DOSING REGIMENS FOR USE IN TREATING MYELOFIBROSIS AND MPN-RELATED DISORDERS WITH NAVITOCLAX

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present Application claims priority to U.S. Provisional Patent Application Serial No. 62/930,951, filed November 5, 2019 and to U.S. Provisional Patent Application Serial No. 62/984,518, filed March 3, 2020. The disclosures of both references are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

[0002] This invention relates to methods for treating myelofibrosis and myeloproliferative neoplasm (MPN)-related disorders in a subject comprising administering to the subject specific doses of navitoclax, optionally in combination with a therapeutically effective amount of ruxolitinib.

BACKGROUND OF THE INVENTION

[0003] Myeloproliferative neoplasms or MPNs, are a group of rare, chronic blood cancers in which a person's bone marrow does not function properly, affecting blood-cell formation. People with MPNs experience an abnormal production of these blood cells, which can cause a host of symptoms and complications. Myelofibrosis (MF) is one such MPN characterized by bone marrow megakaryocytic proliferation, reticulin and/or collagen fibrosis, and presence of mutations of the Janus kinase 2 gene (JAK-2), thrombopoietin receptor gene (MPL), or the calreticulin gene. Myelofibrosis is characterized by constitutional symptoms, splenomegaly, an increased risk of transformation to acute myeloid leukemia (AML) and a shortened life expectancy. The median age at diagnosis is in the sixth decade and 90% of patients are diagnosed after the age of 40 years.

[0004] Ruxolitinib (*e.g.* JAKAFI®) is approved for the treatment of patients with primary myelofibrosis in the United States and European Union. Ruxolitinib induces improvement in splenomegaly and disease-related symptoms as compared to placebo or best available alternative therapy. However, therapy with ruxolitinib does not eradicate the malignant clones, is not known to improve bone marrow fibrosis, and patients who stop ruxolitinib rapidly become symptomatic

again. Some patients do not respond to ruxolitinib, whereas others develop secondary resistance. For example, in patients suffering from intermediate or high-risk primary or secondary myelofibrosis; only approximately 40% of patients achieve a spleen volume reduction of ≥35% (SVR_{35}) with ruxolitinib monotherapy, and SVR_{35}, if it occurs, is typically only observed within the first 12 weeks of the commencement of ruxolitinib monotherapy. Current therapies other than hematopoietic stem cell transplantation are not able to control all the clinical manifestations of myelofibrosis. Therefore, new treatments for myelofibrosis (MF) and MPN-related disorders such as polycythemia vera (PCV), essential thrombocytopenia (ET), and CMML (chronic myelomonocytic leukemia are needed to address the current problems with ruxolitinib therapy, particularly for patients who are not responsive to ruxolitinib monotherapy.

[0005] Navitoclax (ABT-263) is a small-molecule BCL-2 family protein inhibitor that binds with high affinity (Ki ≤ 1 nM) to BCL-X_L, BCL-2, and BCL-W. By competitively binding to these proteins, navitoclax frees pro-apoptotic family members, thus triggering cell death by apoptosis in sensitive populations. Certain cancer cells are particularly sensitive to navitoclax. For example, navitoclax displays potent mechanism-based cytotoxicity (EC_{50} ≤ 1 μM) against human tumor cell lines derived from small cell lung carcinomas and lymphoid malignancies. Navitoclax exhibits potent single agent activity against 10 of 22 cell lines consisting of multiple leukemia and lymphoma types spanning both B-cell and T-cell malignancies. Navitoclax and a different BCL-2 family protein inhibitor compound, ABT-737, have also shown cell killing activity against myeloproliferative neoplasm patient samples cultured ex vivo and myeloproliferative neoplasm-derived cell lines bearing the activating JAK-2 V617F mutation, which is common in polycythemia vera and myelofibrosis.

[0006] Aberrant JAK-2-STAT3/5 signaling has been linked to over-expression of the navitoclax resistance factor MCL-1, and JAK-2 inhibitors have been shown to reduce MCL-1 expression. Conversely, BCL-X_L elevation has been associated with resistance to JAK-2 inhibitors, and navitoclax has shown the ability to overcome that resistance.

[0007] BCL-X_L inhibition alone, achieved using a BCL-X_L selective inhibitor (WEHI-539), was shown to be sufficient for overcoming resistance. ABT-737 has also shown an ability to block the proliferation of myeloproliferative neoplasm cells in long-term colony forming assays, which serve as an indicator of malignant precursor/stem cell survival and proliferation. For example, endogenous erythroid colonies representing malignant PV clones able to grow in the

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

[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

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}); wherein the therapeutically effective amount of navitoclax is administered once a day; and wherein the therapeutically effective amount of ruxolitinib is administered twice a day. In one aspect, the therapeutically effective amount of navitoclax is 100 mg. In another aspect, the therapeutically effective amount of navitoclax is 200 mg.

[0012] 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 of at least 10 mg; wherein the treatment of the human subject results in a spleen volume reduction of at least 35% (SVR_{35}); wherein the therapeutically effective amount of navitoclax is administered once a day; wherein the therapeutically effective amount of ruxolitinib is administered twice a day; and wherein the human subject has been treated with a JAK-2 inhibitor prior to administering the therapeutically effective amount of navitoclax. In one aspect, the therapeutically effective amount of navitoclax is 100 mg; and the therapeutically effective amount of ruxolitinib is 10 mg. In another aspect, the therapeutically effective amount of navitoclax is 200 mg; and the therapeutically effective amount of ruxolitinib is 10 mg.

[0013] In another embodiment, a method for treatment of a human subject with myelofibrosis 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 myelofibrosis is relapsed or refractory (R/R) myelofibrosis; and wherein the treatment of the human subject results a spleen volume reduction of at least 35%. In one aspect, the therapeutically effective amount of ruxolitinib is at least 10 mg.

[0014] In yet another embodiment, a method for treatment of a human subject with myelofibrosis 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 myelofibrosis is relapsed or refractory myelofibrosis; and wherein the treatment of the human subject results a spleen volume reduction of at least 35% (SVR_{35}); wherein the therapeutically effective amount of navitoclax is administered once a day; and wherein the therapeutically effective amount of ruxolitinib is administered twice a day. In one aspect, the therapeutically effective amount of navitoclax is 100 mg. In another aspect, the therapeutically effective amount of navitoclax is 200 mg.

[0015] In one embodiment, a method for treatment of a human subject with myelofibrosis 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 myelofibrosis is relapsed or refractory myelofibrosis; wherein the treatment of the human subject results a spleen volume reduction of at least 35% (SVR_{35}); and wherein the human subject has received at least one dose of ruxolitinib prior to administering a therapeutically effective amount of navitoclax.

[0016] In another embodiment, a method for treatment of a human subject with myelofibrosis 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 myelofibrosis is relapsed or refractory myelofibrosis; wherein the treatment of the human subject results a spleen volume reduction of at least 35% (SVR_{35}); and wherein the human subject has received a dose of at least 10 mg ruxolitinib twice a day for 12 weeks prior to administering a therapeutically effective amount of navitoclax. In one aspect, the therapeutically effective amount of navitoclax is 100 mg. In another aspect, the therapeutically effective amount of navitoclax is 200 mg.

[0017] In yet another embodiment, a method for treatment of a human subject with myelofibrosis 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 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. In one aspect, the therapeutically effective amount of ruxolitinib is at least 10 mg.

[0018] In still another embodiment, a method for treatment of a human subject with myelofibrosis 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 myelofibrosis is relapsed or refractory myelofibrosis; 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; wherein the therapeutically effective amount of navitoclax is administered once a day; and wherein the ruxolitinib dose is administered twice a day. In one aspect, the therapeutically effective amount of navitoclax is 100 mg. In another aspect, the therapeutically effective amount of navitoclax is 200 mg.

[0019] 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 human subject has failed to achieve a spleen volume reduction of at least 35% prior to being administered navitoclax; and wherein the treatment of the human subject results in a spleen volume reduction of at least 35%.

[0020] 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 an initial dose of therapeutically effective amount of navitoclax is 50 mg; 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; and wherein the treatment of the human subject results in a spleen volume reduction of at least 35%.

[0021] 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 human subject has received at least one dose of ruxolitinib of more than 10 mg prior to administering the therapeutically effective amount of navitoclax; wherein the

dose of ruxolitinib is reduced to the therapeutically effective amount of ruxolitinib of 10 mg after administering the therapeutically effective amount of navitoclax; and wherein the treatment of the human subject results in a spleen volume reduction of at least 35%.

[0022] In one embodiment, a method for significantly reducing spleen volume in a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who is refractory to treatment with a JAK-2 inhibitor is provided, comprising orally administering to the human subject once a day a therapeutically effective amount of navitoclax selected from the group consisting of 50 mg, 100 mg, 200 mg, and 300 mg; in combination with orally administering to the human subject twice a day a therapeutically effective amount of ruxolitinib; wherein following 24 weeks of said administering navitoclax in combination with ruxolitinib, the spleen volume of the human subject is reduced by at least 35%.

[0023] In one embodiment, a method for improving bone marrow fibrosis grade in a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who is refractory to treatment with a JAK-2 inhibitor is provided, comprising orally administering to the human subject once a day a therapeutically effective amount of navitoclax selected from the group consisting of 50 mg, 100 mg, 200 mg, and 300 mg; in combination with orally administering to the human subject twice a day a therapeutically effective amount of ruxolitinib; wherein following 24 weeks of said administering navitoclax in combination with ruxolitinib the bone marrow fibrosis grade of the human subject s is improved by at least one grade.

