unit of an active agent (e.g., a therapeutic agent) for administration to a patient. Typically, each such unit contains a predetermined quantity of active agent. It will be appreciated that the total amount of a therapeutic composition or agent administered to a patient may involve administration of multiple unit dosage forms.

In some embodiments, sovleplenib is administered to a patient in a unit dosage form. In some embodiments, a unit dosage form is a capsule or tablet. In some embodiments, a unit dosage form comprises about 100 mg sovleplenib, or a pharmaceutically acceptable salt thereof. In some embodiments, a unit dosage form comprises about 150 mg sovleplenib, or a pharmaceutically acceptable salt thereof.

Pharmaceutically Acceptable Compositions

In some embodiments, provided methods comprise administering one or more compositions comprising sovleplenib, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle. In some embodiments, provided compositions are formulated for oral administration.

The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this disclosure include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium

sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

Compositions may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally.

Pharmaceutically acceptable compositions for use in provided methods may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

The compound can also be in micro-encapsulated form with one or more excipients as noted above.

The descriptions of the various embodiments have been presented for purposes of illustration, but are not intended to be exhaustive or limited to the embodiments disclosed. Many modifications and variations will be apparent to those of ordinary skill in the art without departing from the scope and spirit of the described embodiments.

All patents, patent applications, publications, and other references cited or referred to herein are in their entirety incorporated herein by reference to the extent allowed by law. The discussion of those references is intended merely to summarize the assertions made therein. No admission is made that any such patents, patent applications, publications or references, or any portion thereof, are relevant material or prior art. The right to challenge the accuracy and pertinence of any assertion of such patents, patent applications, publications, and other references as relevant material or prior art is specifically reserved.

EXAMPLES

The disclosure is further illustrated by the following examples, which are not to be construed as limiting this disclosure in scope or spirit to the specific procedures herein described. It is to be understood that the examples are provided to illustrate certain embodiments and that no limitation to the scope of the disclosure is intended thereby. It is to be further understood that resort may be had to various other embodiments, modifications, and equivalents thereof, which may suggest themselves to those skilled in the art without departing from the spirit of the present disclosure and/or scope of the appended claims.

Example 1 Sovleplenib in adult patients with primary immune thrombocytopenia in China: a randomized, double-blind, placebo-controlled phase 1b/2 study

Overall Study Design

The study is a randomized, double-blind, placebo-controlled phase 1b clinical study in subjects with persistent/chronic/refractory ITP with thrombocytopenia > 6 months. Subjects can be included in the study only after signing the informed consent form (ICF) and passing the screening.

The primary objectives of this study are to evaluate the safety and tolerability of different proposed doses of HMPL-523 and to determine the RP2D for subsequent clinical studies of HMPL-523 in adults with primary ITP. In addition, the preliminary efficacy and PK profile of HMPL-523 in the treatment of ITP will be further assessed. Blood samples will be collected from all subjects for PK analysis.

It is estimated that 24-60 subjects will be enrolled. The final sample size depends on the number of study cohorts and the number of subjects entered in each cohort group. Based on a comprehensive analysis of efficacy, safety, and PK data, the actual sample size may be lower than planned.

Three dose groups are preliminarily set: 100 mg, 200 mg and 300 mg dose groups (The safety review committee could include additional dose groups (100 mg increments) if no safety event stopped the dose escalation process.).

A total of 8 subjects will be enrolled in each dose group to receive HMPL-523 or placebo in a 3:1 ratio for 8 weeks. Upon completion of 8 weeks of blinded study treatment, all subjects, allocated in HMPL-523 or placebo group, may receive 16 weeks of open-label treatment with HMPL-523 at the current dose level, after the assessment by the investigator.

From the low dose group, after all subjects in the previous dose group complete 4 weeks of treatment, and safety and tolerability are confirmed, new subjects will be screened and enrolled to the study of the next dose gradient.

Subjects should be dosed at a relatively fixed time each day. The actual administration time on the day before, the day of and the day after PK sampling should be accurately recorded.

The Drug Safety Monitoring Committee (SRC) will summarize the safety data on 28 days after administration to the 8th subject in each dose group, and discuss whether to escalate to the next dose group, or add a new dose group, or increase the sample size in one or several dose groups, or terminate the dose escalation, or terminate the current cohort study, or terminate the entire study. An interim SRC meeting may also be convened during a dose study, if necessary, to decide whether or not to continue the study or to modify the study drug dose level. The composition and responsibilities of the SRC are described in Section 3.4.

Dose escalation will be considered terminated in any of the following circumstances:

- The planned maximum dose has been reached;
- The SRC decides to terminate dose escalation;
- The sponsor decides to terminate dose escalation;
- From the first dosing to 28 days after dosing:
    - Occurrence of one or more SAEs related to HMPL-523 (an individual unblinding of the SAE will be requested by the SRC, as necessary, to exclude subjects in placebo group), excluding SAEs resulting from rescue ITP therapy; or
    - More than half of the subjects experience the same drug-related AE with grade ≥ 2 based on CTCAE v5.0 (without unblinding).

During the study, the SRC will also select one or more dose groups to expand the sample size based on available safety and preliminary efficacy data to further assess the safety, tolerability, and preliminary efficacy and PK profile of HMPL-523 in the treatment of ITP at these dose levels. For the sample size that will be expanded (i.e., patients who are enrolled after the 8th patient in each dose group), the randomization method and treatment process are the same as those in the first 8 patients in this dose group.

The total number of subjects who are planned to enroll in each dose group is tentatively set as 8-20, which could be adjusted based on the obtained safety, efficacy and PK data.

The SRC will combine safety, tolerability, PK data, and preliminary efficacy to determine the RP2D for subsequent studies of HMPL-523 in adults with primary ITP.

Safety Assessments

All adverse events (AEs) from the first dose to 28 days after lase dose or before initiating a new anti-ITP treatment (whichever comes first), and SAEs occurring between the signing of informed consent and 28 days after the last dose of study drug, and SAEs related to study drug treatment post 28 days after the last dose of study drug or after the initiation of new anti-ITP therapy, whichever occurs first, will be collected. Subjects' AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

Efficacy Assessments

During the study, subjects will be assessed for disease-related symptoms/signs and platelet levels at scheduled visits every week for the first 8 weeks (including Week 8) of treatment and every 2 weeks thereafter.

Evaluation of pharmacokinetics

Blood samples will be collected from all subjects for PK analysis.

Randomization Methods and Steps

Subject enrollment will be confirmed by the sponsor prior to randomization, and if eligible, will perform randomization. By login of the Interactive Web Response System (IWRS) via the web, investigators will complete the IWRS worksheet, and register screening. Subjects who meet the criteria will be randomized to receive HMPL-523 or placebo in a blinding method according to the allocation ratio. The randomization number for each subject will be given by IWRS to Investigator.

After randomization, study treatment will be started on the same day.

A subject who terminates the study after signing the ICF and before randomization will be considered a "screen failure". Subjects who previously have failed screening can be allowed to rescreen once, but a new subject number will be provided and the random code will be reassigned via the IWRS. This requires case-by-case review by the sponsor.

Study Objectives

Primary objective:

- To evaluate the safety and tolerability of HMPL-523 in the treatment of adults with primary immune thrombocytopenia (ITP).
- To determine the recommended dose (the recommended Phase 2 dose [RP2D]) for subsequent clinical studies of HMPL-523 in adults with primary ITP.

Secondary objectives:

- To assess the preliminary efficacy of different doses of HMPL-523 in the treatment of adult primary ITP.
- To investigate the pharmacokinetics (PK) characteristics of HMPL-523 and its major metabolites in adult subjects with primary ITP.

Study Evaluation

Safety Evaluation

Adverse events will be adjudicated and graded according to NCI CTCAE 5.0, and safety and tolerability will be comprehensively evaluated by the incidence, severity, and outcome. The investigator should take appropriate treatments in time for the adverse event, and determine the relationship between the adverse event or SAE with the study drug. If serious safety events occur during the study, the sponsor and the investigator will jointly decide whether to terminate the study, and the sponsor may actively request to terminate the clinical study as appropriate.

The safety of the study drug will be evaluated by adverse events/SAEs, vital signs, physical examination, laboratory tests, 12-ECG.

Evaluation of Pharmacokinetics

The PK characteristics of plasma HMPL-523 and its main metabolites will be evaluated by the following indicators: maximum concentration at steady state ($C_{max,ss}$), trough concentration at steady state (Cmin,ss), time to maximum concentration at steady state ($T_{max,ss}$), elimination half-life ($t_{1/2}$), area under the plasma concentration-time curve at steady state within dosing interval ($AUC_{tau,ss}$), apparent clearance at steady state (CL/F_{ss}), apparent volume of distribution at steady state (Vd/F_{ss}) and mean residence time at steady state (MRT_{ss}).

Efficacy Evaluation

Efficacy will be evaluated by platelet count and WHO bleeding scoring criteria.

Primary Efficacy Endpoint:

Percentage of subjects with platelet count $\geq 30 \times 10^9$/L and doubling of the baseline level (without rescue treatment during treatment period) at two consecutive visits during the first 8 weeks (including Week 8) of the treatment period.

Secondary Efficacy Endpoints:

0-8 weeks

1. Percentage of subjects with platelet count $\geq 50 \times 10^9$/L at Week 2, 3, 4, 5, 6, 7 and 8 after dosing;
2. Percentage of subjects with platelet count $\geq 30 \times 10^9$/L and at least with an increase $\geq 20 \times 10^9$/L from baseline at Week 2, 3, 4, 5, 6, 7 and 8 after administration;
3. Percentage of subjects with platelet count $\geq 30 \times 10^9$/L and at least doubling of the baseline level at Week 2, 3, 4, 5, 6, 7 and 8 after administration;
4. Percentage of subjects with at least one platelet count $\geq 50 \times 10^9$/L;
5. Percentage of subjects with at least one platelet count $\geq 30 \times 10^9$/L and with an increase $\geq 20 \times 10^9$/L from baseline;
6. Time from start of dosing until first platelet count $\geq 50 \times 10^9$/L;
7. Time required from dosing initiation to first platelet count $\geq 30 \times 10^9$/L;
8. Time from start of dosing until the first platelet count with an increase $\geq 20 \times 10^9$/L from baseline;
9. Platelet count at each visit;
10. Percentage of subjects receiving rescue treatment;
11. Bleeding score at each visit according to WHO bleeding scoring criteria;
12. The maximum duration for subjects with platelet count $\geq 30 \times 10^9$/L and $\geq 50 \times 10^9$/L, respectively;
13. Cumulative duration of subjects with platelet count $\geq 30 \times 10^9$/L and $\geq 50 \times 10^9$/L, respectively;
14. Percentage of subjects with platelet count $\geq 30 \times 10^9$/L and with an increase $\geq 20 \times 10^9$/L from baseline (without rescue treatment during the treatment period) after 8 weeks of treatment (D57 visit);
15. Percentage of subjects with at least one platelet $\geq 30 \times 10^9$/L and doubling of the baseline level (without rescue treatment during the treatment period).

0-24 weeks

1. Percentage of subjects with platelet count ≥ 50 × 10^9/L in at least 4 of the last 6 scheduled visits (Week 14-24);
2. Percentage of subjects with platelet count ≥ 50 × 10^9/L at Week 24;
3. Proportion of patients with platelet count < 15 × 10^9/L at baseline, and ≥ 30 × 10^9/L with an increase ≥ 20 × 109/L from baseline at Week 24;
4. The maximum duration of platelet count ≥ 30 × 10^9/L and doubling of the baseline level;
5. Cumulative duration of platelet count ≥ 30 × 10^9/L and doubling of the baseline level;
6. Percentage of subjects with at least one platelet count ≥ 50 × 10^9/L at Week 8-24;
7. Maximum duration of platelet count ≥ 50 × 10^9/L;
8. Cumulative duration of platelet count ≥ 50 × 10^9/L;
9. Platelet count at each visit;
10. Percentage of subjects receiving rescue treatment;
11. Incidence of haemorrhages-related events.

Target Population

The population is persistent/chronic/refractory ITP with thrombocytopenia > 6 months.

