absence of erythropoietin were significantly inhibited in the presence of 500 nM ABT-737 and could be further suppressed when 100 – 300 nM ABT-737 was combined with a JAK-2 inhibitor. The addition of navitoclax to a JAK-2 inhibitor has also demonstrated efficacy in animal models of JAK-2-mutated malignancies–for example, significantly slowing the growth of tumors in mice bearing the Eμ-TEL-JAK-2 transgene or patient-derived xenograft (PDX) mice bearing JAK-2-mutated B-ALL cells. The combination was also superior to either agent alone in prolonging the survival of mice with JAK-2-mutated tumors, in some cases effecting cures.

[0008] In view of the advantages that result from administration of a BCL-2 family inhibitor combined with a JAK-2 inhibitor, the present inventors have discovered a combination and dosing therapy that will go beyond symptom relief and offer an impact on the underlying course of disease of myelofibrosis. The present inventors have discovered, for the first time in human patients, that administration of specific doses of navitoclax with specific doses of ruxolitinib, results in a clinically meaningful reduction in spleen volume, allelic burden, total symptom score (TSS) and, importantly, bone marrow fibrosis (BMF) with a manageable safety profile, thus establishing this combination as a potential treatment option.

BRIEF SUMMARY OF THE INVENTION

[0008a] In one aspect, provided herein is a use of a therapeutically effective amount of navitoclax selected from the group consisting of 50 mg, 100 mg, 200 mg, and 300 mg in the manufacture of a first medicament and use of a therapeutically effective amount of ruxolitinib in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder, wherein the treatment of the human subject results in a spleen volume reduction of at least 35%, wherein the MPN-related disorder is selected from the group consisting of polycythemia vera (PCV), essential thrombocytopenia (ET), and chronic monomyelocytic leukemia (CMML).

[0008b] In one aspect, provided herein is a use of a therapeutically effective amount of navitoclax selected from the group consisting of 50 mg, 100 mg, 200 mg, and 300 mg in the manufacture of a first medicament and use of a therapeutically effective amount of ruxolitinib in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat a human subject with myelofibrosis; wherein the myelofibrosis is relapsed or refractory myelofibrosis; and wherein the treatment of the human

subject results a spleen volume reduction of at least 35%.

[0008c] In one aspect, provided herein is a use of a therapeutically effective amount of navitoclax selected from the group consisting of 50 mg, 100 mg, 200 mg, and 300 mg in the manufacture of a first medicament and use of a therapeutically effective amount of ruxolitinib in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat a human subject with myelofibrosis; wherein the myelofibrosis is relapsed or refractory myelofibrosis; and wherein treatment of the human subject results in an improvement in a grade of bone marrow fibrosis relative to a baseline grade of bone marrow fibrosis.

[0008d] In one aspect, provided herein is a use of a therapeutically effective amount of navitoclax selected from the group consisting of 50 mg, 100 mg, 200 mg, and 300 mg in the manufacture of a first medicament and use of a therapeutically effective amount of ruxolitinib in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to significantly reduce spleen volume in a human subject with myelofibrosis who is refractory to treatment with a JAK-2 inhibitor; wherein the navitoclax is to be orally administered to the human subject with myelofibrosis once a day, wherein the ruxolitinib is to be orally administering to the human subject with myelofibrosis twice a day. wherein following 24 weeks of said administration of navitoclax in combination with ruxolitinib, the spleen volume of the human subject with myelofibrosis is reduced by at least 35%.

[0008e] In one aspect, provided herein is a use of a therapeutically effective amount of navitoclax selected from the group consisting of 50 mg, 100 mg, 200 mg, and 300 mg in the manufacture of a first medicament anduse of a therapeutically effective amount of ruxolitinib in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to improve bone marrow fibrosis grade in a human subject with myelofibrosis who is refractory to treatment with a JAK-2 inhibitor; wherein the navitoclax is to be orally administered to the human subject with myelofibrosis once a day, wherein the ruxolitinib is to be orally administered to the human subject with myelofibrosis twice a day, wherein following 24 weeks of said administration of navitoclax in combination with ruxolitinib the bone marrow fibrosis grade of the human subject with myelofibrosis is improved by at least one grade.