[0024] In one embodiment, a method for treatment of myelofibrosis in a human subject in need thereof is provided, comprising orally administering to said subject an effective amount of navitoclax in combination with an effective amount of ruxolitinib, 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.

[0025] In one embodiment, a method for treatment of myelofibrosis in a human subject in

need thereof is provided, comprising orally administering to said subject an effective amount of navitoclax in combination with an effective amount of ruxolitinib, 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; and wherein the myelofibrosis comprises relapsed/refractory (R/R), intermediate or high-risk primary or secondary myelofibrosis, post-polycythemia vera or post-essential thrombocytopenia myelofibrosis.

[0026] In one embodiment, a method for treatment of myelofibrosis in a human subject in need thereof is provided, comprising orally administering to said subject an effective amount of navitoclax in combination with an effective amount of ruxolitinib, 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; and wherein the effective amount of navitoclax is optionally modified or interrupted due to thrombocytopenia or neutropenia.

[0027] In one embodiment, a method for treatment of myelofibrosis in a human subject in need thereof is provided, comprising orally administering to said subject an effective amount of navitoclax in combination with an effective amount of ruxolitinib, 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; wherein the effective amount of navitoclax is optionally modified or interrupted due to thrombocytopenia or neutropenia; and 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.

[0028] In one embodiment, a method for treatment of myelofibrosis in a human subject in need thereof is provided, comprising orally administering to said subject an effective amount of navitoclax in combination with an effective amount of ruxolitinib, 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; and wherein the effective amount of ruxolitinib is modified or interrupted due to thrombocytopenia.

[0029] In one embodiment, a method for treatment of myelofibrosis in a human subject in need thereof is provided, comprising orally administering to said subject an effective amount of navitoclax in combination with an effective amount of ruxolitinib, 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.

[0030] In one embodiment, a method for treatment of myelofibrosis in a human subject in need thereof is provided, comprising orally administering to said subject an effective amount of navitoclax in combination with an effective amount of ruxolitinib, 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; and wherein the myelofibrosis comprises relapsed/refractory (R/R), intermediate or high-risk primary or secondary myelofibrosis, post-polycythemia vera or post-essential thrombocytopenia myelofibrosis.

[0031] In one embodiment, a method for treatment of myelofibrosis in a human subject in need thereof is provided, comprising orally administering to said subject an effective amount of navitoclax in combination with an effective amount of ruxolitinib, 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; and wherein the effective amount of navitoclax is optionally modified or interrupted due to thrombocytopenia or neutropenia.

[0032] In one embodiment, a method for treatment of myelofibrosis in a human subject in need thereof is provided, comprising orally administering to said subject an effective amount of navitoclax in combination with an effective amount of ruxolitinib, 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; wherein the effective amount of navitoclax is optionally modified or interrupted due to thrombocytopenia or neutropenia; and 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.

[0033] In one embodiment, a method for treatment of myelofibrosis in a human subject in need thereof is provided, comprising orally administering to said subject an effective amount of navitoclax in combination with an effective amount of ruxolitinib, 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; and wherein the effective amount of ruxolitinib is modified or interrupted due to thrombocytopenia.

[0034] In one embodiment, a method for treatment of myelofibrosis in a human subject in need thereof is provided, comprising (a) obtaining a baseline platelet count from said human subject; and (b) orally administering to said subject an effective amount of navitoclax in combination with an effective amount of ruxolitinib, 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.

[0035] In one embodiment, a method for treatment of myelofibrosis in a human subject in need thereof is provided, comprising (a) obtaining a baseline platelet count from said human subject; and (b) orally administering to said subject an effective amount of navitoclax in combination with an effective amount of ruxolitinib, 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; and wherein the myelofibrosis comprises relapsed/refractory (R/R), intermediate or high-risk primary or secondary myelofibrosis, post-polycythemia vera or post-essential thrombocytopenia myelofibrosis.

[0036] In one embodiment, a method for treatment of myelofibrosis in a human subject in need thereof is provided, comprising (a) obtaining a baseline platelet count from said human subject; and (b) orally administering to said subject an effective amount of navitoclax in combination with an effective amount of ruxolitinib, 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; and wherein the effective amount of navitoclax is optionally modified or interrupted due to thrombocytopenia or neutropenia.

[0037] In one embodiment, a method for treatment of myelofibrosis in a human subject in

need thereof is provided, comprising (a) obtaining a baseline platelet count from said human subject; and (b) orally administering to said subject an effective amount of navitoclax in combination with an effective amount of ruxolitinib, 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; wherein the effective amount of navitoclax is optionally modified or interrupted due to thrombocytopenia or neutropenia; and 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.

[0038] In one embodiment, a method for treatment of myelofibrosis in a human subject in need thereof is provided, comprising (a) obtaining a baseline platelet count from said human subject; and (b) orally administering to said subject an effective amount of navitoclax in combination with an effective amount of ruxolitinib, 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; and wherein the effective amount of ruxolitinib is modified or interrupted due to thrombocytopenia.

[0039] In one embodiment, a method for treatment of myelofibrosis in a human subject in need thereof is provided, comprising (a) obtaining a baseline platelet count from said human subject; and (b) orally administering to said subject an effective amount of navitoclax in combination with an effective amount of ruxolitinib, 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.

[0040] In one embodiment, a method for treatment of myelofibrosis in a human subject in need thereof is provided, comprising (a) obtaining a baseline platelet count from said human subject; and (b) orally administering to said subject an effective amount of navitoclax in combination with an effective amount of ruxolitinib, 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; and wherein the myelofibrosis comprises relapsed/refractory (R/R), intermediate or high-risk primary or secondary myelofibrosis, post-polycythemia vera or post-essential thrombocytopenia myelofibrosis.

[0041] In one embodiment, a method for treatment of myelofibrosis in a human subject in need thereof is provided, comprising (a) obtaining a baseline platelet count from said human subject; and (b) orally administering to said subject an effective amount of navitoclax in combination with an effective amount of ruxolitinib, 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; and wherein the effective amount of navitoclax is optionally modified or interrupted due to thrombocytopenia or neutropenia.

[0042] In one embodiment, a method for treatment of myelofibrosis in a human subject in need thereof is provided, comprising (a) obtaining a baseline platelet count from said human subject; and (b) orally administering to said subject an effective amount of navitoclax in combination with an effective amount of ruxolitinib, 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; wherein the effective amount of navitoclax is optionally modified or interrupted due to thrombocytopenia or neutropenia; and 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.

[0043] In one embodiment, a method for treatment of myelofibrosis in a human subject in need thereof is provided, comprising (a) obtaining a baseline platelet count from said human subject; and (b) orally administering to said subject an effective amount of navitoclax in combination with an effective amount of ruxolitinib, 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; and wherein the effective amount of ruxolitinib is modified or interrupted due to thrombocytopenia.

BRIEF DESCRIPTION OF THE FIGURES

[0044] **Figure 1** is a waterfall plot describing percent change from baseline in spleen volume at week 24 as described in Example 1. As shown, 29% of patients achieved SVR_{35} at week 24.

[0045] **Figure 2** is a schematic of the exposure-response model for platelet inhibition by combination of navitoclax and ruxolitinib described in Example 2.

[0046] **Figures 3A, 3B** shows the predicted percent incidence of grade 3 (**Figure 3A**) and grade 4 (**Figure 3B**) thrombocytopenia for combination of navitoclax and ruxolitinib (10 mg twice a day (BID)) in naive myelofibrosis and relapsed or refractory myelofibrosis as described in Example 2.

[0047] **Figure 4** is a schematic of the exposure - response model for spleen volume inhibition by combination of navitoclax and ruxolitinib as described in Example 2.

[0048] **Figure 5** shows the predicted average change from baseline of spleen volume over time for different dose combinations of navitoclax and ruxolitinib described in Example 2.

[0049] **Figure 6** shows the predicted percent of subjects with spleen volume reduction of at least 35% (SVR_{35}) over time for different dose combinations of navitoclax and ruxolitinib.

[0050] **Figure 7** shows the design of a Phase 2, multicenter, open-label study to evaluate the tolerability and efficacy of navitoclax alone or in combination with ruxolitinib in subjects with primary or secondary myelofibrosis.

DETAILED DESCRIPTION OF THE INVENTION

[0051] A Phase 2 clinical study was completed to evaluate the effect of the addition of navitoclax to ruxolitinib in subjects with primary or secondary myelofibrosis (Example 1 *supra*), and two Phase 3 clinical studies are underway, evaluating the combination of navitoclax with myelofibrosis in both JAK2 inhibitor naïve patients (Example 4) and in the relapsed or refractory (R/R) setting (Example 5). As shown in Example 1, after 24 weeks of treatment with navitoclax and ruxolitinib, 29% of subjects achieved a spleen volume reduction $\geq$ 35% (SVR_{35}), and 54% of subjects achieved > 50% reduction of the spleen length (cm, below costal margin) as assessed by palpation. Additionally, spleen responses deepened beyond 24 weeks of treatment, and the best

overall SVR_{35} was further improved to 42%, with 79% of subjects achieving reductions in spleen length by palpation of > 50%. Allelic frequency reductions > 5% were observed in 42% of subjects, and reductions in bone marrow fibrosis of ≥ 1 grade were observed in 25% of subjects, suggesting this drug combination may be disease modifying.