Inclusion Criteria

Subjects must meet all of the following criteria to be enrolled:

1. Voluntarily sign the ICF;
2. Male or female patients aged 18-75 years;
3. Performance status score (ECOG score) 0-1;
4. Diagnosed with ITP and with decreased platelet count for more than 6 months prior to randomization;
5. At least for ITP first-line treatment ineffective, or relapse after treatment; or had poor response to splenectomy or postoperative relapse;
6. Relatively stable disease, WHO bleeding grade 0-1, no need of rescue treatment within 2 weeks by the investigator's judgment;
7. Laboratory tests meeting the following conditions (no treatment for this abnormality within one week before blood collection):

- The two platelet counts during the screening period (with an interval of at least 24 hours between the two examinations) are both less than 30 × 10^9/L;
- Hemoglobin ≥ 90 g/L (hemoglobin > 80 g/L can be enrolled if iron deficiency anemia is identified), white blood cells > 2.5 × 10^9/L, neutrophils > 1.8 × 10^9/L;
- Serum creatinine concentration ≤ 1.5 times of the upper limit of the normal reference range (ULN), and creatinine clearance ≥ 50 mL/min;
- Total bilirubin (TBIL), ALT and AST ≤ 1.5 × ULN;
- Serum amylase or lipase not above the ULN;
- International normalized ratio (INR) and activated partial thromboplastin time (APTT) values are not in excess of 20% of the normal range.

8. Male or female subjects of childbearing potential must agree to use effective contraceptive methods during the study and within 90 days after last study drug administration, such as double-barrier contraceptive methods, condoms, oral or injectable contraceptives, intrauterine devices, etc. Postmenopausal women (> 50 years of age and amenorrheic for more than one year) and surgically sterile women are exempt from this condition.

9. This study allows subjects to receive concomitant treatment with a stable dose of an anti-ITP agent as detailed below:

• Corticosteroids: stable dose (equivalent to prednisone ≤ 20 mg/day) for at least 2 weeks before randomization, or discontinued within 2 weeks before randomization;

• Danazol or azathioprine: stable dose for at least 3 months prior to randomization, or discontinued 4 weeks prior to randomization;

Exclusion criteria

The major exclusion criteria were secondary thrombocytopenia, history of severe cardio vascular disease, uncontrolled hypertension, and medical conditions which required long-term use of a drug that affects platelet function. Patients who were pregnant and lactating were excluded on the basis of safety considerations for early phase studies.

Study Treatment

Study Drug

HMPL-523 Tablets or HMPL-523 dummy tablets (placebo) are light yellow tablets in the strengths of 25 mg/tablet, 100 mg/tablet and 150 mg/tablet; packaged in white high-density polyethylene bottles, 30 tablets per bottle, and stored below 25°C.

Administration Method

On each visit day, subjects must be dosed at the study site.

HMPL-523 tablets or HMPL-523 dummy tablets (placebo), will be administered with 250 mL of warm water within 30 minutes after a meal.

- 100 mg dose group: 100 mg/time, QD × 8 weeks
- 200 mg dose group: 200 mg/time, QD × 8 weeks
- 300 mg dose group: 300 mg/time, QD × 8 weeks
- Other: SRC may adjust the above dosing regimen or add a new dosing regimen. If necessary (for example, in case of intolerance, such as abdominal pain), the drug can be administered twice per day at the same total daily dose.

Doses must be taken at the study site on each visit day and must be taken with 250 mL of warm water.

All patients will receive 16 weeks of open-label treatment with the current dose of HMPL-523 as assessed by the investigator following 8 weeks of blinded treatment.

Time of administration: Subjects should take the drug at a relatively fixed time each day. The actual administration time on the day before, the day of and the day after PK sampling should be accurately recorded.

Dose Modification

Study Drug Dose Modification

Eight subjects in each dose group will not undergo dose adjustment in the first 28 days of treatment; in other cases, it is recommended to adjust the dose according to the following rules. HMPL-523 treatment may be suspended in subjects experience the following TRAEs (CTCAE V5.0). If the adverse event recovers to baseline or Grade≤1 within 14 days after discontinuation, the administration can be resumed at a lower dose level, otherwise the drug should be permanently discontinued. The following dose reduction principles are provided for reference: It is recommended to perform dose reduction at 250 mg, 200 mg, 150 mg and 100 mg dose levels in turn (with the current dose level as the highest point), or divided into 2 doses when the total daily dose remains unchanged.

- ≥ G3 ALT increased, AST increased, or TBIL increased
- ≥ G3 lung infection
- ≥ G3 neutropenia
- Concomitant symptomatic interstitial lung disease
- Pancreatitis requiring therapeutic intervention
- Abnormal renal function requiring therapeutic intervention
- Significant AEs as judged by other investigators.

During the treatment period, study drug may be reduced by one dose level if with platelets > 250×10^9/L and < 400×10^9/L for 14 days, and if concomitant other anti-ITP treatment is allowed per protocol, the reduction on other anti-ITP treatment will give priority; if platelets are ≥ 400×10^9/L, study drug may be temporarily discontinued until platelets < 400×10^9/L and then reduced by 1 dose level.

Concomitant anti-ITP treatment dose adjustment

Dose modifications for protocol-allowed concomitant anti-ITP treatment may refer to the following criteria:

Platelet level	**Actions**
> 150×10^9/L and < 250×10^9/L for 14 days	25% dose reduction
> 250×10^9/L for 14 days	50% dose reduction

Up-regulation to a high dose is not allowed during or after a stable dose of concomitant anti-ITP treatment, and is considered rescue treatment if up-upregulated

Concomitant Medication

All medications and significant non-drug treatments (including supplements) must be recorded from 28 days prior to randomization through 28 days after the end of treatment.

Permitted Concomitant Medications

Subjects could not receive other concurrent anti-ITP treatment throughout the study, with the exceptions of:

- One of the agents in stable doses of corticosteroids, azathioprine, or danazol for ITP before randomization;
- Rescue treatment (including: platelet transfusion, intravenous gamma globulin, high-dose glucocorticoid pulse)

Subjects who will receive rescue treatment are considered to be non-responders to treatment during the

rescue treatment period, until the end of rescue treatment and with platelets < 30×10^9/L. It is considered a rescue treatment if adding other new anti-ITP therapy or increasing the dose or frequency of protocol allowed concomitant anti-ITP treatment.

Calculation of Sample Size and Statistical Analysis

Calculation of Sample Size

Three dose groups (cohorts) are initially proposed: 100 mg, 200 mg, and 300 mg, and 8 to 20 subjects per dose group (6 to 15 in HMPL-523 group; 2 to 5 in placebo group). The final sample size depends on the number of study cohorts and the number of subjects in each cohort group. For AEs with an incidence of 10%, 5%, or 1%, the probability of observing at least one AE is 46.9%, 26.5%, and 5.8%, respectively, for a minimum of 6 subjects taking HMPL-523, and 79.4%, 53.7%, and 14.0%, respectively, for a maximum of 15 subjects taking HMPL-523 in a given cohort.

Statistical Analysis

In general, the number of observations, mean, median, standard deviation, minimum, and maximum will be used for statistical description of continuous variables (e.g., age); the frequency of each category and its percentage will be used for statistical description of categorical variables. If data allowed, the Kaplan-Meier method will be used to calculate quartiles as well as the median and its 95% confidence interval (CI) for the time-to-event variables.

Statistical Analysis Set

The following analysis sets will be included in this study:

Intent-to-treat Analysis Set (ITT Set): includes all randomized subjects. Subjects will be grouped according to randomized group. This analysis set will be used for the analysis of all efficacy measures.

Safety Set (SS): includes subjects receiving at least one dose of study drug. Subjects will be grouped according to the actual treatment. This analysis set will be used for the analysis of all safety data.

Pharmacokinetics Analysis Set (PK set): includes subjects who will receive at least one dose of study drug and have PK blood samples collected and analyzed. This analysis set will be used for the analysis of plasma concentrations and PK parameters.

Analysis Method

Safety Analysis

All analyses of safety endpoints will be based on the SS.

The severity of AEs will be graded according to the NCI CTCAE, version 5.0 (Grade 1 to 5).

The incidence of TEAEs will be summarized by system organ class (SOC) and preferred term (PT), and further summarized according to the maximum severity of the TEAE and its closest relationship to the study drug at the SOC and PT levels.

Efficacy Analysis

All efficacy endpoints will be analyzed based on the ITT set.

The primary efficacy endpoint of this study is the percentage of subjects with platelet count ≥ 30×10^9/L and doubling of the baseline level (without rescue treatment during the treatment period) at two consecutive

visits during the first 8 weeks (including Week 8) of treatment. If the subject received rescue treatment due to disease aggravation during treatment, it will be considered as ineffective treatment.

For the primary efficacy endpoint, the Clopper-Pearson method will be used to calculate the exact 95% CI of the rate in each group, and the 95% CI of the difference in the response rate between the placebo group and HMPL-523 groups with different doses will be calculated according to the normal approximation method. The comparison test between groups applies the exact probability method. To explore the potential impact of prognostic factors that may affect efficacy, multivariate logistic regression analysis will be used with treatment (categorical variable) as well as possible prognostic factors in the model. Odds ratios (ORs) and their 95% CIs, as well as corresponding p-values, will be calculated by the model for treatment versus placebo.

For the analysis of other dichotomous secondary efficacy endpoints, the same statistical analysis method as that for the primary efficacy endpoint will be used.

For time-to-event variables (e.g., time from dosing to the first platelet count $\geq 50 \times 10^9$/L, maximum duration for a subject's platelet count persistently $\geq 50 \times 10^9$/L), the median and its 95% CI will be estimated using the Kaplan-Meier method. If there is a comparison, the log-rank test may be considered for the comparison.

Pharmacokinetics Analysis

All PK parameters will be statistically described by dose group based on PK set. Non-compartmental model will be applied to calculate PK parameters for plasma concentration data using Phoenix WinNonlin software. For the summary of PK parameters, the total number of cases, number of missing cases, mean, standard deviation, median, minimum, maximum, geometric mean and coefficient of variation of geometric mean will be reported. If necessary, the exponential model and analysis of variance model are considered to evaluate whether there is a dose proportionality.

Interim Analysis

To more precisely explore the optimal dose of HMPL-523 for the treatment of ITP, subjects in each dose cohort will be unblinded by a third-party statistical team after the first 8 subjects in each dose cohort have completed 8 weeks of treatment, to provide a phase summary data of safety and efficacy for this cohort to the sponsor. The SRC will further determine, based on this phase summary data, whether a new dose group needs to be explored, or a new dosing regimen needs to be explored, or the number of patients in one/several dose groups needs to be increased. Additional unblinded analyses may be added during the conduct of the study based on the data seen. Additional unblinded analyses added will be presented in the statistical analysis plan.

Study Result

Between May 30, 2019, and April 22, 2021, 62 patients were assessed for eligibility and 45 (73%) were randomly assigned (33 in the dose-escalation phase and 12 in the dose-expansion phase). Interim analysis indicated no protocol-specified safety events that would require termination of dose escalation. Based on 28-day safety data and results from the interim analysis, the safety review committee suggested investigating sovleplenib at 400 mg once a day, so an additional group was added. All enrolled patients received at least one dose of the study drug during the 8-week double-blind period (placebo [n=11] and sovleplenib 100 mg [n=6], 200 mg [n=6], 300 mg [n=16; six patients from the dose-escalation phase and ten from the dose-expansion

phase], and 400 mg [n=6]). Rescue unmasking did not occur during the study.

Overall, HMPL-523 was deemed safe and well tolerated in this group of subjects with ITP. MTD was not reached. During the 28-day, safety evaluation period, 2 Grade ≥2 treatment-related adverse events (TRAEs) occurred in the HMPL-523 group (1 event of hypertriglyceridemia in the 100 mg QD dose level and 1 event of anemia in the 200 mg QD dose level). During 0-8 weeks treatment period, the most frequently reported HMPL-523 TRAEs were increased aspartate aminotransferase (29%), alanine aminotransferase (ALT; 27%), and blood lactate dehydrogenase (22%). The safety profile of HMPL-523 was generally similar across all dose levels. There were no drug-related serious adverse events (SAEs) or drug-related treatment discontinuations reported in this study. Notably, there were no drug-related adverse events (AEs) of platelet count increased or thromboembolic events reported.