[0008f] In one aspect, provided herein is a use of an effective amount of navitoclax in the

manufacture of a first medicament and use of an effective amount of ruxolitinib in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat myelofibrosis in a human subject in need thereof, wherein the first and second medicaments are to be orally administered to said subject, wherein (i) if the human subject has a baseline platelet count of greater than or equal to 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg once daily, and if the human subject has a baseline platelet count of less than 150 x 10^9/L, the effective amount of navitoclax comprises 100 mg once daily, escalated to 200 mg once daily after 7 days or more if the human subject has a platelet count greater than or equal to 75 x 10^9/L, and (ii) the effective amount of ruxolitinib comprises 10 mg twice daily; wherein the effective amount of navitoclax is optionally increased to 300 mg once daily if the human subject fails to achieve spleen reduction volume of at least 35% (SVR_{35}) by week 24 of treatment.

[0008g] In one aspect, provided herein is a use of an effective amount of navitoclax in the manufacture of a first medicament and use of an effective amount of ruxolitinib in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat myelofibrosis in a human subject in need thereof, wherein the first and second medicaments are to be orally administered to said subject, wherein (i) if the human subject has a baseline platelet count of greater than or equal to 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg once daily, and if the human subject has a baseline platelet count of less than 150 x 10^9/L, the effective amount of navitoclax comprises 100 mg once daily, escalated to 200 mg once daily after 7 days or more if the human subject has a platelet count greater than or equal to 75 x 10^9/L, and (ii) if the human subject has a baseline platelet count of greater than 200 x 10^9/L, the effective amount of ruxolitinib comprises 20 mg twice daily, if the subject has a baseline platelet count between 100 x 10^9/L and 200 x 10^9/L, the effective amount of ruxolitinib comprises 15 mg twice daily, and if the subject has a baseline platelet count between 50 x 10^9/L to less than 100 x 10^9/L, the effective amount of ruxolitinib comprises 5 mg twice daily; wherein the effective amount of navitoclax is optionally increased to 300 mg once daily if the human subject fails to achieve spleen reduction volume of at least 35% (SVR_{35}) by week 24 of treatment.

[0008h] In one aspect, provided herein is a use of an effective amount of navitoclax in the manufacture of a first medicament and use of an effective amount of ruxolitinib in the

manufacture of a second medicament wherein the first and second medicaments are to be used in combination therapy to treat myelofibrosis in a human subject in need thereof, wherein the first and second medicaments are to be orally administered to said subject, and wherein a baseline platelet count is obtained from said human subject, wherein (i) if the human subject has a baseline platelet count of greater than or equal to 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg once daily, and if the human subject has a baseline platelet count of less than 150 x 10^9/L, the effective amount of navitoclax comprises 100 mg once daily, escalated to 200 mg once daily after 7 days or more if the human subject has a platelet count greater than or equal to 75 x 10^9/L, and (ii) the effective amount of ruxolitinib comprises 10 mg twice daily; wherein the effective amount of navitoclax is optionally increased to 300 mg once daily if the human subject fails to achieve spleen reduction volume of at least 35% (SVR_{35}) by week 24 of treatment.

[0008i] In one aspect, provided herein is a use of an effective amount of navitoclax in the manufacture of a first medicament and use of an effective amount of ruxolitinib in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat myelofibrosis in a human subject in need thereof, wherein the first and second medicaments are to be orally administered, and wherein a baseline platelet count is obtained from said human subject, wherein (i) if the human subject has a baseline platelet count of greater than or equal to 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg once daily, and if the human subject has a baseline platelet count of less than 150 x 10^9/L, the effective amount of navitoclax comprises 100 mg once daily, escalated to 200 mg once daily after 7 days or more if the human subject has a platelet count greater than or equal to 75 x 10^9/L, and (ii) if the human subject has a baseline platelet count of greater than 200 x 10^9/L, the effective amount of ruxolitinib comprises 20 mg twice daily, if the subject has a baseline platelet count between 100 x 10^9/L and 200 x 10^9/L, the effective amount of ruxolitinib comprises 15 mg twice daily, and if the subject has a baseline platelet count between 50 x 10^9/L to less than 100 x 10^9/L, the effective amount of ruxolitinib comprises 5 mg twice daily; wherein the effective amount of navitoclax is optionally increased to 300 mg once daily if the human subject fails to achieve spleen reduction volume of at least 35% (SVR_{35}) by week 24 of treatment.