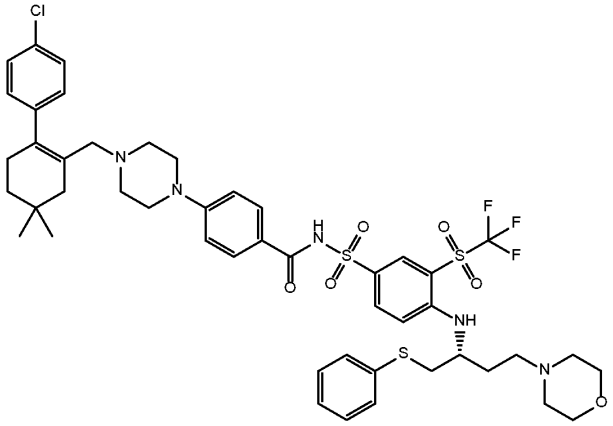
[0052] Currently, ruxolitinib is the only targeted therapy approved and is considered the standard of care for the treatment of patients with intermediate or high-risk myelofibrosis. Ruxolitinib monotherapy has shown clinical benefit in improving splenomegaly and symptoms in subjects with intermediate or high-risk primary or secondary myelofibrosis; however, a significant unmet medical need still exists as only approximately 40% of patients achieve a spleen volume reduction of ≥35% (SVR_{35}) and these improvements are typically only observed within the first 12 weeks of administration if they are to occur at all (Verstovsek S, Mesa R, Gotlib J, et al. A Double-Blind, Placebo-Controlled Trial of Ruxolitinib for Myelofibrosis. N Engl J Med. 2012;366(9):799-807, hereby incorporated by reference in its entirety). Allogeneic transplantation is the only known curative treatment for myelofibrosis; however, that is only feasible in younger and medically fit patients and is associated with substantial morbidity and mortality. The present invention presents a new option for myelofibrosis treatment, particularly for patients who are refractory to ruxolitinib monotherapy, because a majority of patients do not achieve SVR_{35} with ruxolitinib monotherapy, but 42% of patients achieve SVR_{35} while receiving a combination of navitoclax with ruxolitinib even in patients who do not achieve SVR_{35} with ruxolitinib monotherapy.

[0053] The present disclosure relates to methods for treatment of a human subject with myelofibrosis or an MPN-related disorder such as polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic monomyelocytic leukemia (CMML), comprising administering a therapeutically effective amount of specific doses of navitoclax in combination with a therapeutically effective amount of ruxolitinib. In some embodiments, pre-dosing of ruxolitinib or another JAK2 inhibitor begins at least twelve weeks prior to administering navitoclax, followed by administration of a therapeutically effective amount of navitoclax.

Navitoclax

[0054] Navitoclax (also known as ABT-263) is a novel small-molecule BCL-2 family protein inhibitor that binds with high affinity ($K_i \leq 1$ nM) to BCL-X_L, BCL-2, and BCL-W. Navitoclax has a CAS Registry Number of 923564-51-6; has an empirical formula of

$C_{47}H_{55}ClF_3N_5O_6S_3$; a gram molecular weight of 974.61; and is described in U.S. Patent 7,390,799, published February 1, 2007, hereby incorporated by reference in its entirety.



Chemical Structure of Navitoclax

[0055] Use of the term "4-(4-{[2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohexen-1-yl]methyl}-1-piperazinyl)-*N*-[(4-{[(2*R*)-4-(4-morpholinyl)-1-(phenylsulfanyl)-2-butanyl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide" or "*N*-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1*R*)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide" encompasses (unless otherwise indicated) solvates (including hydrates) and polymorphic forms of navitoclax or its salts. Pharmaceutical compositions of "4-(4-{[2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohexen-1-yl]methyl}-1-piperazinyl)-*N*-[(4-{[(2*R*)-4-(4-morpholinyl)-1-(phenylsulfanyl)-2-butanyl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide" or "*N*-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1*R*)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide" include all pharmaceutically acceptable compositions comprising "4-(4-{[2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohexen-1-yl]methyl}-1-piperazinyl)-*N*-[(4-{[(2*R*)-4-(4-morpholinyl)-1-(phenylsulfanyl)-2-butanyl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide" or "*N*-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1*R*)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide" and one or more diluents, vehicles and/or excipients.

Recommended Navitoclax Dosage Regimen for Myelofibrosis

[0056] The recommended starting dose of navitoclax for most patients with a baseline platelet count ≥150 x 10^9/L is 200 mg navitoclax once daily. For subjects with a baseline platelet count ≤150 x 10^9/L, the recommended starting dose is 100 mg navitoclax once daily. *See* Table 1 below. Further dose modifications based on toxicities after starting navitoclax are described in Table 2 below. Mechanism of action for navitoclax-induced thrombocytopenia can be found at Kaefer *et al.*, Cancer Chemother Pharmacol (2014) 74:593–602, hereby incorporated by reference in its entirety. Additionally, at the discretion of the physician or prescribing agent, patients may increase dosage of navitoclax up to 300 mg once daily for subjects with suboptimal spleen response, *e.g.* a failure to achieve SVR_{35} by week 24. Subjects should be instructed to take navitoclax tablets, preferably with a meal and water, at approximately the same time each day. Navitoclax tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing. Bioavailability and food effect of navitoclax in healthy volunteers can be found at Xiong *et al.*, Anticancer Research 34: 3739-3746 (2014), hereby incorporated by reference in its entirety.

Table 1. Recommended Starting Dose for Navitoclax for Myelofibrosis

Platelet count	**Starting Dose**	**Escalation**
(> 150 x 10^9/L)	200 mg	n/a
(≤ 150 x 10^9/L)	100 mg	200 mg (after approximately 7 or more days provided the platelet count is ≥ 75 x 10^9/L)

Table 2. Recommended Navitoclax Dose Modifications for Toxicities

Event		**Action**
Thrombocytopenia	≥75 x 10^9/L	Maintain current dose of navitoclax. Platelet count should be rechecked approximately 7

		days after navitoclax dose increase.
	<75 x 10^9/L - ≥50 x 10^9/L	Maintain current navitoclax dose or consider dose reduction. Platelet count should be rechecked approximately every 7 days until ≥2 consecutive lab values indicate stable platelet count.
	<50 x 10^9/L	Interrupt navitoclax. Recheck platelets every 2-3 days until recovery to ≥50 10^9/L. Then resume navitoclax at a lower dose. Platelet count should be rechecked approximately every 7 days until ≥2 consecutive lab values indicate stable platelet count.
Grade 3 neutropenia	ANC <1.0 – 0.5 x 10^9/L	Monitor neutrophils at least weekly until ANC >1.0 x 10^9/L. Support with G-CSF and/or prophylaxis with antibiotics if clinically indicated.

Grade 4 neutropenia	ANC <0.5 x 10^9/L	Interrupt navitoclax. Monitor neutrophils at least weekly until ANC >1.0 x 10^9/L. Support with G-CSF and/or prophylaxis with antibiotics if clinically indicated. Reinitiate navitoclax at a lower dose upon recover of ANC >1.0 x 10^9/L.

[0057] If a subject misses a dose of navitoclax within 8 hours of the time it is usually taken, the subject should take the missed dose as soon as possible and resume the normal daily dosing schedule. If a subject misses a dose by more than 8 hours, the subject should not take the missed dose and should resume the usual dosing schedule the next day.

[0058] If a subject vomits following dosing no additional dose should be taken that day. The next prescribed dose should be taken at the usual time.

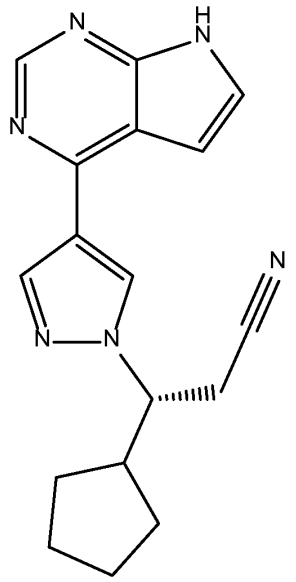
Dose Modifications for Use with CYP3A Inhibitors/ Inducers

[0059] Co-administration of navitoclax with CYP3A4 inhibitors or inducers or P-gp inhibitors should be undertaken with caution. For example, prescribing agents should consider modifying the dosage of navitoclax and/or a CYP3A4 inhibitor when co-administered with strong CYP3A4 inhibitors, or avoid co-administration with strong CYP3A4 inhibitors altogether, such as by discontinuing navitoclax for the duration of treatment with the strong CYP3A4 inhibitor. Increased dosage should be made with frequent monitoring of safety and efficacy. Co-administration of 400 mg once daily ketoconazole, a strong CYP3A, P-gp and BCRP inhibitor, in 10 subjects with cancer increased navitoclax AUC_∞ by 1.55-fold, and had no impact on C_{max}. Co-administration of 600 mg once daily rifampin, a strong CYP3A inducer, for 4 days in 11 subjects with cancer decreased navitoclax C_{max} by 16% and AUC_∞ by 41%. In a combination study of navitoclax with paclitaxel alone or carboplatin/paclitaxel in subjects with solid tumors, navitoclax had negligible effect (< 13% change) on C_{max} and AUC of paclitaxel and its

metabolite, 6-α-hydroxypaclitaxel whose formation is primarily mediated by CYP28 enzyme. Effects of navitoclax with CYP3A4 inhibitors in patients with cancer are described at Yang *et al.*, Journal of Clinical Pharmacy and Therapeutics, 2014, 39, 680–684, hereby incorporated by reference in its entirety.