Efficacy was assessed with ORR (defined as the percentage of subjects whose platelet count reached $\geq 50 \times 10^9$/L at least once during the treatment period in the absence of rescue therapy) and durable response rate (DRR; defined as percentage of subjects whose platelet count reached $\geq 50 \times 10^9$/L at least 4 visits of 6 biweekly visits between Weeks 14 and 24 (inclusive) during the treatment period). As shown in Table 1, in the 8-week, double-blind treatment period, overall response with HMPL-523 administration (N = 34) was noted in 3 (50.0%), 2 (33.3%), 11 (68.8%), and 2 (33.3%) subjects at 100 (N = 6), 200 (N = 6), 300 (N = 16), and 400 (N = 6) mg QD dose levels, respectively. Durable responses were noted in 5 (31.3%) of subjects in 300 mg QD level but were not demonstrated in any of the subjects at the 200 and 400 mg QD dose levels (no subjects in 100 mg dose level were evaluable for this measure). Subjects responded to therapy quickly, with the first onset of response (defined as platelet counts $\geq 30 \times 10^9$/L) observed in 75% of subjects within median of 1.1 weeks of initiation of HMPL-523 treatment at 300 mg QD dose. No subjects reached a platelet count beyond 300×10^9/L, indicating potential for low thromboembolic risk.

Based on the safety and overall efficacy profile, 300 mg QD was determined as the RP2D. The ORR in the 300 mg QD dosing group for all subjects, including the double-blind and open-label periods (N = 20), was 80% (16 subjects). The DRR in this subject population was 40% (8 subjects).

Table 1: Efficacy in Subjects Treated at Different Dose Levels

Criteria		**HMPL-523, N = 34**				**Placebo**
		100 mg N = 6	**200 mg N = 6**	**300 mg N = 16**	**400 mg N = 6**	**N = 11**
Overall response rate, n (%)	PLT $\geq 50 \times 10^9$/L at least once during the treatment period in the absence of rescue therapy[a]	3 (50.0)	2 (33.3)	11 (68.8)	2 (33.3)	1(9.1)
Durable response rate, n (%)	PLT $\geq 50 \times 10^9$/L in at least 4 visits of 6 biweekly visits between	NA[b]	0[c]	5 (31.3)	0	

Criteria		HMPL-523, N = 34				Placebo
		100 mg N = 6	200 mg N = 6	300 mg N = 16	400 mg N = 6	N = 11
	Weeks 14 and 24 (inclusive) during the treatment period					

Abbreviations: NA = not applicable; ORR = overall response rate; PLT = platelet

[a] This table presents ORR for 0–8-week double-blind period only.

[b] For 100-mg dose, N = 0 in open-label period.

[c] For 200-mg dose, N = 4 in open-label period.

The Pharmacokinetic of HMPL-523 in this study has been characterized on Day 15 following multiple 100 to 400 mg QD doses in the dose-escalation phase and 300 mg QD doses in the dose-expansion phase in Chinese subjects with ITP. All subjects were instructed to take HMPL-523 at approximately 30 minutes after a meal in this study.

Following multiple doses of HMPL-523 from 100 to 400 mg QD, the median t_{max} value for HMPL-523 was 4.0 hours postdose. The systemic exposure (maximum steady-state plasma drug concentration [$C_{max,ss}$] and $AUC_{tau,ss}$) increased in a dose-proportional manner across the dose range of 100 to 400 mg QD. The geometric mean $C_{max,ss}$, minimum steady-state plasma drug concentration ($C_{min,ss}$), and $AUC_{tau,ss}$ of HMPL-523 following the RP2D 300 mg QD were 163 ng/mL, 41.3 ng/mL, and 2070 h × ng/mL, respectively. The CL_{ss}/F on Day 15 ranged from 130 to 173 L/h. (see table 2)

Table 2 Pharmacokinetic parameters of HMPL-523

PK parameters	100 mg (N=6)	200 mg (N=6)	300 mg (N=16)	400 mg (N=6)
$C_{max,ss}$(ng/mL)	49.456	86.137	**163.231**	238.05
$C_{min,ss}$(ng/mL)	15.192	19.864	**41.334**	66.963
$t_{1/2}$(h)	12.660 ±2.6723	11.676 ±2.1022	12.348 ±3.6727	11.687 ±0.8872
$AUC_{tau,ss}$(h*ng/mL)	**661.1081**	**1156.9678**	**2067.2371**	**3065.6213**

Example 2 Efficacy and safety of sovleplenib in adult patients with primary immune thrombocytopenia in China (ESLIM-01): a randomized, double-blind, placebo-controlled phase 3 study

Overall Study Design

This is a randomized, double-blind, placebo-controlled phase III clinical study in adult patients with persistent or chronic primary ITP. This study is intended to evaluate the efficacy and safety of HMPL-523 versus placebo in treatment of the ITP patients who had an insufficient response to previously at least **one anti-ITP standard** therapy.

This study includes one primary study and one sub-study.

Primary study: 24-week randomized, double-blind, placebo-controlled treatment

About 186 screening eligible patients will be 2:1 randomized (HMPL-523: placebo=2:1) based on baseline platelet count ($\leq 15\times10^9$ /L vs. $>15\times10^9$ /L), history of splenectomy (yes/no) and combined anti-ITP treatment at baseline (yes/no), and receive HMPL-523 and placebo 300 mg once per day orally for 24 weeks, respectively.

The efficacy and safety will be evaluated regularly.

PK blood will also be collected in this period, as to analyze PK profile and PK/PD;

The impact of study treatment on the quality of life will be evaluated using SF-36.

Sub-study: a 24-week open-label HMPL-523 study design

Cohort 1: The patients with persistent platelet count $<50\times10^9$ /L with12 weeks of treatment in the primary study, or those who have been completed 24 weeks of treatment in the primary study can be considered to be included in the sub-study to receive HMPL-523 open-label therapy (the dosage was consistent with that received at the end of study of primary study) until 76 weeks after enrolment of the last patient in sub-study Cohort 2, if they are judged by investigators that they can benefit from HMPL-523 treatment and they also meet the eligibility criteria for the sub-study.

Cohort 2: Adult ITP patients (platelet count $< 30 \times 10^9$ /L within the 24 hours prior to enrolment, disease duration > 3 months, previously received at least one anti-ITP treatment) were enrolled and received HMPL-523 300 mg QD open-label therapy until 76 weeks after enrolment of the last patient in the cohort.

PK blood can be collected in this period, as to analyze PK profile and PK/PD. (only for patients enrolled in cohort 1)

The efficacy and safety will be evaluated regularly.

Follow-up period:

The patients will enter the 28-day safety follow-up after the last dose of primary study treatment (patients who entered the sub-study at 12 weeks of treatment in the main study are excluded).

The efficacy will be evaluated through platelet counts, WHO bleeding scale and the proportion of rescue therapy. The safety will be evaluated through adverse events, laboratory examinations, vital signs and ECG. The PK profile of HMPL-523 will also be evaluated in this study. The effect of study treatment on the quality of life in the primary study, and the efficacy of HMPL-523 in treatment of ITP in the sub-study will also be explored.

Study Objectives and Endpoints

Primary Objectives and endpoint

The Primary Objectives is to evaluate the efficacy of HMPL-523 in terms of sustained platelet response in treatment of ITP in adults in the primary study, as compared with placebo.

The primary endpoint is durable response rate, defined as proportion of patients with a platelet count of $\geq50\times10^9$/L on at least 4 of 6 ≥scheduled visits between week 14–24.

Secondary Objectives and Endpoints

1. To evaluate the efficacy of HMPL-523 compared with placebo in the 24-week double-blind treatment period

- The endpoints included: overall response rate (defined as proportion of patients with at least one

platelet count of ≥50×10⁹/L, except for that induced by rescue treatment) in 0–12 weeks; proportion of patients with platelet count of ≥30×10⁹/L plus an increase of ≥20×10⁹/L from baseline in 0–12 weeks, for the patients with baseline platelet count below 15 ×10⁹/L(except for that induced by rescue treatment); proportion of patients with platelet count of ⩾30×10⁹/L plus an increase of ⩾ 20×10⁹/L from baseline in 0–24 weeks, for the patients with baseline platelet count below 15 ×10⁹/L(except for that induced by rescue treatment); time to response (defined as time from treatment initiation to first platelet count reaching ≥50×10⁹/L, except for that induced by rescue treatment); bleeding incidence and severity per WHO bleeding score in 0–12 weeks and 0–24 weeks; proportion of patients with two consecutive platelet count of ≥30×10⁹/L and doubling from the baseline in 0–24 weeks (except for that induced by rescue treatments); proportion of patients who received rescue treatment pre-defined in protocol in 0–24 weeks; proportion of patients who reduced or interrupted baseline concomitant treatment for anti-ITP in 0–24 weeks.

2. To evaluate the safety and tolerability of HMPL-523 in the 24-week double-blind treatment period, as compared with placebo

- Endpoint: Adverse events (AE), clinical laboratory examination, vital sign, physical examination and electrocardiography (ECG);

3. To evaluate the pharmacokinetic (PK) profile of HMPL-523 in Chinese adult patients with ITP

- Endpoint: Plasma concentration of HMPL-523 and its main metabolites at steady state 2 and 4 hours post dose ($C_{2h,ss}$, $C_{4h,ss}$) and steady-state trough concentration ($C_{min,ss}$)

Exploratory Objectives and Endpoints

1. To evaluate the effect of HMPL-523 treatment in the primary study on the quality of life in Chinese adult patients with ITP

- Endpoint: Quality of life was assessed using the 36-Item Short Form Health Survey (SF-36) scale at baseline, week 12, week 24 or the end of double-blind treatment, in terms of physical functioning, general health status, social functioning, and emotional role to determine the degree of improvement in quality of life compared with baseline.

2. Pharmacokinetic/pharmacodynamics (PK/PD) correlation between drug exposure and platelet response

- Endpoint: Correlation between steady-state C_{min} etc. and efficacy variables.

3. The long-term safety of HMPL-523 in treatment of Chinese adults with ITP in sub-study

- Endpoint: Adverse events (AE), clinical laboratory examination, vital sign, physical examination and electrocardiography (ECG);

4. The sustained efficacy of HMPL-523 in treatment of Chinese adults with ITP in sub-study

- Endpoint: Percentage of patients with platelet counts <50×10^9 /L (except that induced by rescue treatment) for ≤2 times (at an interval of at least 2 weeks) within 12 weeks after the first platelet count ≥50×10^9 /L in sub-study.

Study Evaluation

Efficacy Evaluation

The efficacy will be evaluated through platelet count, WHO bleeding scale and the proportion of rescue therapy. The efficacy will be evaluated once every 2 weeks during treatment.

Safety Evaluation

All the recruited patients need to be closely monitored for safety upon acquisition of informed consent form, until 28 days after the last dose or withdrawal of informed consent and refusal of subsequent safety visit, whichever comes first. All the serious adverse events (SAEs) need to be collected from the signature of informed consent form to the first dose; all the AEs/SAEs need to be collected from the first dose to 28 days after the last dose; the SAEs confirmed by investigators as having a reasonable possibility of correlation with the study drug need to be reported upon 28 days after the last dose or end of study treatment and the start of other anti-ITP treatment. The fatal event occurred within 28 days after the last dose needs to be reported as SAE. The Adverse Events will be graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

Pharmacokinetic Evaluation

The concentrations of HMPL-523 and its metabolites in blood samples will be detected in central laboratory. The collection, storage and transshipment of blood samples will be described in detail in the laboratory manual. The biological analysis method and experiment process will be described in detail in the clinical study report. The steady-state pharmacokinetic profile of HMPL-523 and its metabolites will be mainly evaluated in ITP patients. The PK blood specimen will be collected from all the patients in the master study, and from the patients who have signed the optional informed consent for PK blood collection only in the sub-study.

Quality of Life Assessments

The effect of study treatment on the quality of life will be evaluated using SF-36.

Visit Frequency

In the screening period, patients must go to the study site for collection of basic information and baseline evaluation of each efficacy and safety variable.

During the screening period, patients will undergo basic information collection and baseline assessment of efficacy and safety indicators at the study site.

The treatment duration of the master study will be 24 weeks, the efficacy and safety evaluation will be performed weekly at W1 and W2, and biweekly from W2 (not inclusive) to W24. Among them, 12-lead ECG, biochemistry, urinalysis, fecal routine test will be performed once every 4 weeks; pregnancy test will be performed once every 4 weeks; SF-36 assessment will be performed at baseline, W12, W24 or end of double-blind period. PK samples will be collected biweekly during W1 to W8.