[0009] In one embodiment, a method for treatment of a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder is provided, comprising administering a

therapeutically effective amount of navitoclax selected from the group consisting of 50 mg, 100 mg, 200 mg, and 300 mg; in combination with administering a therapeutically effective amount of ruxolitinib; wherein the treatment of the human subject results in a spleen volume reduction of at least 35%. In one aspect, the treatment of the human subject results in a spleen volume reduction of at least 35% (SVR_{35}) by week 24.

[0010] In another embodiment, a method for treatment of a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 50 mg, 100 mg, 200 mg, and 300 mg; in combination with administering a therapeutically effective amount of ruxolitinib of at least 10 mg; wherein the treatment of the human subject results in a spleen volume reduction of at least 35% (SVR_{35}).

[0011] In yet another embodiment, a method for treatment of a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder is provided, comprising

What is claimed is:

1. Use of a therapeutically effective amount of navitoclax selected from the group consisting of 50 mg, 100 mg, 200 mg, and 300 mg in the manufacture of a first medicament and use of a therapeutically effective amount of ruxolitinib in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder,

   wherein the treatment of the human subject results in a spleen volume reduction of at least 35%,

   wherein the MPN-related disorder is selected from the group consisting of polycythemia vera (PCV), essential thrombocytopenia (ET), and chronic monomyelocytic leukemia (CMML).
2. The use of claim 1, wherein the therapeutically effective amount of ruxolitinib is at least 10 mg.
3. The use of claim 2, wherein the therapeutically effective amount of navitoclax is to be administered once a day; and wherein the therapeutically effective amount of ruxolitinib is to be administered twice a day.
4. The use of claim 3, wherein the therapeutically effective amount of navitoclax is 100 mg.
5. The use of claim 3, wherein the therapeutically effective amount of navitoclax is 200 mg.
6. The use of claim 3, wherein the human subject has been treated with a JAK-2 inhibitor prior to administration of the therapeutically effective amount of navitoclax.
7. The use of claim 6, wherein the therapeutically effective amount of navitoclax is 100 mg; and wherein the therapeutically effective amount of ruxolitinib is 10 mg.
8. The use of claim 6, wherein the therapeutically effective amount of navitoclax is 200 mg; and wherein the therapeutically effective amount of ruxolitinib is 10 mg.
9. The use of claim 1, wherein the treatment of the human subject results in a spleen volume reduction of at least 35% by week 24.
10. Use of a therapeutically effective amount of navitoclax selected from the group consisting of 50 mg, 100 mg, 200 mg, and 300 mg in the manufacture of a first medicament and use of a therapeutically effective amount of ruxolitinib in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat a human subject with myelofibrosis;

wherein the myelofibrosis is relapsed or refractory myelofibrosis; and

wherein the treatment of the human subject results a spleen volume reduction of at least 35%.

11. The use of claim 10, wherein the therapeutically effective amount of ruxolitinib is at least 10 mg.
12. The use of claim 11, wherein the therapeutically effective amount of navitoclax is to be administered once a day; and wherein the therapeutically effective amount of ruxolitinib is to be administered twice a day.
13. The use of claim 12, wherein the therapeutically effective amount of navitoclax is 100 mg.
14. The use of claim 12, wherein the therapeutically effective amount of navitoclax is 200 mg.
15. The use of claim 10, wherein the human subject has received at least one dose of ruxolitinib prior to administration of a therapeutically effective amount of navitoclax.
16. The use of claim 15, wherein the human subject has received a dose of at least 10 mg ruxolitinib twice a day for 12 weeks prior to administration of a therapeutically effective amount of navitoclax.
17. The use of claim 16, wherein the therapeutically effective amount of navitoclax is 100 mg.
18. The use of claim 16, wherein the therapeutically effective amount of navitoclax is 200 mg.
19. Use of a therapeutically effective amount of navitoclax selected from the group consisting of 50 mg, 100 mg, 200 mg, and 300 mg in the manufacture of a first medicament and use of a therapeutically effective amount of ruxolitinib in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat a human subject with myelofibrosis;

wherein the myelofibrosis is relapsed or refractory myelofibrosis; and

wherein treatment of the human subject results in an improvement in a grade of bone marrow fibrosis relative to a baseline grade of bone marrow fibrosis.