Ruxolitinib

[0060] As known in the art, ruxolitinib, a dual JAK1 and JAK2 inhibitor, has a CAS Registry Number of 1092939-17-7; has an empirical formula of $C_{17}H_{18}N_6 \cdot H_3PO_4$; and a gram molecular weight of 404.36.



Chemical Structure of Ruxolitinib

[0061] Use of the term "(*R*)-3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile" or "(3*R*)-3-cyclopentyl-3-[4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]propanenitrile", or "(3*R*)-3-cyclopentyl-3-[4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]propanenitrile" encompasses (unless otherwise indicated) the free base, solvates (including hydrates), and polymorphic forms of ruxolitinib or its salts. Pharmaceutical compositions of ruxolitinib include all pharmaceutically acceptable compositions comprising ruxolitinib or ruxolitinib phosphate, and one or more diluents, vehicles and/or excipients.

[0062] One example of a pharmaceutical composition comprising ruxolitinib phosphate is JAKAFI® (Incyte). JAKAFI® tablets contains ruxolitinib phosphate equivalent to 5 mg, 10 mg, 15 mg, 20 mg and 25 mg of ruxolitinib free base together with inactive ingredients

microcrystalline cellulose, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, sodium starch glycolate, povidone and hydroxypropyl cellulose.

[0063] Suggested starting doses per indication are below, and doses of JAKAFI® should be individualized based on safety and efficacy.

[0064] For myelofibrosis, the FDA-approved starting dose of JAKAFI® is based on patient's baseline platelet count as follows: if baseline platelet count greater than 200 x 10^9 /L, then 20 mg is given orally twice daily; if baseline platelet count is 100 x 10^9 /L to 200 X 10^9 /L, then 15 mg given orally twice daily; and if baseline platelet count is 50 x 10^9 /L to less than 100 X 10^9 /L, then 5 mg is given orally twice daily. Complete blood counts should be monitored every 2 to 4 weeks until doses are stabilized, and then monitored as clinically indicated. Dosing should be modified or interrupted for thrombocytopenia.

[0065] For polycythemia vera, the FDA-approved starting dose of JAKAFI® is 10 mg given orally twice daily.

[0066] For acute graft versus host disease, the FDA-approved starting dose of JAKAFI® is 5 mg given orally twice daily.

[0067] JAKAFI® is FDA-approved for treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF in adults. JAKAFI® is also indicated for treatment of polycythemia vera, and for treatment of polycythemia vera (PV) in adults who have had an inadequate response to or are intolerant of hydroxyurea.

[0068] The following section of the present disclosure relates to the FDA-approved dosing regimens for JAKAFI®, which is one example of a commercial formulation containing ruxolitinib. This section and its contents are not meant to be limiting in any way and are intended to supplement the Examples and the embodiments/disclosure of the inventions disclosed herein. For example, the dose/dosing regimens for JAKAFI®, including but not limited to dose/dosing regimen modifications related to, *e.g.*, thrombocytopenia, neutropenia, hepatic and/or renal impairment disclosed below, for myelofibrosis and any MPN-related disorder, can be incorporated into any of the embodiments and regimens disclosed herein and are expressly intended to be considered within the scope of the present disclosure.

JAKAFI®- FDA Label Summary

[0069] The recommended starting dose of JAKAFI® for myelofibrosis is based on platelet

count (Table 3). Before starting therapy, a complete blood count (CBC) and platelet count must be performed, and every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. Doses may be titrated based on safety and efficacy.

Table 3: JAKAFI® Starting Doses for Myelofibrosis

Platelet Count	Starting Dose
Greater than 200 x 10^9 /L	20 mg orally twice daily
100 x 10^9 /L to 200 x 10^9 /L	15 mg orally twice daily
50 x 10^9 /L to less than 100 x 10^9 /L	5 mg orally twice daily

Dose Modification Guidelines for Hematologic Toxicity for Patients with Myelofibrosis Starting Treatment with a Platelet Count of 100 x 10^9/L or Greater

Treatment Interruption and Restarting Dosing

[0070] Treatment should be interrupted for platelet counts less than 50 x 10^9 /L or absolute neutrophil count (ANC) less than 0.5 x 10^9 /L. Once platelet counts have recovered to above 50 x 10^9 /L and ANC above 0.75 x 10^9 /L, dosing may be restarted. Table 4 illustrates the maximum allowable dose that may be used in restarting JAKAFI® after a previous interruption.

Table 4: Myelofibrosis: Maximum Restarting Doses for JAKAFI® after Safety Interruption for Thrombocytopenia for Patients Starting Treatment with a Platelet Count of 100 x 10^9/L or Greater

Current Platelet Count	Maximum Dose When Restarting JAKAFI® Treatment[a]
Greater than or equal to 125 x 10^9 /L	20 mg twice daily
100 to less than 125 x 10^9 /L	15 mg twice daily
75 to less than 100 x 10^9 /L	10 mg twice daily for at least 2 weeks; if stable, may increase to 15 mg twice daily
50 to less than 75 x 10^9 /L	5 mg twice daily for at least 2 weeks; if stable, may increase to 10 mg twice daily
Less than 50 x 10^9 /L	Continue hold

[a]Maximum doses are displayed. When restarting, begin with a dose at least 5 mg twice daily below the dose at interruption.

[0071] Following treatment interruption for ANC below 0.5 x 10^9 /L, after ANC recovers to 0.75 x 10^9 /L or greater, dosing can be restarted at the higher of 5 mg once daily or 5 mg twice daily below the largest dose in the week prior to the treatment interruption.

[0072] Dose reductions should be considered if the platelet counts decrease as outlined in Table 5 with the goal of avoiding dose interruptions for thrombocytopenia.

Table 5: Myelofibrosis: Dosing Recommendations for Thrombocytopenia for Patients Starting Treatment with a Platelet Count of 100 x 10^9/L or Greater

Platelet Count	**Dose at Time of Platelet Decline**				
	25 mg twice daily	**20 mg twice daily**	**15 mg twice daily**	**10 mg twice daily**	**5 mg twice daily**
	New Dose	**New Dose**	**New Dose**	**New Dose**	**New Dose**
100 to less than 125 x 10^9 /L	20 mg twice daily	15 mg twice daily	no change	no change	no change
75 to less than 100 x 10^9 /L	10 mg twice daily	10 mg twice daily	10 mg twice daily	no change	no change
50 to less than 75 x 10^9 /L	5 mg twice daily	5 mg twice daily	5 mg twice daily	5 mg twice daily	no change
Less than 50 x 10^9 /L	hold	hold	hold	hold	hold

Dose Modification Based on Insufficient Response for Patients with Myelofibrosis Starting Treatment with a Platelet Count of 100 x 10^9/L or Greater

[0073] If the response is insufficient and platelet and neutrophil counts are adequate, doses may be increased in 5 mg twice daily increments to a maximum of 25 mg twice daily. Doses should not be increased during the first 4 weeks of therapy and not more frequently than every 2 weeks. Consider dose increases in patients who meet all of the following conditions: a. Failure to achieve a reduction from pretreatment baseline in either palpable spleen length of 50% or a 35% reduction in spleen volume as measured by computed tomography (CT) or magnetic resonance imaging (MRI); b. Platelet count greater than 125 x 10^9 /L at 4 weeks and platelet count never below 100 x 10^9 /L; c. ANC Levels greater than 0.75 x 10^9 /L. Based on limited

clinical data, long-term maintenance at a 5 mg twice daily dose has not shown responses and continued use at this dose should be limited to patients in whom the benefits outweigh the potential risks. Discontinue JAKAFI® if there is no spleen size reduction or symptom improvement after 6 months of therapy.

Treatment Interruption and Restarting Dosing

[0074] Treatment should be interrupted for platelet counts less than 25 x 10^9 /L or ANC less than 0.5 x 10^9 /L. After recovery of platelet counts above 35 x 10^9 /L and ANC above 0.75 x 10^9 /L, dosing may be restarted. Restart dosing at the higher of 5 mg once daily or 5 mg twice daily below the largest dose in the week prior to the decrease in platelet count below 25 x 10^9 /L or ANC below 0.5 x 10^9 /L that led to dose interruption.

Dose Reductions

[0075] Reduce the dose of JAKAFI® for platelet counts less than 35 x 10^9 /L as described in Table 6.

Table 6: Myelofibrosis: Dosing Modifications for Thrombocytopenia for Patients with Starting Platelet Count of 50 x 10^9 /L to Less Than 100 x 10^9/L

Platelet Count	Dosing Recommendations
Less than 25 x 10^9 /L	Interrupt dosing.
25 x 10^9 /L to less than 35 x 10^9 /L and the platelet count decline is less than 20% during the prior four weeks	Decrease dose by 5 mg once daily. For patients on 5 mg once daily, maintain dose at 5 mg once daily.
25 x 10^9 /L to less than 35 x 10^9 /L AND the platelet count decline is 20% or greater during the prior four weeks	Decrease dose by 5 mg twice daily. For patients on 5 mg twice daily, decrease the dose to 5 mg once daily. For patients on 5 mg once daily, maintain dose at 5 mg once daily.