For Cohort 1 in sub-study, efficacy and safety evaluations will be performed at W1, W4, and once every 4 weeks thereafter, and once every 4 weeks for pregnancy test; for Cohort 2 in sub-study, efficacy and safety evaluations will be performed once every 4 weeks during the first 24 weeks (inclusive), and once every 8 weeks thereafter. PK samples will be collected during W1 to W8 (for Cohort 1 in sub-study only).

The follow-up period for this study will be 4 weeks, and patients must return to the study site weekly for follow-up 4 weeks after the last dose.

The investigator may conduct unscheduled visits as necessary during the study.

Study Population

Primary study and sub-study cohort 1: Diagnosed chronic primary immune thrombocytopenia in adults (duration ≥12 months); Average platelet count <30×10^9/L at 3 visits (platelet count <35×10^9/L at any of them) within 3 months prior to randomization; insufficient response or recurrence after previous one or more anti-ITP treatments.

Sub-study cohort 2: Adult patients with immune thrombocytopenia (platelet count <30×10^9/L before enrollment, duration >3 months, previously received at least one anti-ITP treatments) are enrolled.

Inclusion/exclusion criteria for the primary study

Inclusion Criteria:

Patients must meet all the following conditions to be enrolled in this study:

1. Voluntarily signed ICF;
2. Male or female aged 18 to 75 years;
3. Performance status score (Eastern Cooperative Oncology Group [ECOG] score) 0-1;
4. Primary ITP diagnosed more than 12 months prior to randomization;
5. Failed or relapsed after treatment with at least one standard anti-ITP medication, including glucocorticoids, immunoglobulins, and altrombopag (or one of the agents with the same mechanism). Ineffectiveness is defined as a platelet count < 30×10^9/L or < 2 times the baseline value, or bleeding after treatment; recurrence defined as platelet count < 30×10^9/L or < 2 times the baseline value or bleeding again after effective treatment;
6. Patients must have a history of responding to prior ITP therapy;
7. One concomitant anti-ITP treatment is allowed in this study, however, and the following criteria are required if the patient is receiving concomitant anti- ITP treatment:
    a. Glucocorticoids: daily dose <20 mg prednisone equivalent and stable dose for 4 weeks prior to randomization;
    b. Danazol: stable dose for 3 months prior to randomization;
    c. Immunosuppressants: only one of azathioprine, cyclosporine A, mycophenolate mofetil is allowed and the dose has been stable for 3 months prior to randomization.
8. Relatively stable disease, WHO bleeding grade 0-1, not requiring rescue treatment within 2 weeks at the discretion of the investigator;
9. Results of laboratory tests meeting the following requirements (no treatment for this abnormality 1 week prior to blood sampling):
    a. The average platelet count of 3 times tests within 3 months prior to randomization was <30×10^9/L, and any of them was ≤35×10^9/L, where one value was the most recent test result performed in 28 days prior to randomization provided by the patient (excluding result induced by the rescue treatment), and the other 2 values were tested during the screening period with

the interval as at least 3 days. The first test during the screening period must be completed at least 4 days before randomization (excluding results induced by rescue treatment);

b. Hemoglobin ≥100 g/L, neutrophil count >1.5×10^9/L;

c. Total bilirubin (TBIL), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤1.5 × upper limit of the normal reference range (ULN);

d. Serum creatine ≤1.5×ULN and creatinine clearance ≥50 mL/min;

e. Serum amylase and lipase ≤1.5×ULN;

f. International normalized ratio (INR) and activated partial thromboplastin time (APTT) values are within 20% of the normal ranges.

10. Male or female patients of childbearing potential must agree to use effective contraceptive methods during the study and within 90 days after last dose of study drug, e.g., double barrier contraceptive method, condom, oral or injectable contraceptives, intrauterine device, etc. Postmenopausal women (>50 years old and no menses for >1 year) and surgically sterilized women are not subject to this condition.

Exclusion Criteria:

The subjects must be excluded from this study when any one of the following criteria is met:

1. Patients with documented secondary etiology of ITP (e.g., untreated Helicobacter pylori infection, leukemia, lymphoma, common variable immunodeficiency, systemic lupus erythematosus, past history of autoimmune thyroid disease) or medical therapy (e.g., heparin, quinine, antimicrobial agents, anticonvulsants), or multiple immune cytopenias (e.g., Evan's syndrome);
2. Patients who developed clinical significant bleeding requiring immediate platelet adjustment (e.g., menorrhagia with significant decrease in hemoglobin);
3. Patients who presented with clinically symptomatic gastrointestinal bleeding (e.g., hematemesis, tarry stool, but a positive occult blood test without any signs or symptoms of gastrointestinal bleeding was not considered "clinically symptomatic", or with exceptioni of bleeding from hemorrhoids) within 6 months prior to the screening visit;
4. Patients with a history of significant organ transplantation or hematopoietic stem cell/bone marrow transplantation;
5. Patients have received vaccination 8 weeks prior to randomization; or is scheduled to receive vaccination during the course of the study;
6. Patients who have undergone splenectomy within 12 weeks before randomization;
7. Patients who have undergone major surgery within 4 weeks prior to randomization, or need major elective surgery during the study;
8. Patients with a past history of malignant tumor (except cured cutaneous basal cell carcinoma or cervical carcinoma in situ);
9. History of significant arterial/venous embolic disease;
10. History of intracranial hemorrhage or severe bleeding from other vital organs;

11. History of serious cardiovascular disease, such as Grade III/IV congestive heart failure, arrhythmia or angina requiring medical treatment, unstable angina pectoris, coronary artery stenting, angioplasty, or coronary artery bypass grafting, or corrected Q-T interval (QTc) ≥ 450 ms;
12. Hypertension uncontrolled by medications (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg);
13. Patients with severe gastrointestinal diseases, such as dysphagia, active gastric ulcer, unable to take oral drugs or oral drugs with absorption disorders;
14. Human immunodeficiency virus (HIV) infection, or hepatitis B (if hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb] positive, hepatitis B virus deoxyribonucleic acid (HBV DNA) should be confirmed if it is positive), or hepatitis C virus infection (hepatitis C virus ribonucleic acid [HCV RNA] positive), or cirrhosis;
15. Clinically significant active infection that is not controlled (e.g., sepsis, pneumonia, or abscess), or is associated with serious infection (leading to hospitalization or requiring injection of antibiotics) within 6 weeks prior to therandomization;
16. Patients who have received intravenous gamma globulin or platelet transfusion within 2 weeks prior to randomization, or other treatment to elevate platelets (including but not limited to glucocorticoids, thrombopoietin, thrombopoietin receptor agonists, cyclosporine A, mycophenolate mofetil, etc.) within 4 weeks prior to randomization, except for those meeting the inclusion criteria 7;
17. Patients who have received rituximab treatment within 14 weeks prior to randomization;
18. Patients who have received Traditional Chinese Medicine treatment within 1 week before randomization;
19. Requiring long-term/continuous treatment with drugs that have an effect on platelet function, including but not limited to aspirin, clopidogrel, ticagrelor, non-steroidal anti-inflammatory drugs (NSAIDs), or anticoagulant therapy;
20. Taking strong CYP3A inhibitors or inducers (3 weeks for Hypericum Perforatum) 2 weeks or 5 half-lives (whichever is longer) prior to randomization;
21. Have participated in a clinical study of a drug or invasive medical device 4 weeks prior to randomization (or within 5 half-lives of the study drug prior to randomization, whichever is longer);
22. Prior treatment with Syk inhibitors (e.g., fostamatinib);
23. Known hypersensitivity to the active ingredient or excipients of the study drug;
24. Patients with severe psychological or mental disorders;
25. Alcoholics or drug abusers;
26. Female patients who are pregnant and lactating;
27. Patients who, in the opinion of the investigator, are not suitable for this study.

Inclusion/exclusion criteria for the sub-study

Inclusion Criteria:

For cohort 1 only (patients previously treated in the primary study):

Patients must meet all the following conditions to be enrolled in this study:

1. Voluntary signning of the ICF for the sub-study;
2. Performance status score (ECOG score) 0-1;
3. Relatively stable disease, WHO bleeding grade 0-1, not requiring rescue treatment within 2 weeks as judged by the investigator;
4. There is no increase in the type, dose, or frequency of concomitant anti- ITP therapy compared with the master study;
5. Patients who have received the treatment in the primary study for 12 weeks and have persistent platelet count of $<50\times10^9$/L during this period (platelet count should be $<50\times10^9$/L before enrollment if rescue treatment was received during the mast study), or have received the treatment in the master study for 24 weeks (for patients who have already received free-of-charge drugs, the anti-ITP therapy at the end of the master study should be remained consistently), and be assessed by the investigation as having a benefit. Benefit is defined as patients who have durable response (platelet count $\geqslant50\times10^9$/L on at least 4 of 6 scheduled visits of Week 14 to 24), or durable clinical benefiters (platelet count $\geqslant30\times10^9$/L on at least 4 of 6 scheduled visits of Week 14 to 24, and with an increase from baseline for 20×10^9/L), or an improvement in bleeding score;
6. The W12 visit date for the master study and the first dose date for the sub-study are expected to have an interval of $\leqslant$ 7 days, and patients who do not have a drop in platelet count to $< 50\times10^9$/L due to rescue treatment during the master study may extend to 14 days (only for patients who enter the sub-study at 12 weeks of the master study treatment);
7. Laboratory tests meeting the following conditions within 7 days (inclusive) prior to enrollment in the sub-study:
    a. Hemoglobin $\geqslant$100 g/L, neutrophil count $>1.5\times10^9$/L;
    b. TBIL, ALT and AST$\leqslant1.5\times$ULN;
    c. Serum creatinine $\leqslant1.5\times$ULN, and creatinine clearance $\geqslant$50 mL/min;
    d. Serum amylase and lipase $\leqslant1.5\times$ULN;
    e. INR and APTT values are not exceeding 20% of normal ranges.
8. Female patients of childbearing potential must agree to use highly effective treatment of contraception from screening until 30 days after discontinuation of study treatment, and agree not to donate eggs (oocytes) for reproductive purposes during this period. Subjects must not be breastfeeding and must have a negative pregnancy test (if with a childbearing potential).
9. Male subjects with fertile female partners must consent to use barrier contraception during the study period and for 30 days after the termination of study treatment. Subjects should refrain from donating or freezing sperm between the start of dosing and 30 days after termination of study treatment.

For Cohort 2 only:

Patients must meet all of the following criteria to be enrolled:

1. Voluntary signning of the ICF for the sub-study;
2. Males of females aged 18-75 years old;
3. Performance status score (ECOG score) 0-1;
4. Relatively stable disease, WHO bleeding grade 0-1;
5. Platelet count < 30×109/L within 24 hours prior to enrollment, with duration of disease longer than 3 months, and have received at least one anti-ITP treatment;
6. Laboratory tests meeting the following conditions within 7 days (inclusive) prior to enrollment in the sub-study (no treatment for this abnormality within 1 week prior to blood collection):
   a. hemoglobin ≥90 g/L, neutrophil count >1.5×10^9/L;
   b. TBIL, ALT and AST≤1.5×ULN;
   c. serum creatinine ≤1.5×ULN and creatinine clearance ≥50 mL/min;
   d. serum amylase and lipase ≤1.5×ULN;
   e. INR and APTT values are not exceeding 20% of normal ranges.
7. Concomitant anti-ITP therapy is permitted in this study, regardless of the type, number, and dose, but the dose should be stable for 4 weeks before enrollment (2 weeks for glucocorticoids stable dose);
8. Female patients of childbearing potential must agree to use highly effective treatment of contraception from screening until 30 days after discontinuation of study treatment and agree not to donate eggs (oocytes) for reproductive purposes during this period. Subjects must not be breastfeeding and must have a negative pregnancy test (if with a childbearing potential).
9. Male subjects with fertile female partners must consent to use barrier contraception during the study period and for 30 days after the termination of study treatment. Subjects should refrain from donating or freezing sperm between the start of dosing and 30 days after termination of study treatment.