20. The use of claim 19, wherein the therapeutically effective amount of ruxolitinib is at least 10 mg.
21. The use of claim 20, and wherein the therapeutically effective amount of navitoclax is to be administered once a day; and wherein the ruxolitinib dose is to be administered twice a day.
22. The use of claim 21, wherein the therapeutically effective amount of navitoclax is 100 mg.
23. The use of claim 21, wherein the therapeutically effective amount of navitoclax is 200 mg.

24. The use of claim 1, wherein the human subject has failed to achieve a spleen volume reduction of at least 35% prior to being administered navitoclax.
25. The use of claim 1, wherein an initial dose of therapeutically effective amount of navitoclax is 50 mg; and

    wherein after at least 7 days the therapeutically effective amount of navitoclax is increased to a next higher dose of the therapeutically effective amount of navitoclax.
26. The use of claim 1, wherein the human subject has received at least one dose of ruxolitinib of more than 10 mg prior to administration of the therapeutically effective amount of navitoclax;

    wherein the dose of ruxolitinib is reduced to the therapeutically effective amount of ruxolitinib of 10 mg after administration of the therapeutically effective amount of navitoclax.
27. Use of a therapeutically effective amount of navitoclax selected from the group consisting of 50 mg, 100 mg, 200 mg, and 300 mg in the manufacture of a first medicament and use of a therapeutically effective amount of ruxolitinib in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to significantly reduce spleen volume in a human subject with myelofibrosis who is refractory to treatment with a JAK-2 inhibitor;

    wherein the navitoclax is to be orally administered to the human subject with myelofibrosis once a day,

    wherein the ruxolitinib is to be orally administering to the human subject with myelofibrosis twice a day.

    wherein following 24 weeks of said administration of navitoclax in combination with ruxolitinib, the spleen volume of the human subject with myelofibrosis is reduced by at least 35%.
28. Use of a therapeutically effective amount of navitoclax selected from the group consisting of 50 mg, 100 mg, 200 mg, and 300 mg in the manufacture of a first medicament anduse of a therapeutically effective amount of ruxolitinib in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to improve bone marrow fibrosis grade in a human subject with myelofibrosis who is refractory to treatment with a JAK-2 inhibitor;

wherein the navitoclax is to be orally administered to the human subject with myelofibrosis once a day,

wherein the ruxolitinib is to be orally administered to the human subject with myelofibrosis twice a day,

wherein following 24 weeks of said administration of navitoclax in combination with ruxolitinib the bone marrow fibrosis grade of the human subject with myelofibrosis is improved by at least one grade.

29. Use of an effective amount of navitoclax in the manufacture of a first medicament and use of an effective amount of ruxolitinib in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat myelofibrosis in a human subject in need thereof, wherein the first and second medicaments are to be orally administered to said subject, wherein

(i) if the human subject has a baseline platelet count of greater than or equal to 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg once daily, and if the human subject has a baseline platelet count of less than 150 x 10^9/L, the effective amount of navitoclax comprises 100 mg once daily, escalated to 200 mg once daily after 7 days or more if the human subject has a platelet count greater than or equal to 75 x 10^9/L, and

(ii) the effective amount of ruxolitinib comprises 10 mg twice daily;

wherein the effective amount of navitoclax is optionally increased to 300 mg once daily if the human subject fails to achieve spleen reduction volume of at least 35% (SVR_{35}) by week 24 of treatment.

30. The use of claim 29, wherein the myelofibrosis comprises relapsed/refractory (R/R), intermediate or high-risk primary or secondary myelofibrosis, post-polycythemia vera or post-essential thrombocytopenia myelofibrosis.

31. The use of claim 29, wherein the effective amount of navitoclax is optionally modified or interrupted due to thrombocytopenia or neutropenia.