Dose Modifications Based on Insufficient Response for Patients with Myelofibrosis and Starting Platelet Count of 50 x 10^9/L to Less Than 100 x 10^9/L

[0076] Doses should not be increased during the first 4 weeks of therapy, or more frequently

than every 2 weeks. If the response is insufficient (see Dose Modification Based on Insufficient Response with Myelofibrosis Starting Treatment with a platelet count of 100 x 10^9/L or Greater), doses may be increased by increments of 5 mg daily to a maximum of 10 mg twice daily if: a) the platelet count has remained at least 40 x 10^9 /L, and b) the platelet count has not fallen by more than 20% in the prior 4 weeks, and c) the ANC is more than 1 x 10^9 /L, and d) the dose has not been reduced or interrupted for an adverse event or hematological toxicity in the prior 4 weeks. Continuation of treatment for more than 6 months should be limited to patients in whom the benefits outweigh the potential risks. JAKAFI® should be discontinued if there is no spleen size reduction or symptom improvement after 6 months of therapy.

Dose Modification for Bleeding

[0077] Interrupt treatment for bleeding requiring intervention regardless of current platelet count. Once the bleeding event has resolved, consider resuming treatment at the prior dose if the underlying cause of bleeding has been controlled. If the bleeding event has resolved but the underlying cause persists, consider resuming treatment with JAKAFI® at a lower dose.

Polycythemia Vera (PCV)

[0078] The recommended starting dose of JAKAFI® for polycythemia vera, an MPN-related disorder, is 10 mg twice daily. Doses may be titrated based on safety and efficacy. Dose Modification Guidelines for Patients with Polycythemia Vera A complete blood count (CBC) and platelet count must be performed before initiating therapy, every 2 to 4 weeks until doses are stabilized, and then as clinically indicated.

Dose Reductions

[0079] Dose reductions should be considered for hemoglobin and platelet count decreases as described in Table 7.

Table 7: Polycythemia Vera: Dose Reductions

Hemoglobin and/or Platelet Count	Dosing Recommendations
Hemoglobin greater than or equal to 12 g/dL AND platelet count greater than or equal to 100 x 10^9 /L	No change required
Hemoglobin 10 to less than 12 g/dL AND platelet count 75 to less than 100 x 10^9 /L	Dose reductions should be considered with the goal of avoiding dose interruptions for

	anemia and thrombocytopenia
Hemoglobin 8 to less than 10 g/dL OR platelet count 50 to less than 75 x 10^9 /L	Reduce dose by 5 mg twice daily For patients on 5 mg twice daily, decrease the dose to 5 mg once daily
Hemoglobin less than 8 g/dL OR platelet count less than 50 x 10^9 /L	Interrupt dosing

Treatment Interruption and Restarting Dosing

[0080] Treatment should be interrupted for hemoglobin less than 8 g/dL, platelet counts less than 50 x 10^9 /L or ANC less than 1.0 x 10^9 /L. After recovery of the hematologic parameter(s) to acceptable levels, dosing may be restarted. Table 8 illustrates the dose that may be used in restarting JAKAFI® after a previous interruption. Use the most severe category of a patient's hemoglobin, platelet count, or ANC abnormality to determine the corresponding maximum restarting dose.

Table 8: Polycythemia Vera: Restarting Doses for JAKAFI® after Safety Interruption for Hematologic Parameter(s)

Hemoglobin, Platelet Count, or ANC	**Maximum Restarting Dose**
Hemoglobin less than 8 g/dL OR platelet count less than 50 x 10^9 /L OR ANC less than 1 x 10^9 /L	Continue hold
Hemoglobin 8 to less than 10 g/dL OR platelet count 50 to less than 75 x 10^9 /L OR ANC 1 to less than 1.5 x 10^9 /L	5 mg twice daily[a] or no more than 5 mg twice daily less than the dose which resulted in dose interruption
Hemoglobin 10 to less than 12 g/dL OR platelet count 75 to less than 100 x 10^9 /L OR ANC 1.5 to less than 2 x 10^9 /L	10 mg twice daily[a] or no more than 5 mg twice daily less than the dose which resulted in dose interruption
Hemoglobin greater than or equal to 12 g/dL OR platelet count greater than or equal to 100 x 10^9 /L OR ANC greater than or equal to 2 x 10^9 /L	15 mg twice daily[a] or no more than 5 mg twice daily less than the dose which resulted in dose interruption

[a] Continue treatment for at least 2 weeks; if stable, may increase dose by 5 mg twice daily.

[0081] Patients who had required dose interruption while receiving a dose of 5 mg twice daily, may restart at a dose of 5 mg twice daily or 5 mg once daily, but not higher, once hemoglobin is greater than or equal to 10 g/dL, platelet count is greater than or equal to 75 x 10^9 /L, and ANC is greater than or equal to 1.5 x 10^9 /L.

Dose Management after Restarting Treatment

[0082] After restarting JAKAFI® following treatment interruption, doses may be titrated, but the maximum total daily dose should not exceed 5 mg less than the dose that resulted in the dose interruption. An exception to this is dose interruption following phlebotomy-associated anemia, in which case the maximal total daily dose allowed after restarting JAKAFI® would not be limited.

Dose Modifications Based on Insufficient Response for Patients with Polycythemia Vera

[0083] If the response is insufficient and platelet, hemoglobin, and neutrophil counts are adequate, doses may be increased in 5 mg twice daily increments to a maximum of 25 mg twice daily. Doses should not be increased during the first 4 weeks of therapy and not more frequently than every two weeks.

[0084] Consider dose increases in patients who meet all of the following conditions:

1. Inadequate efficacy as demonstrated by one or more of the following:
   a. Continued need for phlebotomy
   b. WBC greater than the upper limit of normal range
   c. Platelet count greater than the upper limit of normal range
   d. Palpable spleen that is reduced by less than 25% from Baseline
2. Platelet count greater than or equal to 140 x 10^9 /L
3. Hemoglobin greater than or equal to 12 g/dL
4. ANC greater than or equal to 1.5 x 10^9 /L

Dose Modifications for Concomitant Use with Strong CYP3A4 Inhibitors or Fluconazole

[0085] JAKAFI® dosage can be modified when co-administered with strong CYP3A4 inhibitors and fluconazole doses of less than or equal to 200 mg according to Table 10. Additional dose modifications should be made with frequent monitoring of safety and efficacy. The use of fluconazole doses of greater than 200 mg daily with JAKAFI® should be avoided.

Table 10: Dose Modifications for Concomitant Use with Strong CYP3A4 Inhibitors or Fluconazole

For patients co-administered strong CYP3A4 inhibitors or fluconazole doses of less than or equal to 200 mg	**Recommended Dose Modification**
Starting dose for patients with MF with a platelet count:	
• Greater than or equal to 100 x 10^9 /L	10 mg twice daily
50 x 10^9 /L to less than 100 x 10^9 /L	5 mg once daily
Starting dose for patients with PV:	5 mg once daily
If on stable dose for patients with MF or PV:	
Greater than or equal to 10 mg twice daily	Decrease dose by 50% (round up to the closest available tablet strength)
5 mg twice daily	5 mg once daily
5 mg once daily	Avoid strong CYP3A4 inhibitor or fluconazole treatment or interrupt JAKAFI® treatment for the duration of strong CYP3A4 inhibitor or fluconazole use

[a]With coadministration of itraconazole, monitor blood counts more frequently for toxicity and adjust the dose of JAKAFI® if necessary.

Dose Modifications for Renal or Hepatic Impairment Renal Impairment

Patients with Moderate or Severe Renal Impairment

[0086] JAKAFI® dosage for patients with moderate or severe renal impairment can be modified according to Table 11. Patients with End Stage Renal Disease on Dialysis Modify the JAKAFI® dosage for patients with end stage renal disease (ESRD) on dialysis according to Table 12. Make additional dose modifications with frequent monitoring of safety and efficacy. Use of JAKAFI® in patients with ESRD (CLcr less than 15 mL/min) not requiring dialysis should be avoided.

Table 11: Dose Modifications for Renal Impairment

Renal Impairment Status	Platelet Count	Recommended Starting Dosage
Patients with MF		
Moderate (CLcr 30 to 59 mL/min) or Severe (CLcr 15 to 29 mL/min)	Greater than 150 x 10^9 /L	No dose modification needed
	100 to 150 x 10^9 /L	10 mg twice daily
	50 to less than 100 x 10^9 /L	5 mg daily
	Less than 50 x 10^9 /L	Avoid use
ESRD (CLcr less than 15 mL/min) on dialysis	100 to 200 x 10^9 /L	15 mg once after dialysis session
	Greater than 200 x 10^9 /L	20 mg once after dialysis session
Patients with PV		
Moderate (CLcr 30 to 59 mL/min) or Severe (CLcr 15 to 29 mL/min)	Any	5 mg twice daily
ESRD (CLcr less than 15 mL/min) on dialysis	Any	10 mg once after dialysis session

ESRD = end stage renal disease, and CLcr = creatinine clearance

Hepatic Impairment

[0087] JAKAFI® dosage can be modified for patients with hepatic impairment according to Table 12.