Exclusion Criteria:

Only for cohort 1 (patients previously treated in the primary study):

The subjects must be excluded from this study when any one of the following criteria is met:

1. Treatment < 12 weeks in the primary study for any reason other than lack of efficacy;
2. Has received live vaccine within 8 weeks prior to Day 1 (baseline visit); or plan for immunization with live vaccine during the study;
3. History of important arterial / venous embolic disease;
4. History of serious cardiovascular disease (e.g., grade III/IV congestive heart failure, arrhythmia or angina pectoris requiring drug therapy, unstable angina pectoris, intracoronary stent implantation, angioplasty or coronary artery bypass grafting, or QTc ≥450 ms);
5. Significant active infection that is not controlled clinically (e.g., sepsis, pneumonia or abscess),

or serious infection within 6 weeks prior to randomization (leading to hospitalization or requiring treatment with antibiotic injections);

6. Hypertension that can not be controlled with drugs (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg);

7. Received a blood transfusion or blood product (except IVIg for rescue therapy) within 2 weeks prior to enrolment;

8. Requiring long-term/continuous use of the drugs that may affect platelet function [including but not limited to aspirin, Clopidogrel, ticagrelor, NSAIDs, etc.], or anticoagulants;

9. Intake of potent CYP3A inhibitor or inducer two weeks (three weeks for Hypericum perforatum) or 5 half-lives prior to randomization (whichever is longer);

10. Known allergy to the active ingredient or excipient of study drug;

11. Presence of serious psychological or mental disorder;

12. Alcoholic or drug abuser;

13. Female patients in pregnancy or breast feeding;

14. Being unsuitable to participate in this study, as considered by investigators.

Only for cohort 2:

The subjects must be excluded from this study when any one of the following criteria is met:

1. Evidence on the presence of secondary causes of immune thrombocytopenia;

2. Clinically symptomatic gastrointestinal hemorrhage within 6 months prior to screening visit (e.g., haematemesis, tarry stool, however, the positive occult blood test without any sign or symptom of gastrointestinal hemorrhage will not be considered as "clinically symptomatic", or hemorrhoids hemorrhage is one exception);

3. known history of vital organ transplantation or hematopoietic stem cell / bone marrow transplantation;

4. Has received live vaccine within 8 weeks prior to Day 1 (baseline visit); or plan for immunization with live vaccine during the study;

5. Splenectomy within 12 weeks prior to randomization;

6. Major surgery within 4 weeks prior to the randomization, or plan for major elective surgery during the study;

7. Previous history of malignant tumors (except for the basal cell carcinoma of skin or cervical carcinoma in situ that have been cured);

8. History of important arterial / venous embolic disease;

9. History of intracranial hemorrhage or severe bleeding of other important organs;

10. History of serious cardiovascular disease (e.g., grade III/IV congestive heart failure, arrhythmia or angina pectoris requiring drug therapy, unstable angina pectoris, intracoronary stent implantation, angioplasty or coronary artery bypass grafting, or QTc ≥450 ms);

11. Hypertension that can not be controlled with drugs (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg);

12. Previous history of serious gastrointestinal disease, such as dysphagia, active gastric ulcer, inability to take drugs orally or absorption disorder for oral drugs;

13. Human immunodeficiency virus (HIV) infection, or hepatitis B (in case of positive HBsAg or HBcAb, positive HBV DNA needs to be determined), or hepatitis C (positive HCV RNA), or liver cirrhosis;

14. Significant active infection that is not controlled clinically (e.g., sepsis, pneumonia or abscess), or serious infection within 6 weeks prior to randomization (leading to hospitalization or requiring treatment with antibiotic injections);

15. Having received Rituximab within 14 weeks prior to randomization;

16. Having received traditional Chinese medicine within 1 week prior to randomization;

17. Requiring long-term/continuous use of the drugs that may affect platelet function [including but not limited to aspirin, Clopidogrel, ticagrelor, NSAIDs, etc.], or anticoagulants;

18. Intake of potent CYP3A inhibitor or inducer, as well as sensitive or narrow therapeutic window substrates of CYP3A, CYP1A2 or CYP2B6 two weeks (three weeks for Hypericum perforatum) or 5 half-lives prior to randomization (whichever is longer);

19. Having participated in the clinical study for drugs or invasive medical device 4 weeks prior to randomization (or within 5 half-lives of the study drug prior to randomization, whichever is longer);

20. Known allergy to the active ingredient or excipient of study drug;

21. Presence of serious psychological or mental disorder;

22. Alcoholic or drug abuser;

23. Female patients in pregnancy or breast feeding;

24. Being unsuitable to participate in this study, as considered by investigators.

Restrictions during the study

During the study, patients are not allowed to use grapefruit or grapefruit juice, should not eat large amount of grapefruit and bigarade (as well as other products containing them, e.g., grapefruit juice or marmalade), and should not eat more than one cup (120mL) grapefruit juice or half grapefruit, or 1-2 spoons (15g) marmalade per day. Intake of drugs or excessive alcohol is prohibited.

Study Treatment

Study drug

HMPL-523 Acetate tablet or HMPL-523 placebo is light yellow tablet, in a specification of 100 mg and 150 mg; packaged in a white high-density polyethylene bottle, 30 tablets per bottle, and stored below 25°C.

Administration method

Patients must take the drugs at the study site on each visit day.

HMPL-523 tablet or HMPL-523 analogue tablet (placebo) will be taken with 240 mL warm water within one hour after meal.

During the study, every effort should be made to guarantee that the patients receive the study drug according to the study protocol. It is recommended to take the drug at a fixed time every day; if the dose of

study drug is missed for any reason for more than 12 hours, it can not be supplemented, and the next dose will be administered as fixed at the next scheduled time. In case of vomiting after administration, it is not advised to supplement the dose, unless intact tablet is seen. Missed dose or vomiting after administration must be recorded.

Primary study

Screening eligible patients will be randomized into HMPL-523 group or placebo group to receive 300 mg HMPL-523 or placebo once per day (QD) orally for 24 weeks, respectively.

Sub-study

Cohort 1: patients with persistent platelet count of $<50\times10^9$/L through the first 12 weeks of treatment in the primary study, or complete 24-week treatment (patients who have already received the free-of-charge drugs need to remain consistent with their anti-ITP treatment at the end of the primary study), and at the discretion of investigator, who are benefiting from receiving current study treatment, and meet the inclusion criteria for the sub-study, could be considered for entering the sub-study to receive open-label HMPL-523 treatment, with the dose consistent with that currently receiving. The maximum duration of sub-study treatment could be up to 76 weeks after enrolment of the last patient in Sub-study Cohort 2.

Cohort 2: Adult ITP patients (platelet count $< 30 \times 10^9$ /L in the 24 hours prior to enrolment, disease duration > 3 months, previously received at least one anti-ITP treatment) were enrolled and received HMPL-523 300 mg QD open-label treatment until 76 weeks after enrolment of the last patient in this study.

Dose adjustment of study drug

Recommendations on dose adjustment of study drug for adverse events:

Dose of HMPL-523 can be interrupted in case the following drug related adverse events occur (CTCAE v5.0). If the adverse event is recovered to baseline or ≤grade 1 within 14 days after drug discontinuation, the dose can be resumed at one lower dose level, or the drug needs to be discontinued permanently. The following principles on dose down-titration are for reference: it is recommended to down-titrate the dose according to 200 mg and 100 mg dose level, and it can also be considered that the total daily dose can be divided into two doses when it remains unchanged. If dose down-titration occurs for drug related adverse event, the dose of HMPL-523 can be considered to be recovered upon evaluation by investigators, after the event is recovered.

- ≥ Grade 3 pulmonary infection
- ≥Grade 3 neutropenia
- Interstitial lung disease with symptoms
- Pancreatitis requiring treatment intervention
- Abnormal renal function requiring treatment intervention
- Other important adverse events judged by investigators

Recommendations on dose adjustment of study drug for elevated platelet count during treatment:

When the platelet count is $\geq250\times10^9$ /L for consecutive 2 weeks or $\geq400\times10^9$ /L at any time, reduction of the dose of study drug can be considered, to 200 mg and 100 mg sequentially.

Concomitant medications

Concomitant anti-ITP treatment

At most one combined anti-ITP treatment is allowed during primary study and sub-study Cohort 1, and the following criteria need to be met:

- The dose of glucocorticoid has been stable for 4 weeks prior to randomization (<20mg Prednisone equivalent)
- The dose of Danazol has been stable for 3 months prior to randomization
- The dose of immunosuppressant (only including Azathioprine, Ciclosporin A, Mycophenolate mofetil) has been stable for 3 months prior to randomization.

Concomitant anti-ITP treatment with no restrictions on the type, number and dose of treatments is allowed during sub-study Cohort 2, provided that the dose is stable for 4 weeks prior to enrolment (with a 2-week stabilization period for glucocorticoid doses).

Rules for dose adjustment of concomitant anti-ITP treatment during the study:

Dose reduction or discontinuation is allowed only for dose adjustment, and dose increase is not permitted, otherwise it will be regarded as rescue therapy. Dose reduction of concomitant anti-ITP treatment can be considered when platelet counts meet the following criteria during the study period:

- platelet count of $\geq 100\times10^9$/L lasting for 4 weeks
- platelet count of $\geq 250\times10^9$ lasting for 2 weeks;

Rescue treatment

The rescue treatment allowed in the protocol includes platelet transfusion, intravenous gamma globulin (IVIg), and glucocorticoid shock therapy. When patients require rescue treatment during the study period, IVIg is recommended in preference to glucocorticoid shock therapy, which is generally not recommended unless very necessary.

At any time during the study, patients can receive rescue treatment if considered by investigators as necessary. The patients receiving rescue treatment will be considered as no response to treatment during rescue treatment, until end of rescue treatment and platelet count $<50\times10^9$ /L.

Statistical Analysis and Calculation of Sample Size

Determination of Sample Size

The sample size is calculated based on the following assumptions:

- The response rate of the primary endpoint is 18% in HMPL-523 treatment group;
- The response rate of the primary endpoint is 2% in placebo group;
- The overall significance level is one-sided 0.025;
- The power is 90%;
- The dropout rate is 15%;
- The randomization ratio of treatment group: control group = 2:1;

Based on the above assumptions, 186 patients are expected to be enrolled in this study and will be randomized in a 2:1 ratio into HMPL-523 group (124 patients) and placebo group (62 patients). The sample size is calculated using PASS 11, based on Mantel-Haenszel test.

Based on clinical trial results for other Syk inhibitor, the proportion of patients randomly assigned to sovleplenib or placebo reaching the primary endpoint was hypothesized to be 18% or 2%, respectively. With this assumption, combining with the 2:1 allocation ratio and a dropout rate of 20%, a sample size of 186 patients (124 for sovleplenib group and 62 for placebo group) with primary ITP was estimated to provide the power of 90% to reject a null hypothesis at a two-sided significance level α of 0.05.

All the efficacy endpoints were assessed in the intention-to-treat (ITT) analysis set, defined as all randomized patients. Sensitivity analyses of the primary endpoint were performed in the per-protocol set (PPS), defined as patients in ITT analysis set without any major protocol deviations that could affect the assessment of the primary endpoint. The safety analysis set included patients who had received at least one dose of study drug during the treatment.

Platelet values which were affected by rescue therapy were not used for efficacy endpoints derivation.

For the primary endpoint, the exact 95% CIs of the response rate were calculated using the Clopper-Pearson method, and the difference between treatment groups was analyzed using a Cochran-Mantel-Haenszel chi-square test, adjusted for stratification factors. For sensitivity analyses, the Fisher exact test was used for the difference between treatment groups for the primary endpoint. Subgroup analyses were conducted of the primary endpoint, considering factors such as gender, platelet count at baseline, prior splenectomy, prior use of TPO and/or TPO-RA, concomitant treatment for anti-ITP at baseline.

Key secondary endpoints for platelet count responses, and the dichotomous variables (proportion of patients who received rescue treatment pre-defined in protocol, and who had reduced or interrupted concomitant treatment for anti-ITP at baseline, during 24-week double-blind treatment) were also calculated by the Clopper-Pearson method and analyzed using the Cochran-Mantel-Haenszel test. The severity of bleeding events was classified based on the WHO bleeding scale, which used a dichotomization to indicate no bleeding (grade 0 = 0) vs bleeding (grade 1 = 1, 2, 3 or 4). The mean WHO bleeding score at all post-baseline visits were analysed during the first 12 and 24 weeks of double-blind treatment, and the incidence of bleeding events was summarized by visits. The WHO bleeding score difference between treatment groups was analysed using an analysis of covariance (ANCOVA) model, which included the baseline WHO bleeding grade and randomization stratification factors as covariates. For the secondary endpoint of time-to-event (time to response), the median and 95% CIs were estimated using the Kaplan-Meier method.