32. The use of claim 31, wherein

(i) if the subject has a platelet count between 75 x 10^9/L and greater than or equal to 50 x 10^9/L the effective amount of navitoclax is optionally reduced;

(ii) if the subject has a platelet count less than 50 x 10^9/L, the navitoclax is interrupted or discontinued until platelets levels stabilize above a level greater than or equal to 50 x 10^9/L;

(iii) if the subject has an absolute neutrophil count (ANC) less than 1.0 but greater than 0.5 x 10^9/L, the subject is optionally supported with G-CSF or antibiotics until ANC is greater than 1.0 x 10^9/L; and

(iv) if the subject has an absolute neutrophil count (ANC) less than 0.5 x 10^9/L, the subject is optionally supported with G-CSF or antibiotics until ANC is greater than 1.0 x 10^9/L and navitoclax is interrupted or discontinued until ANC is greater than 1.0 x 10^9/L.

33. The use of claim 29, wherein the effective amount of ruxolitinib is modified or interrupted due to thrombocytopenia.

34. Use of an effective amount of navitoclax in the manufacture of a first medicament and use of an effective amount of ruxolitinib in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat myelofibrosis in a human subject in need thereof, wherein the first and second medicaments are to be orally administered to said subject, wherein

(i) if the human subject has a baseline platelet count of greater than or equal to 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg once daily, and if the human subject has a baseline platelet count of less than 150 x 10^9/L, the effective amount of navitoclax comprises 100 mg once daily, escalated to 200 mg once daily after 7 days or more if the human subject has a platelet count greater than or equal to 75 x 10^9/L, and

(ii) if the human subject has a baseline platelet count of greater than 200 x 10^9/L, the effective amount of ruxolitinib comprises 20 mg twice daily, if the subject has a baseline platelet count between 100 x 10^9/L and 200 x 10^9/L, the effective amount of ruxolitinib comprises 15 mg twice daily, and if the subject has a baseline platelet count between 50 x 10^9/L to less than 100 x 10^9/L, the effective amount of ruxolitinib comprises 5 mg twice daily;

wherein the effective amount of navitoclax is optionally increased to 300 mg once daily if the human subject fails to achieve spleen reduction volume of at least 35% (SVR_{35}) by week 24 of treatment.

35. The use of claim 34, wherein the myelofibrosis comprises relapsed/refractory (R/R), intermediate or high-risk primary or secondary myelofibrosis, post-polycythemia vera or post-essential thrombocytopenia myelofibrosis.

36. The use of claim 34, wherein the effective amount of navitoclax is optionally modified or interrupted due to thrombocytopenia or neutropenia.

37. The use of claim 36, wherein

(i) if the subject has a platelet count between 75 x 10^9/L and greater than or equal to 50 x 10^9/L the effective amount of navitoclax is optionally reduced;

(ii) if the subject has a platelet count less than 50 x 10^9/L, the navitoclax is interrupted or discontinued until platelets levels stabilize above a level greater than or equal to 50 x 10^9/L;

(iii) if the subject has an absolute neutrophil count (ANC) less than 1.0 but greater than 0.5 x 10^9/L, the subject is optionally supported with G-CSF or antibiotics until ANC is greater than 1.0 x 10^9/L; and

(iv) if the subject has an absolute neutrophil count (ANC) less than 0.5 x 10^9/L, the subject is optionally supported with G-CSF or antibiotics until ANC is greater than 1.0 x 10^9/L and navitoclax is interrupted or discontinued until ANC is greater than 1.0 x 10^9/L.

38. The use of claim 34, wherein the effective amount of ruxolitinib is modified or interrupted due to thrombocytopenia.

39. Use of an effective amount of navitoclax in the manufacture of a first medicament and use of an effective amount of ruxolitinib in the manufacture of a second medicament wherein the first and second medicaments are to be used in combination therapy to treat myelofibrosis in a human subject in need thereof, wherein the first and second medicaments are to be orally administered to said subject, and wherein a baseline platelet count is obtained from said human subject, wherein

(i) if the human subject has a baseline platelet count of greater than or equal to 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg once daily, and if the human subject has a baseline platelet count of less than 150 x 10^9/L, the effective amount of navitoclax comprises 100 mg once daily, escalated to 200 mg once daily after 7 days or more if the human subject has a platelet count greater than or equal to 75 x 10^9/L, and

(ii) the effective amount of ruxolitinib comprises 10 mg twice daily;

wherein the effective amount of navitoclax is optionally increased to 300 mg once daily if the human subject fails to achieve spleen reduction volume of at least 35% (SVR_{35}) by week 24 of treatment.