Table 12: Dose Modifications for Hepatic Impairment

Hepatic Impairment Status	Platelet Count	Platelet Count
Patients with MF Mild, Moderate, or Severe (ChildPugh Class A, B, C)	Greater than 150 x 10^9 /L	No dose modification needed
	100 x 10^9 /L to 150 x 10^9 /L	10 mg twice daily
	50 to less than 100 x 10^9 /L	5 mg daily
	Less than 50 x 10^9 /L	Avoid use
Patients with PV Mild, Moderate, or Severe	Any	5 mg twice daily

(ChildPugh Class A, B, C)		

[0088] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with administering a therapeutically effective amount of ruxolitinib; wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35% . In one aspect, the therapeutically effective amount of ruxolitinib is at least 10 mg. In another aspect, the therapeutically effective amount of ruxolitinib is 10 mg. It is to be understood that various combinations of a therapeutically effective amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib are contemplated. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0089] For example, in the method for treatment of a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder comprising administering a therapeutically effective amount of navitoclax; in combination with administering a therapeutically effective amount of ruxolitinib; wherein treatment of the human subject optionally results in a spleen volume reduction of at least 35%, the therapeutically effective amount of navitoclax may be 50 mg and the therapeutically effective amount of ruxolitinib may be 10 mg; or the therapeutically effective amount of navitoclax may be 100 mg and the therapeutically effective amount of ruxolitinib may be 10 mg; or the therapeutically effective amount of navitoclax may be 200 mg and the therapeutically effective amount of ruxolitinib may be 10 mg; or the therapeutically effective amount of navitoclax may be 300 mg and the therapeutically effective amount of ruxolitinib may be 10 mg. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0090] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 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 optionally results in a spleen volume reduction of at least 35%; wherein the therapeutically effective amount of navitoclax is administered once a day; and wherein the therapeutically effective amount of ruxolitinib is administered twice a day. In one aspect, the therapeutically effective amount of navitoclax is 50 mg. In another aspect, the therapeutically effective amount of navitoclax is 100 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg. In still another aspect, the therapeutically effective amount of navitoclax is 300 mg. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0091] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with administering a therapeutically effective amount of ruxolitinib; wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35% by week 24. In one aspect, the spleen volume reduction may be measure by MRI. In one aspect, the therapeutically effective amount of ruxolitinib is at least 10 mg. In another aspect, the therapeutically effective amount of ruxolitinib is 10 mg. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0092] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 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 optionally results in a spleen volume reduction of at least 35% by week 24; wherein the therapeutically effective amount of navitoclax is administered once a day; and wherein the therapeutically effective amount of ruxolitinib is administered twice a day. In one aspect, the therapeutically effective amount of navitoclax is 50 mg. In another aspect, the therapeutically effective amount of navitoclax is 100 mg. In yet

another aspect, the therapeutically effective amount of navitoclax is 200 mg. In still another aspect, the therapeutically effective amount of navitoclax is 300 mg. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0093] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 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 optionally results in a spleen volume reduction of at least 35%; wherein the therapeutically effective amount of navitoclax is administered once a day; wherein the therapeutically effective amount of ruxolitinib is administered twice a day; and wherein the human subject has been treated with a JAK-2 inhibitor prior to administering the therapeutically effective amount of navitoclax. In one aspect, the therapeutically effective amount of navitoclax is 100 mg. In another aspect, the therapeutically effective amount of navitoclax is 100 mg and the therapeutically effective amount of ruxolitinib is 10 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg and the therapeutically effective amount of ruxolitinib is 10 mg. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0094] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 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 optionally results in a spleen volume reduction of at least 35%; wherein the therapeutically effective amount of navitoclax is administered once a day; wherein the therapeutically effective amount of ruxolitinib is administered twice a day; wherein the human subject has been treated with a JAK2 inhibitor prior to administering the therapeutically effective amount of navitoclax; and wherein the JAK2 inhibitor is ruxolitinib. In

some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0095] In one embodiment, a method for significantly reducing spleen volume in a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who is refractory to treatment with a JAK2 inhibitor is provided, comprising orally administering to the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder once a day a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with orally administering to the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder twice a day a therapeutically effective amount of ruxolitinib; wherein following 24 weeks of said administering navitoclax in combination with ruxolitinib, the spleen volume of the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder is optionally reduced by at least 35%. In one aspect, the therapeutically effective amount of ruxolitinib is selected from the group consisting of 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 40 mg and 50 mg. In another aspect, the therapeutically effective amount of ruxolitinib is selected from the group consisting of 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 40 mg and 50 mg. In another aspect, the therapeutically effective amount of ruxolitinib is 5 mg. In one aspect, the therapeutically effective amount of ruxolitinib is at least 10 mg. In another aspect, the therapeutically effective amount of ruxolitinib is 10 mg. In another aspect, the therapeutically effective amount of ruxolitinib is 5 mg. In yet another aspect, the therapeutically effective amount of ruxolitinib is 15 mg. In yet another aspect, the therapeutically effective amount of ruxolitinib is 20 mg. In another aspect, the therapeutically effective amount of ruxolitinib is 25 mg. In still another aspect, the therapeutically effective amount of ruxolitinib is 30 mg. In another aspect, the therapeutically effective amount of ruxolitinib is 40 mg. In yet another aspect, the therapeutically effective amount of ruxolitinib is 50 mg. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0096] In one embodiment, a method for significantly reducing spleen volume in a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who is refractory to treatment with a JAK2 inhibitor is provided, comprising orally administering to the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder once

a day a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with orally administering to the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder twice a day a therapeutically effective amount of ruxolitinib of 10 mg twice a day; wherein following 24 weeks of said administering navitoclax in combination with ruxolitinib, the spleen volume of the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder is optionally reduced by at least 35%. In one aspect, the therapeutically effective amount of navitoclax is 50 mg. In another aspect, the therapeutically effective amount of navitoclax is 100 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg. In still another aspect, the therapeutically effective amount of navitoclax is 300 mg. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0097] In one embodiment, a method for significantly reducing spleen volume in a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who is refractory to treatment with a JAK-2 inhibitor is provided, comprising orally administering to the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder once a day a therapeutically effective amount of navitoclax of 50 mg; in combination with orally administering to the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder twice a day a therapeutically effective amount of ruxolitinib of 10 mg twice a day; wherein after at least 7 days, the therapeutically effective amount of navitoclax is increased from 50 mg to 100 mg; wherein following 24 weeks of said administering navitoclax in combination with ruxolitinib, the spleen volume of the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder is optionally reduced by at least 35%. In one aspect, the human subject has a platelet count of at least 75 x 10^9 / L prior to increasing the therapeutically effective amount of navitoclax. In another aspect, after at least 7 days at 100 mg of navitoclax, the therapeutically effective amount of navitoclax is increased from 100 mg to 200 mg. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0098] In one embodiment, a method for significantly reducing spleen volume in a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who is

refractory to treatment with a JAK-2 inhibitor is provided, comprising orally administering to the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder once a day a therapeutically effective amount of navitoclax is 100 mg; in combination with orally administering to the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder twice a day a therapeutically effective amount of ruxolitinib of 10 mg twice a day; wherein after at least 7 days, the therapeutically effective amount of navitoclax is increased to 200 mg; wherein following 24 weeks of said administering navitoclax in combination with ruxolitinib, the spleen volume of the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder is optionally reduced by at least 35%. In one aspect, the human subject has a platelet count of at least 75 x 10^9 / L prior to increasing the therapeutically effective amount of navitoclax. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0099] In one embodiment, a method for significantly reducing spleen volume in a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who is refractory to treatment with a JAK-2 inhibitor is provided, comprising orally administering to the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder once a day a therapeutically effective amount of navitoclax is 200 mg; in combination with orally administering to the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder twice a day a therapeutically effective amount of ruxolitinib of 10 mg twice a day; wherein the human subject has a platelet count of at least 150 x 10^9 / L prior to administering navitoclax a first time; wherein following 24 weeks of said administering navitoclax in combination with ruxolitinib, the spleen volume of the human subject with myelofibrosis is optionally reduced by at least 35%. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0100] In one embodiment, a method for treatment of a human subject with is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with administering a therapeutically effective amount of ruxolitinib; wherein the myelofibrosis is relapsed or refractory myelofibrosis; and

wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%. In one aspect, the therapeutically effective amount of ruxolitinib is at least 10 mg. In another aspect, the therapeutically effective amount of ruxolitinib is selected from the group consisting of 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 40 mg and 50 mg. In yet another aspect, the therapeutically effective amount of ruxolitinib is selected from the group consisting of 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 40 mg and 50 mg. In one aspect, the therapeutically effective amount of ruxolitinib is 10 mg. In another aspect, the therapeutically effective amount of ruxolitinib is 5 mg. In another aspect, the therapeutically effective amount of ruxolitinib is 15 mg. In yet another aspect, the therapeutically effective amount of ruxolitinib is 20 mg. In another aspect, the therapeutically effective amount of ruxolitinib is 25 mg. In still another aspect, the therapeutically effective amount of ruxolitinib is 30 mg. In another aspect, the therapeutically effective amount of ruxolitinib is 40 mg. In yet another aspect, the therapeutically effective amount of ruxolitinib is 50 mg. It is to be understood that various combinations of a therapeutically effective amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib are contemplated.