A post-hoc analysis was performed on the primary endpoint, considering the prior lines of treatment and prior usage of anti-CD20 antibody. To further characterize the increase in platelet after treatment, median platelet count was calculated for the durable responders (who met the primary endpoint criteria) and patients in two treatment groups at baseline and scheduled visits during double-blind period. Post-treatment assessment were performed weekly within 4 weeks after end of treatment.

In order to address the differences baseline WHO bleeding score characteristics between the two groups, post-hoc analyses were performed for the bleeding events by baseline WHO bleeding score and various

comprehensive analyses. Furthermore, for patients reporting grade ≥3 hemorrhage and serious hemorrhage, post-hoc analysis of major bleeding events was conducted based on the International Society of Thrombosis and Haemostasis (ISTH) criteria, which included fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin levels of 1.24 mmol/L (≥20 g/L) or more, or leading to a transfusion of ≥2 U of whole blood or red cells.

A p-value of <0.05 was considered statistically significant, and p-values for secondary endpoints and subgroup analyses were nominal. SAS version 9.4 software was used for all statistical analyses. This study is registered with ClinicalTrials.gov (NCT05029635).

Study Results

Between September 29, 2021 and December 31, 2022, 236 patients were screened and 188 were randomized, with 126 in the sovleplenib group and 62 in the placebo group. All randomized patients were included in the ITT analysis set and safety analysis set.

As of the data cutoff (July 14, 2023), 87 (69.0%) patients completed the 24-week study treatment in the sovleplenib group, compared with 8 (12.9%) patients in the placebo group. Overall, 99 (78.6%) patients in the sovleplenib group and 53 (85.5%) patients in the placebo group entered the open-label treatment. 31 patients with sovleplenib and 51 patients with placebo had no efficacy within the first 12 weeks treatment. Of them, 26 (83.9%) patients and 49 (96.1%) patients, respectively, in the two groups early ended double-blind treatment and received open-label treatment with sovleplenib. During the double-blind treatment period, the median duration of treatment exposure was 24.1 weeks (IQR 12.4–24.3) in sovleplenib group and 12.1 weeks (IQR 12.0–12.9) in placebo group.

Baseline characteristics were generally similar between the two treatment groups (table 3). Most patients had chronic ITP for ≥3 years (75.4% [95/126] with sovleplenib *vs* 82.3% [51/62] with placebo), were heavily pre-treated (median prior treatment lines 4.0 *vs* 4.0), and had received prior thrombopoietin (TPO)/TPO receptor agonists (TPO-RA) treatment (74.6% [94/126] *vs* 64.5% [40/62]). Twenty (15.9%) patients with sovleplenib and 7 patients (11.3%) with placebo had received prior anti-CD20 antibody treatment. Over half of the patients had a baseline WHO bleeding scale score of 1, with a higher proportion of patients in the sovleplenib group compared to the placebo group (69.0% [87/126] *vs* 53.2% [33/62]). At baseline, 85 (67.5%) of patients with sovleplenib and 42 (67.7%) patients with placebo had not received concomitant treatment for anti-ITP.

The primary endpoint of durable response rate was significantly higher with sovleplenib compared with placebo (48.4% [61/126] *vs* 0% [0/62], Cochran-Mantel-Haenszel test p<0.0001; difference in response, 48.3% [95% CI 39.6–57.1]; table 4). The post-hoc analysis indicated that the median platelet counts were higher in the sovleplenib group (≥50×10^9/L to ≥90×10^9/L) than that in the placebo group (<30×10^9/L) at all post-baseline visits, with a range of 80–100×10^9/L for the durable responders in the sovleplenib group (Figure 1). Among the 61 durable responders, 51 (83.6%) responded at ≥5 of 6 visits and 39 (63.9%) responded at all 6 visits

between week 14–24. All the sensitivity analyses in ITT analysis set and PPS showed consistent results with the primary endpoint analysis.

The secondary efficacy endpoints are shown in table 4. Most of the secondary endpoints favored the sovleplenib group. A significantly higher overall response rate was observed with sovleplenib compared with placebo in 0–12 weeks (68.3% *vs* 14.5%, p<0.0001) and 0–24 weeks (70.6% *vs* 16.1%, p<0.0001). During the double-blind period, patients treated with sovleplenib demonstrated a significant reduction in the use of rescue medication compared to those who received the placebo (22.2% *vs* 35.5%, p=0.0451).

The reduction or interruption of baseline concomitant anti-ITP treatment tended to be higher for patients with sovleplenib compared with those with placebo, though the difference was not significant (26.8% *vs* 10.0%, p=0.1471).

The sovleplenib group exhibited a quicker response to the treatment compared to the placebo group, with a median time to response of 1.1 weeks compared to 4.3 weeks.

The incidence of WHO bleeding scale showed a decreased trend in sovleplenib group in 24 weeks. The mean of WHO bleeding scale was significantly lower in the sovleplenib group compared to the placebo group in 0–12 weeks (least squares mean: 0.6 *vs* 0.8, p=0.0019) and 0–24 weeks (0.6 vs 0.8, p=0.0002). The hemorrhage of grade ≥3 was less frequent with sovleplenib than with placebo (7 [5.6%] *vs* 6 [9.7%]).

There were 11 (8.7%) patients with sovleplenib and 5 (8.1%) patients with placebo reported serious hemorrhage. Post-hoc analysis indicated for patients with baseline WHO bleeding score of 1, incidence of hemorrhage of grade ≥3 were lower in the sovleplenib group than in the placebo group (6 [6.9%] *vs* 5 [15.2%]). For patients reporting grade ≥3 hemorrhage and serious hemorrhage, incidences of major bleeding events per ISTH criteria were lower in the sovleplenib group than in the placebo group (grade ≥3: 2 [1.6%] *vs* 5 [8.1%]; seriousness: 2 [1.6%] vs 4 [6.5%]).

Results for durable response rate were consistent across most predefined subgroups, showing a higher durable response rate in the sovleplenib group compared with the placebo group; the exception was the subgroup of patients with prior splenectomy, which had a small sample size. In the subgroup of prior TPO/TPO-RA therapy, the durable response rate was significantly increased in the sovleplenib group (46.8%, 44/94) than in the placebo (0%, 0/40) (p<0.0001; difference in response, 46.8% [95% CI 36.1–57.6]).

The post-hoc analyses of durable response rate also favored sovleplenib over placebo in patients who received 4 or more prior lines of treatment (47.7% [42/88] *vs* 0%], p<0.0001) and those who had received prior anti-CD20 antibody (50.0% [10/20] *vs* 0%], p=0.0261).

Quality of life analysis based on SF-36 indicated that during the double-blind treatment period, a significant improvement was observed on two of the eight domains with sovleplenib compared with placebo: physical functioning (mean least squares difference: 5.61, p=0.0346) and energy/fatigue (mean least squares difference: 6.09, p=0.0340) (table 5). Four of the eight domains (role limitations due to physical health, role limitations due to emotional problems, emotional well-being, and general health) showed a trend of improvement with sovleplenib, but without statistical significances. Patients receiving sovleplenib demonstrated a significant difference on the domain of pain (mean least squares difference: -5.95, p=0.0360) (table 5).

TEAEs of any grade occurred in 125 (99.2%) patients in the sovleplenib group and 53 (85.5%) patients in the placebo group, and the majority of TEAEs were mild or moderate in severity (grade 1 or 2). A total of 32 (25.4%) patients in the sovleplenib group and 15 (24.2%) patients in the placebo group reported grade ≥3 TEAEs. Serious TEAEs occurred in 26 (20.6%) and 11 (17.7%) patients in the sovleplenib and placebo groups, respectively, of whom, only 2 (1.6%) and 1 (1.6%) patients had treatment related serious TEAEs: pain in extremity (grade 2) and rash maculo-papular (grade 1) was reported in one patient and hypertension (grade 3) was reported in the other one patient receiving sovleplenib; cerebral hemorrhage (grade 3) occurred in one patient receiving placebo.

No deaths occurred in the study. The TEAEs reported in 10% or more of patients are listed in table 6. The most frequent TEAEs were upper respiratory tract infections (36 [28.6%] with sovleplenib *vs* 6 [9.7%] with placebo), COVID-19 infection (30 [23.8%] vs 8 [12.9%]), and blood lactate dehydrogenase increased (30 [23.8%] *vs* 4 [6.5%]).

Hypertension was reported in 15 (11.9%) patients with sovleplenib and 3 (4.8%) patients with placebo. Among the patients in the sovleplenib group, 4 (3.2%) experienced grade 3 hypertension, with only one (0.8%) patient reporting a serious case.

At baseline, 3 (2.4%) patients in the sovleplenib group and 2 (3.2%) patients in the placebo showed a systolic blood pressure ≥140 and <160 mmHg and/or diastolic blood pressure ≥90 and <100 mmHg. Post baseline, a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg was reported in 42 (33.3%) patients with sovleplenib and 20 (32.3%) patients with placebo; a systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg was reported in 8 (6.3%) and 4 (6.5%) patients, respectively.

The incidences of gastrointestinal related events were low, including diarrhea (5 [4.0%] patients with sovleplenib *vs* 0 with placebo), vomiting (3 [2.4%] *vs* 1 [1.6%]), nausea (3 [2.4%] *vs* 2 [3.2%]).

A post hoc analysis was performed to evaluate the platelet response among 5 subgroups patients with prior TPO/TPO-RA treated in this study, including TPO only, TPO-RA only, both TPO and TPO-RA, 1 kind and ≥2 kinds of TPO/TPO-RA regimens. 134 (71.3%) patients (sovleplenib, n=94; placebo, n=40) had received prior TPO/ TPO-RA treatment. Among them, the patient numbers in two groups (sovleplenib vs placebo) for TPO treatment only, TPO-RA treatment only, both TPO treatment and TPO-RA treatment, 1 kind and ≥ 2 kinds of TPO/TPO-RA, were 29 vs 8, 34 vs 19, 31 vs 13, 51 vs 16, and 43 vs 24, respectively. The patients received 5 types of TPO/TPO- RA regimens, including recombinant human thrombopoietin (81, 60.4%), eltrombopag (73, 54.5%), hetrombopag (28, 20.9%), avatrombopag (28, 20.9%) and romiplostim (10, 7.5%). Main efficacy data are shown in Table 7. The durable response rate and overall response rate in patients with prior TPO/TPO-RA treatment was significantly higher in sovleplenib group, compared with placebo group (46.8% vs. 0%, 68.1% vs 7.5%, respectively; all p <0.0001). Compared to placebo group, the durable response rates were 58.6% vs 0, 47.1% vs 0, and 35.5% vs 0%, for subgroups of TPO only, TPO-RA only, both TPO and TPO-RA, respectively; and the overall response rate was 72.4% vs 25.0%, 73.5% vs 5.3%, 58.1% vs 0 (all p<0.05), which further demonstrated the significant efficacy of sovleplenib across these subgroups on platelet response. Meanwhile, the results showed a trend of improved durable and overall response benefits of sovleplenib in subgroup of TPO treatment only or TPO-RA treatment

only than both TPO treatment and TPO-RA treatment. Furthermore, sovleplenib showed significantly improved durable response rate (51.0% vs 0; 41.9% vs 0) and overall response rates (70.6% vs 12.5%; 65.1% vs 4.2%), compared with placebo, in subgroups of 1 kind or ≥ 2 kinds of prior TPO/TPO-RA regimens (all $p<0.0001$).

Sovleplenib was significantly and consistently efficacious in increasing platelet counts in primary ITP patients with prior TPO/TPO-RA treatments, regardless of TPO/TPO-RA treatment types and treatment numbers, even if in patients who had received ≥ 2 kinds of TPO/TPO-RA treatment prior to sovleplenib initiation.