40. The use of claim 39, wherein the myelofibrosis comprises relapsed/refractory (R/R), intermediate or high-risk primary or secondary myelofibrosis, post-polycythemia vera or post-essential thrombocytopenia myelofibrosis.

41. The use of claim 39, wherein the effective amount of navitoclax is optionally modified or interrupted due to thrombocytopenia or neutropenia.

42. The use of claim 41, wherein

(i) if the subject has a platelet count between 75 x 10^9/L and greater than or equal to 50 x 10^9/L the effective amount of navitoclax is optionally reduced;

(ii) if the subject has a platelet count less than 50 x 10^9/L, the navitoclax is interrupted or discontinued until platelets levels stabilize above a level greater than or equal to 50 x 10^9/L;

(iii) if the subject has an absolute neutrophil count (ANC) less than 1.0 but greater than 0.5 x 10^9/L, the subject is optionally supported with G-CSF or antibiotics until ANC is greater than 1.0 x 10^9/L; and

(iv) if the subject has an absolute neutrophil count (ANC) less than 0.5 x 10^9/L, the subject is optionally supported with G-CSF or antibiotics until ANC is greater than 1.0 x 10^9/L and navitoclax is interrupted or discontinued until ANC is greater than 1.0 x 10^9/L.

43. The use of claim 39, wherein the effective amount of ruxolitinib is modified or interrupted due to thrombocytopenia.

44. Use of an effective amount of navitoclax in the manufacture of a first medicament and use of an effective amount of ruxolitinib in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat myelofibrosis in a human subject in need thereof, wherein the first and second medicaments are to be orally administered, and wherein a baseline platelet count is obtained from said human subject, wherein

(i) if the human subject has a baseline platelet count of greater than or equal to 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg once daily, and if the human subject has a baseline platelet count of less than 150 x 10^9/L, the effective amount of navitoclax comprises 100 mg once daily, escalated to 200 mg once daily after 7 days or more if the human subject has a platelet count greater than or equal to 75 x 10^9/L, and

(ii) if the human subject has a baseline platelet count of greater than 200 x 10^9/L, the effective amount of ruxolitinib comprises 20 mg twice daily, if the subject has a baseline

platelet count between 100 x 10^9/L and 200 x 10^9/L, the effective amount of ruxolitinib comprises 15 mg twice daily, and if the subject has a baseline platelet count between 50 x 10^9/L to less than 100 x 10^9/L, the effective amount of ruxolitinib comprises 5 mg twice daily;

wherein the effective amount of navitoclax is optionally increased to 300 mg once daily if the human subject fails to achieve spleen reduction volume of at least 35% (SVR_{35}) by week 24 of treatment.

45. The use of claim 44, wherein the myelofibrosis comprises relapsed/refractory (R/R), intermediate or high-risk primary or secondary myelofibrosis, post-polycythemia vera or post-essential thrombocytopenia myelofibrosis.

46. The use of claim 44, wherein the effective amount of navitoclax is optionally modified or interrupted due to thrombocytopenia or neutropenia.

47. The use of claim 46, wherein

(i) if the subject has a platelet count between 75 x 10^9/L and greater than or equal to 50 x 10^9/L the effective amount of navitoclax is optionally reduced;

(ii) if the subject has a platelet count less than 50 x 10^9/L, the navitoclax is interrupted or discontinued until platelets levels stabilize above a level greater than or equal to 50 x 10^9/L;

(iii) if the subject has an absolute neutrophil count (ANC) less than 1.0 but greater than 0.5 x 10^9/L, the subject is optionally supported with G-CSF or antibiotics until ANC is greater than 1.0 x 10^9/L; and

(iv) if the subject has an absolute neutrophil count (ANC) less than 0.5 x 10^9/L, the subject is optionally supported with G-CSF or antibiotics until ANC is greater than 1.0 x 10^9/L and navitoclax is interrupted or discontinued until ANC is greater than 1.0 x 10^9/L.

48. The use of claim 44, wherein the effective amount of ruxolitinib is modified or interrupted due to thrombocytopenia.