[0101] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with administering a therapeutically effective amount of ruxolitinib of at least 10 mg; wherein the myelofibrosis is relapsed or refractory myelofibrosis; wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%; wherein the therapeutically effective amount of navitoclax is administered once a day; and wherein the therapeutically effective amount of ruxolitinib is administered twice a day. In one aspect, the therapeutically effective amount of navitoclax is 100 mg. In another aspect, the therapeutically effective amount of navitoclax is 100 mg and the therapeutically effective amount of ruxolitinib is 10 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg. In still another aspect, the therapeutically effective amount of navitoclax is 200 mg and the therapeutically effective amount of ruxolitinib is 10 mg.

[0102] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective amount of navitoclax selected

from the group consisting 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with administering a therapeutically effective amount of ruxolitinib; wherein the myelofibrosis is relapsed or refractory myelofibrosis; wherein the human subject has received at least one dose of ruxolitinib prior to administering a therapeutically effective amount of navitoclax; and wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%. In one aspect, the human subject has received at least one dose at least 10 mg of ruxolitinib prior to administering a therapeutically effective amount of navitoclax. In another aspect, the human subject has received at least one dose of 10 mg of ruxolitinib prior to administering a therapeutically effective amount of navitoclax.

[0103] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg in combination with administering a therapeutically effective amount of ruxolitinib; wherein the human subject has received at least one dose of ruxolitinib prior to administering the therapeutically effective amount of navitoclax; and wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%. In one aspect, the therapeutically effective amount of navitoclax is 50 mg. In another aspect, the therapeutically effective amount of navitoclax is 100 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg. In still another aspect, the therapeutically effective amount of navitoclax is 300 mg. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0104] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with administering a therapeutically effective amount of ruxolitinib; wherein the human subject has received at least one dose of ruxolitinib of at least 10 mg prior to administering the therapeutically effective amount of navitoclax; and wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%. In some

embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0105] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with administering a therapeutically effective amount of ruxolitinib; wherein the human subject has received at least one dose of ruxolitinib prior to administering the therapeutically effective amount of navitoclax; wherein the dose of ruxolitinib is more than 10 mg, wherein the dose of ruxolitinib is reduced to the therapeutically effective amount of ruxolitinib of 10 mg prior to administering the therapeutically effective amount of navitoclax; and wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%. In one aspect, the therapeutically effective amount of ruxolitinib of 10 mg is administered twice a day. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0106] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with administering a therapeutically effective amount of ruxolitinib; wherein the human subject has received at least one dose of ruxolitinib prior to administering the therapeutically effective amount of navitoclax; wherein the dose of ruxolitinib is more than 10 mg, wherein the dose of ruxolitinib is reduced to the therapeutically effective amount of ruxolitinib of 10 mg after administering the therapeutically effective amount of navitoclax; and wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%. In one aspect, the therapeutically effective amount of ruxolitinib of 10 mg is administered twice a day. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0107] In one embodiment, a method for treatment of a human subject with myelofibrosis is

provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with administering a therapeutically effective amount of ruxolitinib of at least 10 mg; wherein the myelofibrosis is relapsed or refractory myelofibrosis; wherein the human subject has received a dose of at least 10 mg ruxolitinib twice a day for 12 weeks prior to administering a therapeutically effective amount of navitoclax; and wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%. In one aspect, the therapeutically effective amount of navitoclax is 100 mg. In another aspect, the therapeutically effective amount of navitoclax is 100 mg and the therapeutically effective amount of ruxolitinib is 10 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg and the therapeutically effective amount of ruxolitinib is 10 mg.

[0108] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with administering a therapeutically effective amount of ruxolitinib; wherein the human subject has failed to achieve a spleen volume reduction of at least 35% prior to being administered navitoclax; and wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%. In one aspect, the therapeutically effective amount of ruxolitinib is at least 10 mg. In another aspect, the therapeutically effective amount of ruxolitinib is selected from the group consisting of 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 40 mg and 50 mg. In yet another aspect, the therapeutically effective amount of ruxolitinib is selected from the group consisting of 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 40 mg and 50 mg. In one aspect, the therapeutically effective amount of ruxolitinib is 10 mg. In another aspect, the therapeutically effective amount of ruxolitinib is 5 mg. In another aspect, the therapeutically effective amount of ruxolitinib is 15 mg. In yet another aspect, the therapeutically effective amount of ruxolitinib is 20 mg. In another aspect, the therapeutically effective amount of ruxolitinib is 25 mg. In still another aspect, the therapeutically effective amount of ruxolitinib is 30 mg. In another aspect, the therapeutically effective amount of ruxolitinib is 40 mg. In yet

another aspect, the therapeutically effective amount of ruxolitinib is 50 mg. It is to be understood that various combinations of a therapeutically effective amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib are contemplated. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0109] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with administering a therapeutically effective amount of ruxolitinib of at least 10 mg; wherein the human subject has failed to achieve a spleen volume reduction of at least 35% prior to being administered navitoclax; wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%; wherein the therapeutically effective amount of navitoclax is administered once a day; and wherein the therapeutically effective amount of ruxolitinib is administered twice a day. In one aspect, the therapeutically effective amount of navitoclax is 100 mg. In another aspect, the therapeutically effective amount of navitoclax is 100 mg and the therapeutically effective amount of ruxolitinib is 10 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg. In still another aspect, the therapeutically effective amount of navitoclax is 200 mg and the therapeutically effective amount of ruxolitinib is 10 mg. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0110] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with administering a therapeutically effective amount of ruxolitinib; wherein the human subject has failed to achieve a spleen volume reduction of at least 35% prior to being administered navitoclax; wherein the human subject has received at least one dose of ruxolitinib prior to administering a therapeutically effective amount of navitoclax; and wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%.

In one aspect, the human subject has received at least one dose at least 10 mg of ruxolitinib prior to administering a therapeutically effective amount of navitoclax. In another aspect, the human subject has received at least one dose of 10 mg of ruxolitinib prior to administering a therapeutically effective amount of navitoclax. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0111] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with administering a therapeutically effective amount of ruxolitinib of at least 10 mg; wherein the human subject has failed to achieve a spleen volume reduction of at least 35% prior to being administered navitoclax; wherein the human subject has received a dose of at least 10 mg ruxolitinib twice a day for 12 weeks prior to administering a therapeutically effective amount of navitoclax; and wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%. In one aspect, the therapeutically effective amount of navitoclax is 100 mg. In another aspect, the therapeutically effective amount of navitoclax is 100 mg and the therapeutically effective amount of ruxolitinib is 10 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg and the therapeutically effective amount of ruxolitinib is 10 mg. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0112] In one embodiment, a method for improving bone marrow fibrosis grade in a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who is refractory to treatment with a JAK-2 inhibitor is provided, comprising orally administering to the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who once a day a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with orally administering to the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who twice a day a therapeutically effective

amount of ruxolitinib; wherein following 24 weeks of said administering navitoclax in combination with ruxolitinib the bone marrow fibrosis grade of the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who is improved by at least one grade. In one aspect, the grade of the bone marrow fibrosis is measured according to the European Consensus grading system. In one aspect, the bone marrow fibrosis grade is improved to MF-2. In one aspect, the bone marrow fibrosis grade is improved to MF-1. In one aspect, the bone marrow fibrosis grade is improved to MF-0. In one aspect, the baseline grade of bone marrow fibrosis is ≥ 1. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0113] In one embodiment, a method for improving bone marrow fibrosis grade in a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who is refractory to treatment with a JAK-2 inhibitor is provided, comprising orally administering to the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who once a day a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with orally administering to the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who twice a day a therapeutically effective amount of ruxolitinib of at least 10 mg; wherein following 24 weeks of said administering navitoclax in combination with ruxolitinib the bone marrow fibrosis grade of the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who is improved by at least one grade. In one aspect, the therapeutically effective amount of navitoclax is 100 mg. In one aspect, the therapeutically effective amount of navitoclax is 200 mg. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0114] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with administering a therapeutically effective amount of ruxolitinib; wherein the myelofibrosis is relapsed or refractory myelofibrosis; and wherein the 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.

[0115] In one embodiment, a method for treatment of a human subject with is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with administering a therapeutically effective amount of ruxolitinib; wherein the myelofibrosis is relapsed or refractory myelofibrosis; wherein the 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; and wherein the improvement in the grade of the bone marrow fibrosis is measured according to the European consensus grading system.

[0116] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with administering a therapeutically effective amount of ruxolitinib; wherein the myelofibrosis is relapsed or refractory myelofibrosis; and wherein the 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 of ≥ 1. In one aspect, the therapeutically effective amount of navitoclax is 100 mg. In another aspect, the therapeutically effective amount of navitoclax is 100 mg and the therapeutically effective amount of ruxolitinib is 10 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg and the therapeutically effective amount of ruxolitinib is 10 mg.

[0117] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with administering a therapeutically effective amount of ruxolitinib; wherein the myelofibrosis is relapsed or refractory myelofibrosis; wherein the 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 of ≥ 1; wherein the therapeutically effective amount of navitoclax is administered once a day; and wherein the therapeutically effective amount of ruxolitinib is administered twice a day. In one aspect, the therapeutically effective amount of navitoclax is 100 mg. In another aspect, the therapeutically

effective amount of navitoclax is 100 mg and the therapeutically effective amount of ruxolitinib is 10 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg and the therapeutically effective amount of ruxolitinib is 10 mg.