Table 3: Baseline characteristics (ITT analysis set)

	Sovleplenib (N=126)	Placebo (N=62)
Age, years	43.5 (18–72)	42.0 (18–69)
<65 years	119 (94.4%)	59 (95.2%)
≥65 years	7 (5.6%)	3 (4.8%)
Gender		
Male	39 (31.0%)	25 (40.3%)
Female	87 (69.0%)	37 (59.7%)
Asian ethnicity	126 (100.0%)	62 (100.0%)
ECOG performance status		
0	99 (78.6%)	54 (87.1%)
1	27 (21.4%)	8 (12.9%)
Patients who are diagnosed with ITP	126 (100.0%)	62 (100.0%)
Time since first reduction in platelet count in years to randomization	7.6 (1.1–36.1)	7.8 (1.1–41.2)
≥3 years	95 (75.4%)	51 (82.3%)
<3 years	31 (24.6%)	11 (17.7%)
Baseline platelet count		
$<15\times10^9$/L	75 (59.5%)	37 (59.7%)
$\geq15\times10^9$/L	51 (40.5%)	25 (40.3%)
Prior splenectomy		
Yes	5 (4.0%)	3 (4.8%)
No	121 (96.0%)	59 (95.2%)
Concomitant anti-ITP treatment at baseline		
Yes	41 (32.5%)	20 (32.3%)
No	85 (67.5%)	42 (67.7%)
Lines of prior anti-ITP therapies*	4.0 (1–10)	4.0 (1–9)
Therapy type (≥10%)		
Glucocorticoid	121 (96.0%)	60 (96.8%)
Traditional Chinese medicine	74 (58.7%)	37 (59.7%)
TPO-RA	65 (51.6%)	32 (51.6%)
IVIG	63 (50.0%)	29 (46.8%)
TPO	60 (47.6%)	21 (33.9%)
Platelet transfusion	53 (42.1%)	13 (21.0%)
Danazol/Stanozolol	41 (32.5%)	21 (33.9%)
Caffeic acid	23 (18.3%)	11 (17.7%)
anti-CD20 antibody	20 (15.9%)	7 (11.3%)
Other†	19 (15.1%)	8 (12.9%)
Ciclosporin	18 (14.3%)	10 (16.1%)
IL-11	16 (12.7%)	10 (16.1%)
Prior TPO and/or TPO-RA medication		
Yes	94 (74.6%)	40 (64.5%)
No	32 (25.4%)	22 (35.5%)
Baseline WHO bleeding scale scores		
0 (No hemorrhage)	39 (31.0%)	29 (46.8%)
1 (Petechia)	87 (69.0%)	33 (53.2%)

Data are median (range), or n (%). ECOG = Eastern Cooperative Oncology Group; ITP = immune thrombocytopenia; IVIG = intravenous immunoglobulin; TPO = thrombopoietin; TPO-RA = thrombopoietin receptor agonists; WHO = World Health Organization. *Numbers of prior unique anti-ITP treatment types of medications and prior surgeries were summarised, TPO and TPO-RA were counted as the same line, in addition, splenectomy and splenic artery embolization were counted as the same line. †Almost all medications in "Other" category are traditional Chinese medications or blinded therapies.

Table 4: Overview of the primary and secondary efficacy endpoints

	Sovleplenib (N=126)	Placebo (N=62)	Difference between treatment group (95% CI)	p-value
Primary endpoint				
Durable response rate*	61 (48.4)	0	48.3 (39.6–57.1)	<0.0001
Secondary endpoints				
Overall response rate in 0-12 weeks*	86 (68.3)	9 (14.5)	53.2 (41.7–64.8)	<0.0001
Overall response rate in 0-24 weeks*	89 (70.6)	10 (16.1)	54.4 (42.9–66.0)	<0.0001
For patients with a platelet count <15×10⁹/L at baseline	75 (59.5)	37 (59.7)	NA	NA
Patients with platelet count ≥30×10⁹/L and an increase ≥20×10⁹/L from baseline in 0-12 weeks*	55 (73.3)	8 (21.6)	51.7 (35.7–67.8)	<0.0001
Patients with platelet count ≥30×10⁹/L and an increase ≥20×10⁹/L from baseline in 0-24 weeks*	56 (74.7)	8 (21.6)	53.1 (37.1–69.0)	<0.0001
Patients with two consecutive platelet count ≥ 30×10⁹/L and doubling from the baseline in 0-24 weeks*	92 (73.0)	4 (6.5)	66.5 (56.9–76.1)	<0.0001
Patient who received rescue treatment in 24-week treatment	28 (22.2)	22 (35.5)	-13.4 (-26.7 – -0.1)	0.0451
Patients who received concomitant treatment for anti-immune thrombocytopenia at baseline	41 (32.5)	20 (32.3)	NA	NA
Patients who reduced or interrupted baseline concomitant treatment for anti-immune thrombocytopenia in 0-24 weeks	11 (26.8)	2 (10.0)	16.3 (-2.6–35.1)	0.1471
Time to response (from treatment initiation to first platelet count ≥50×10⁹/L), weeks, median (IQR) †	1.1 (1.1–1.7)	4.3 (3.4–6.6)	NA	NA
Means of WHO bleeding scale, mean (SE)				
in 0-12 weeks	0.586 (0.0766)	0.786 (0.0838)	-0.199 (-0.324 – -0.075)	0.0019
in 0-24 weeks	0.555 (0.0743)	0.786 (0.0813)	-0.231 (-0.351 – -0.110)	0.0002

Data are n (%), % (95% CI), least squares mean (SE) (for bleeding scale), or median (IQR) (for time to response). NA=not applicable.
* Not causing by rescue treatment during the treatment period. † Results are from patients who initially signed ICF version 3.0 and above and had response.

Table 5: Mean change in SF-36 scores.

		Sovleplenib				Placebo							
Parameter	**Visit**	**N (%)**	**LS Mean**	**95% CI**	**SE**	**N (%)**	**LS Mean**	**95% CI**	**SE**	**LS Mean Difference**	**95% CI**	**p-value**	**SE**
Physical functioning	Week 12	112 (88.9)	86.81	(84.43, 89.19)	1.20	56 (90.3)	84.77	(81.41, 88.14)	1.70	2.04	(-2.09, 6.16)	0.3308	2.09
	Week 24	87 (69.0)	87.57	(84.77, 90.37)	1.41	8 (12.9)	78.40	(70.73, 86.06)	3.87	9.17	(1.01, 17.33)	0.0279	4.12
	All	113 (89.7)	87.19	(84.86, 89.52)	1.18	56 (90.3)	81.59	(76.94, 86.23)	2.35	5.61	(0.41, 10.80)	0.0346	2.63
Role limitations due to physical health	Week 12	112 (88.9)	63.85	(57.81, 69.89)	3.06	56 (90.3)	63.79	(55.23, 72.35)	4.33	0.06	(-10.42, 10.55)	0.9904	5.31
	Week 24	87 (69.0)	63.31	(56.12, 70.50)	3.63	8 (12.9)	58.08	(37.13, 79.03)	10.56	5.23	(-16.92, 27.38)	0.6407	11.17
	All	113 (89.7)	63.58	(57.82, 69.34)	2.92	56 (90.3)	60.93	(48.69, 73.18)	6.20	2.65	(-10.89, 16.18)	0.7001	6.86
Role limitations due to emotional problems	Week 12	112 (88.9)	72.75	(66.71, 78.78)	3.06	56 (90.3)	62.87	(54.23, 71.52)	4.38	9.87	(-0.77, 20.51)	0.0687	5.39
	Week 24	87 (69.0)	68.58	(61.56, 75.60)	3.54	8 (12.9)	59.88	(38.74, 81.03)	10.66	8.70	(-13.61, 31.02)	0.4411	11.25
	All	113 (89.7)	70.66	(65.09, 76.24)	2.82	56 (90.3)	61.38	(49.12, 73.63)	6.20	9.29	(-4.24, 22.81)	0.1770	6.85
Energy/fatigue	Week 12	112 (88.9)	72.60	(69.78, 75.43)	1.43	56 (90.3)	69.53	(65.50, 73.56)	2.04	3.07	(-1.88, 8.02)	0.2223	2.51
	Week 24	87 (69.0)	71.82	(69.01, 74.63)	1.42	8 (12.9)	62.71	(54.44, 70.99)	4.17	9.11	(0.35, 17.87)	0.0417	4.42

		Sovleplenib				Placebo							
Parameter	**Visit**	**N (%)**	**LS Mean**	**95% CI**	**SE**	**N (%)**	**LS Mean**	**95% CI**	**SE**	**LS Mean Difference**	**95% CI**	**p-value**	**SE**
	All	113 (89.7)	72.21	(69.77, 74.66)	1.24	56 (90.3)	66.12	(61.09, 71.15)	2.55	6.09	(0.47, 11.71)	0.0340	2.85
Emotional well-being	Week 12	112 (88.9)	69.24	(66.65, 71.83)	1.31	56 (90.3)	68.69	(65.01, 72.36)	1.86	0.55	(-3.95, 5.06)	0.8083	2.28
	Week 24	87 (69.0)	70.52	(67.30, 73.74)	1.62	8 (12.9)	68.85	(59.07, 78.62)	4.93	1.68	(-8.63, 11.98)	0.7476	5.19
	All	113 (89.7)	69.88	(67.41, 72.35)	1.25	56 (90.3)	68.77	(63.21, 74.33)	2.81	1.12	(-4.98, 7.21)	0.7181	3.08
Social functioning	Week 12	112 (88.9)	81.00	(77.75, 84.26)	1.65	56 (90.3)	81.28	(76.68, 85.88)	2.33	-0.28	(-5.92, 5.36)	0.9223	2.86
	Week 24	87 (69.0)	82.97	(79.89, 86.05)	1.55	8 (12.9)	86.59	(77.23, 95.96)	4.72	-3.62	(-13.49, 6.25)	0.4684	4.97
	All	113 (89.7)	81.99	(79.30, 84.67)	1.36	56 (90.3)	83.94	(78.32, 89.55)	2.84	-1.95	(-8.18, 4.28)	0.5378	3.16
Pain	Week 12	112 (88.9)	84.38	(81.56, 87.20)	1.43	56 (90.3)	89.28	(85.26, 93.30)	2.04	-4.90	(-9.83, 0.02)	0.0512	2.50
	Week 24	87 (69.0)	87.50	(84.73, 90.27)	1.40	8 (12.9)	94.49	(86.27, 102.71)	4.14	-6.99	(-15.68, 1.70)	0.1137	4.38
	All	113 (89.7)	85.94	(83.53, 88.35)	1.22	56 (90.3)	91.89	(86.90, 96.87)	2.52	-5.95	(-11.50, -0.39)	0.0360	2.81
General health	Week 12	112 (88.9)	58.71	(55.88, 61.53)	1.43	56 (90.3)	55.92	(51.93, 59.92)	2.03	2.78	(-2.11, 7.68)	0.2635	2.48
	Week 24	87 (69.0)	58.98	(55.62, 62.33)	1.69	8 (12.9)	49.48	(40.08, 58.88)	4.74	9.49	(-0.48, 19.47)	0.0620	5.04
	All	113 (89.7)	58.84	(56.10, 61.59)	1.39	56 (90.3)	52.70	(47.09, 58.31)	2.84	6.14	(-0.11, 12.38)	0.0540	3.17

Abbreviations: LS=least squares; SE=standard error.

Note: For each scale, statistical comparison between the two treatment groups was based on a longitudinal repeated measures analysis using a mixed effects model. The model will include the fixed categorical effects of treatment group, time point (week 12 and 24), and treatment group-by-time point interaction, and the continuous fixed covariate of baseline score.

Table 6: Treatment-emergent adverse events reported in 10% or more of patients (safety analysis set)

	Sovleplenib (N = 126)					Placebo (N = 62)				
	All grade	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**All grade**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Any treatment-emergent adverse event	**125 (99.2)**	**24 (19.0)**	**69 (54.8)**	**19 (15.1)**	**13 (10.3)**	**53 (85.5)**	**20 (32.3)**	**18 (29.0)**	**7 (11.3)**	**8 (12.9)**
Upper respiratory tract infections	36 (28.6)	3 (2.4)	31 (24.6)	2 (1.6)	0	6 (9.7)	0	6 (9.7)	0	0
COVID-19 infection	30 (23.8)	11 (8.7)	18 (14.3)	1 (0.8)	0	8 (12.9)	1 (1.6)	7 (11.3)	0	0
Blood lactate dehydrogenase increased	30 (23.8)	30 (23.8)	0	0	0	4 (6.5)	4 (6.5)	0	0	0
Haemorrhage subcutaneous	24 (19.0)	16 (12.7)	8 (6.3)	0	0	8 (12.9)	5 (8.1)	3 (4.8)	0	0
Hyperuricemia	23 (18.3)	23 (18.3)	0	0	0	3 (4.8)	3 (4.8)	0	0	0
Hypokalemia	23 (18.3)	18 (14.3)	4 (3.2)	0	1 (0.8)	3 (4.8)	2 (3.2)	1 (1.6)	0	0
Anaemia	23 (18.3)	11 (8.7)	9 (7.1)	2 (1.6)	1 (0.8)	8 (12.9)	0	4 (6.5)	4 (6.5)	0
Rash	22 (17.5)	11 (8.7)	10 (7.9)	1 (0.8)	0	1 (1.6)	0	1 (1.6)	0	0
Aspartate aminotransferase increased	20 (15.9)	16 (12.7)	4 (3.2)	0	0	1 (1.6)	1 (1.6)	0	0	0
Occult blood positive	20 (15.9)	20 (15.9)	0	0	0	9 (14.5)	9 (14.5)	0	0	0
Alanine aminotransferase increased	19 (15.1)	15 (11.9)	1 (0.8)	3 (2.4)	0	1 (1.6)	1 (1.6)	0	0	0
Neutrophil count decreased	19 (15.1)	7 (5.6)	8 (6.3)	4 (3.2)	0	0	0	0	0	0
Abnormal liver function	17 (13.5)	14 (11.1)	3 (2.4)	0	0	2 (3.2)	2 (3.2)	0	0	0
Gingival bleeding	16 (12.7)	12 (9.5)	4 (3.2)	0	0	7 (11.3)	5 (8.1)	2 (3.2)	0	0
Hypertension	15 (11.9)	0	11 (8.7)	4 (3.2)	0	3 (4.8)	1 (1.6)	2 (3.2)	0	0
Blood creatine phosphokinase increased	14 (11.1)	14 (11.1)	0	0	0	2 (3.2)	2 (3.2)	0	0	0

Note: Data are n (%). TEAEs of all grades occurring in ≥10% of patients in each group are listed.

Table 7 Main efficacy data of patients in the intention-to-treat population

	Durable response rate	difference between treatment group (95% CI)	P-value	Overall response rate	Difference between treatment group (95% CI)	P-value
TPO/TPO-RA						
Sovleplenib (N=94)	44 (46.8)	46.81 (36.128 - 57.570)	<0.0001	64 (68.1)	60.15 (47.506 - 72.784)	<0.0001
Placebo (N=40)	0			3 (7.5)		
TPO only						
Sovleplenib (N=29)	17 (58.6)	66.51 (46.581 - 86.447)	0.0012	21 (72.4)	52.75 (13.268 - 92.237)	0.0137
Placebo (N=8)	0			2 (25.0)		
TPO-RA only						
Sovleplenib (N=34)	16 (47.1)	51.74 (32.970 - 70.506)	0.0003	25 (73.5)	63.37 (40.113 - 86.634)	<0.0001
Placebo (N=19)	0			1 (5.3)		
Both TPO and TPO						
Sovleplenib (N=31)	11 (35.5)	35.97 (18.029 - 53.906)	0.0060	18 (58.1)	59.67 (41.587 - 77.759)	0.0004
Placebo (N=13)	0			0		
1 type of TPO / TPO-RA						
Sovleplenib (N=51)	26 (51.0)	54.63 (40.750 - 68.506)	<0.0001	36 (70.6)	59.75 (39.400 - 80.096)	<0.0001
Placebo (N=16)	0			2 (12.5)		
≥ 2 types of TPO / TPO-RA						
Sovleplenib (N=43)	18 (41.9)	44.64 (29.905 - 59.369)	<0.0001	28 (65.1)	60.31 (43.255 - 77.357)	<0.0001
Placebo (N=24)	0			1 (4.2)		

Table 7: Data are n (%), or % (95% CI), or otherwise specified. Clopper-Pearson method is used to calculate the exact 95% CI of the response rate in each group; Cochran-Mantel-Haenszel test is used to analyze the difference of the response rate between two groups.

CLAIMS

1. A method of treating immune thrombocytopenia (ITP) in a subject in need thereof, comprising administering to the subject sovleplenib or a pharmaceutically acceptable salt thereof at a daily dosage of about 100-600 mg (optionally about 100-400 mg, about 300-500 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, or about 600mg), or at a dosage sufficient to achieve an $AUC_{tau,ss}$ value of about 600-5000 h × ng/mL (optionally about 600-800, about 1000-1300, about 1900-2200, or about 2900-3200 h ×ng/mL, optionally about 650-670, about 1145-1165, about 2055-2175, or about 3055-3075 h ×ng/mL, optionally about 661, about 1156, about 2067, or about 3065 h × ng/mL).
2. The method of claim 1, wherein the ITP is primary ITP.
3. The method of any one of claims 1-2, wherein the ITP is newly diagnosed ITP, persistent ITP, or chronic ITP.
4. The method of any one of claims 1-2, wherein the subject has relapsed or refractory ITP.
5. The method of any one of claims 1-4, wherein the subject has previously received at least one prior anti-ITP treatment.
6. The method of any one of claims 1-5, wherein the subject has had an insufficient response or intolerance to at least one prior anti-ITP treatment, or has relapsed after at least one prior anti-ITP treatment.
7. The method of any one of claims 5-6, wherein the at least one prior anti-ITP treatment is one, two, three, four, five, six, seven, eight or more prior anti-ITP treatments.
8. The method of any one of claims 5-7, wherein the at least one prior anti-ITP treatment comprises at least one treatment of first-line anti-ITP treatment, second-line anti-ITP treatment, third-line anti-ITP treatment and a further treatment.
9. The method of any one of claims 5-8, wherein the at least one prior anti-ITP treatment comprises one or more treatments selected from corticosteroids, an intravenous immunoglobulin treatment (IVIg), anti-D immunoglobulin, thrombopoietin (TPO) treatment, thrombopoietin receptor agonist (TPO-RA) treatment, anti-CD20 antibody treatment, immunosuppressants, vinca alkaloids alemtuzumab, danazol, dapsone, platelet transfusion, danazol/stanozolol, caffeic acid, IL-11, Traditional Chinese medicine and splenectomy.
10. The method of any one of claims 5-9, wherein the at least one prior anti-ITP treatment comprises TPO treatment and/or TPO-RA treatment.
11. The method of any one of claims 5-9, wherein the at least one prior anti-ITP treatment comprises either TPO treatment or TPO-RA treatment.
12. The method of any one of claims 5-9, wherein the at least one prior anti-ITP treatment comprises both TPO treatment and TPO-RA treatment.
13. The method of any one of claims 5-10, wherein the at least one prior anti-ITP treatment comprises only one medication of TPO/TPO-RA treatment.

14. The method of any one of claims 5-10, wherein the at least one prior anti-ITP treatment comprises at least two medications of TPO/TPO-RA treatment.
15. The method of any one of claims 5-10, wherein the at least one prior anti-ITP treatment comprises one or more agents selected from a recombinant human thrombopoietin, eltrombopag, hetrombopag, avatrombopag and romiplostim.
16. The method of any one of claims 5-15, wherein the at least one prior anti-ITP treatment comprises an anti-CD20 antibody treatment.
17. The method of any one of claims 5-16, wherein the at least one prior anti-ITP treatment comprises splenectomy.
18. The method of any one of claims 5-17, wherein the at least one prior anti-ITP treatment comprises a rescue treatment.
19. The method of any one of claims 1-18, wherein the subject has a platelet count of less than 30×10^9 per liter prior to the treatment of sovleplenib or a pharmaceutically acceptable salt thereof.
20. The method of any one of claims 1-19, wherein the subject has a platelet count of less than 15×10^9 per liter prior to the treatment of sovleplenib or a pharmaceutically acceptable salt thereof.
21. The method of any one of claims 1-19, wherein the subject has a platelet count of more than 15×10^9 per liter and less than 30×10^9 per liter prior to the treatment of sovleplenib or a pharmaceutically acceptable salt thereof.
22. The method of any one of claims 1-21, wherein the subject has a hemoglobin ≥100 g/L and neutrophil count $>1.5\times10^9$ per liter prior to the treatment of sovleplenib or a pharmaceutically acceptable salt thereof.
23. The method of any one of claims 1-22, wherein the subject has an WHO Bleeding Scale score of 0 or 1, and/or has chronic ITP for ≥3 years, prior to the treatment of sovleplenib or a pharmaceutically acceptable salt thereof.
24. The method of any one of claims 1-23, wherein the subject has not responded to sovleplenib or a pharmaceutically acceptable salt thereof during the first 12 weeks treatment.
25. The method of any one of claims 1-24, wherein the subject is human adult.
26. The method of any one of claims 1-25, wherein the subject is Asian population.
27. The method of any one of claims 1-25, wherein the subject is non-Asian population, optionally American population, European population, Caucasian population, Oceanian population, and/or African population.
28. The method of any one of claims 1-27, wherein sovleplenib or a pharmaceutically acceptable salt thereof is administered at a dosage sufficient to achieve an $AUC_{tau,ss}$ value of about 2067 h × ng/mL.

29. The method of any one of claims 1-27, wherein sovleplenib or a pharmaceutically acceptable salt thereof is administered at a daily dosage of about 300mg.
30. The method of any one of claims 1-27, wherein sovleplenib or a pharmaceutically acceptable salt thereof is administered at a daily dosage of about 500mg.
31. The method of any one of claims 1-30 wherein the dosage of sovleplenib or a pharmaceutically acceptable salt thereof is reduced during the treatment, when

(1) the subject has a platelet count of $\geqslant 250 \times 10^9$ platelets for about two weeks or a platelet count of $\geqslant 400 \times 10^9$/L for any time in a treatment period;

(2) the subject is concurrently with a concomitant anti-ITP treatment and has a platelet count of $\geq 100 \times 10^9$/L lasting for about 4 weeks, or platelet count of $\geq 250 \times 10^9$/L lasting for about 2 weeks in a treatment period; or

(3) the subject experiences drug related adverse event.

32. The method of any one of claims 1-31, wherein the dosage is administered once per day (QD), or in divided doses, e.g., twice per day (BID).
33. The method of any one of claims 1-32, wherein sovleplenib or a pharmaceutically acceptable salt thereof is administered orally.
34. The method of any one of claims 1-33, wherein sovleplenib or a pharmaceutically acceptable salt thereof is administered as a monotherapy, or in combination with one or more additional therapeutic agents.
35. The method of any one of claims 1-34, wherein sovleplenib or a pharmaceutically acceptable salt thereof is administered in combination with a concomitant anti-ITP treatment.
36. The method of any one of claims 1-35, wherein the subject has been receiving a stable dose of concomitant anti-ITP treatment.
37. The method of any one of claims 34-36, wherein the additional therapeutic agents or the concomitant anti-ITP treatment is one concomitant medication selected from corticosteroids, TPO-RAs, danazol, and immunosuppressants.
38. The method of any one of claims 34-36, wherein the additional therapeutic agents or the concomitant anti-ITP treatment is not a rescue treatment.
39. The method of any one of claims 1-38, wherein the subject has durable response (including an improved durable response rate), improved overall response (including improved overall response rate), improved platelet counts, a fast onset of action or improved time to response, a reduction of bleeding incidence or severity, including reduction in the WHO bleeding scale score, less frequency of hemorrhage of grade ≥3, improved hemoglobin level, long-term ITP remission, improved health-related quality of life (HRQoL), a reduction in the use of rescue treatment and/or reduction or interruption of baseline concomitant anti-ITP treatment, and/or is

safe and tolerable over time, optionally with low risk gastrointestinal toxicity, after treatment with sovleplenib or a pharmaceutically acceptable salt thereof.

40. The method of any one of claims 1-39, wherein the pharmaceutically acceptable salt of sovleplenib is sovleplenib acetate.

41. An article of manufacture comprising:

a sovleplenib or a pharmaceutically acceptable salt thereof, and

a package insert comprising instructions for using sovleplenib or a pharmaceutically acceptable salt thereof to treat immune thrombocytopenia (ITP) in a subject in need thereof, wherein the instructions indicate that sovleplenib or a pharmaceutically acceptable salt thereof is administrated as defined in any one of claims 1-40.