[0118] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with administering a therapeutically effective amount of ruxolitinib; wherein an initial dose of therapeutically effective amount of navitoclax is 50 mg; and wherein the treatment of the human subject results in a spleen volume reduction of at least 35%. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0119] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with administering a therapeutically effective amount of ruxolitinib; wherein an initial dose of therapeutically effective amount of navitoclax is 50 mg; 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; and wherein the treatment of the human subject results in a spleen volume reduction of at least 35%. In one aspect, a maximum dose of navitoclax is 200 mg. In one aspect, a maximum dose of navitoclax is 300 mg. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0120] 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 ruxolitinib to the human subject, the improvement comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with said ruxolitinib, wherein the treatment of the

human subject results in a spleen volume reduction of at least 35%, and wherein the MPN-related disorder is selected from the group consisting of polycythemia vera (PCV), essential thrombocytopenia (ET), and chronic monomyelocytic leukemia (CMML).

[0121] In one embodiment, a method for treatment of a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder is provided, comprising administering 10 mg of ruxolitinib to the human subject, the improvement comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with said ruxolitinib, wherein the treatment of the human subject results in a spleen volume reduction of at least 35%, and wherein the MPN-related disorder is selected from the group consisting of polycythemia vera (PCV), essential thrombocytopenia (ET), and chronic monomyelocytic leukemia (CMML).

[0122] In one embodiment, a method for treatment of a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder is provided, comprising administering 20 mg of ruxolitinib to the human subject, the improvement comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with said ruxolitinib, wherein the treatment of the human subject results in a spleen volume reduction of at least 35%, and wherein the MPN-related disorder is selected from the group consisting of polycythemia vera (PCV), essential thrombocytopenia (ET), and chronic monomyelocytic leukemia (CMML).

[0123] In one embodiment, a method for treatment of a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder is provided, comprising administering 10 mg of ruxolitinib to the human subject twice daily, the improvement comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with said ruxolitinib, wherein the treatment of the human subject results in a spleen volume reduction of at least 35%, and wherein the MPN-related disorder is selected from the group consisting of polycythemia vera (PCV), essential thrombocytopenia (ET), and chronic monomyelocytic leukemia (CMML).

[0124] In one embodiment, a method for treatment of a human subject with myelofibrosis or

a myeloproliferative neoplasm (MPN)-related disorder is provided, comprising administering 20 mg of ruxolitinib to the human subject twice daily, the improvement 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 said ruxolitinib, wherein the treatment of the human subject results in a spleen volume reduction of at least 35%, and wherein the MPN-related disorder is selected from the group consisting of polycythemia vera (PCV), essential thrombocytopenia (ET), and chronic monomyelocytic leukemia (CMML).

[0125] 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 ruxolitinib to the human subject, the improvement comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with said ruxolitinib, 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), wherein the therapeutically effective amount of navitoclax is administered once a day; and wherein the therapeutically effective amount of ruxolitinib is administered twice a day.

[0126] 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 ruxolitinib to the human subject, the improvement comprising administering 100 mg of navitoclax to the human subject, wherein the treatment of the human subject results in a spleen volume reduction of at least 35%, and wherein the MPN-related disorder is selected from the group consisting of polycythemia vera (PCV), essential thrombocytopenia (ET), and chronic monomyelocytic leukemia (CMML).

[0127] 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 ruxolitinib to the human subject, the improvement comprising administering 200 mg of navitoclax to the human subject, wherein the treatment of the human subject results in a spleen volume reduction of at least 35%, and wherein the MPN-related disorder is selected from the group consisting of polycythemia vera (PCV), essential

thrombocytopenia (ET), and chronic monomyelocytic leukemia (CMML).

[0128] 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 ruxolitinib to the human subject, the improvement comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with said ruxolitinib, 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), wherein the human subject has been treated with a JAK-2 inhibitor prior to administering the therapeutically effective amount of navitoclax.

[0129] In one embodiment, a method for treatment of a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder is provided, comprising administering 10 mg of ruxolitinib to the human subject, the improvement comprising administering 100 mg of navitoclax to the human subject, wherein the treatment of the human subject results in a spleen volume reduction of at least 35%, and wherein the MPN-related disorder is selected from the group consisting of polycythemia vera (PCV), essential thrombocytopenia (ET), and chronic monomyelocytic leukemia (CMML).

[0130] In one embodiment, a method for treatment of a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder is provided, comprising administering 20 mg of ruxolitinib to the human subject, the improvement comprising administering 100 mg of navitoclax to the human subject, wherein the treatment of the human subject results in a spleen volume reduction of at least 35%, and wherein the MPN-related disorder is selected from the group consisting of polycythemia vera (PCV), essential thrombocytopenia (ET), and chronic monomyelocytic leukemia (CMML).

[0131] In one embodiment, a method for treatment of a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder is provided, comprising administering 10 mg of ruxolitinib to the human subject, the improvement comprising administering 100 mg of navitoclax to the human subject, wherein the treatment of the human subject results in a spleen volume reduction of at least 35%, and wherein the MPN-related disorder is selected from the

group consisting of polycythemia vera (PCV), essential thrombocytopenia (ET), and chronic monomyelocytic leukemia (CMML).

[0132] In one embodiment, a method for treatment of a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder is provided, comprising administering 20 mg of ruxolitinib to the human subject, the improvement comprising administering 100 mg of navitoclax to the human subject, wherein the treatment of the human subject results in a spleen volume reduction of at least 35%, and wherein the MPN-related disorder is selected from the group consisting of polycythemia vera (PCV), essential thrombocytopenia (ET), and chronic monomyelocytic leukemia (CMML).

[0133] In one embodiment, a method for treatment of a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder is provided, comprising administering 10 mg of ruxolitinib to the human subject, the improvement comprising administering 200 mg of navitoclax to the human subject, wherein the treatment of the human subject results in a spleen volume reduction of at least 35%, and wherein the MPN-related disorder is selected from the group consisting of polycythemia vera (PCV), essential thrombocytopenia (ET), and chronic monomyelocytic leukemia (CMML).

[0134] In one embodiment, a method for treatment of a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder is provided, comprising administering 20 mg of ruxolitinib to the human subject, the improvement comprising administering 200 mg of navitoclax to the human subject, wherein the treatment of the human subject results in a spleen volume reduction of at least 35%, and wherein the MPN-related disorder is selected from the group consisting of polycythemia vera (PCV), essential thrombocytopenia (ET), and chronic monomyelocytic leukemia (CMML).

[0135] 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 ruxolitinib to the human subject, the improvement 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 said ruxolitinib, 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),

wherein the treatment of the human subject results in a spleen volume reduction of at least 35% by week 24.

[0136] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0137] For example, in the method for treatment of a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder comprising administering a therapeutically effective amount of navitoclax; wherein treatment of the human subject optionally results in a spleen volume reduction of at least 35%, the therapeutically effective amount of navitoclax may be 50 mg or the therapeutically effective amount of navitoclax may be 100 mg; or the therapeutically effective amount of navitoclax may be 200 mg; or the therapeutically effective amount of navitoclax may be 300 mg. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0138] 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; wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%; wherein the therapeutically effective amount of navitoclax is administered once a day; In one aspect, the therapeutically effective amount of navitoclax is 50 mg. In another aspect, the therapeutically effective amount of navitoclax is 100 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg. In still another aspect, the therapeutically effective amount of navitoclax is 300 mg. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0139] 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; wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35% by week 24. In one aspect, the spleen volume reduction may be measure by MRI. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0140] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35% by week 24; wherein the therapeutically effective amount of navitoclax is administered once a day. In one aspect, the therapeutically effective amount of navitoclax is 50 mg. In another aspect, the therapeutically effective amount of navitoclax is 100 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg. In still another aspect, the therapeutically effective amount of navitoclax is 300 mg. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0141] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%; wherein the therapeutically effective amount of navitoclax is administered once a day; and wherein the human subject has been treated with a JAK-2 inhibitor prior to administering the therapeutically effective amount of navitoclax. In one aspect, the therapeutically effective amount of navitoclax is 100 mg. In another aspect, the therapeutically effective amount of navitoclax is 100 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 150 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 250 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 300 mg. In some embodiments, the

MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0142] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 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 optionally results in a spleen volume reduction of at least 35%; wherein the therapeutically effective amount of navitoclax is administered once a day; wherein the therapeutically effective amount of ruxolitinib is administered twice a day; wherein the human subject has been treated with a JAK2 inhibitor prior to administering the therapeutically effective amount of navitoclax; and wherein the JAK2 inhibitor is ruxolitinib. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0143] In one embodiment, a method for significantly reducing spleen volume in a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who is refractory to treatment with a JAK2 inhibitor is provided, comprising orally administering to the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder once a day a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; wherein following 24 weeks of said administering navitoclax in combination with ruxolitinib, the spleen volume of the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder is optionally reduced by at least 35%. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0144] In one embodiment, a method for significantly reducing spleen volume in a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who is refractory to treatment with a JAK2 inhibitor is provided, comprising orally administering to the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder once a day a therapeutically effective amount of navitoclax selected from the group consisting of 50 mg, 100 mg, 200 mg, and 300 mg; wherein following 24 weeks of said administering navitoclax

in combination with ruxolitinib, the spleen volume of the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder is optionally reduced by at least 35%. In one aspect, the therapeutically effective amount of navitoclax is 50 mg. In another aspect, the therapeutically effective amount of navitoclax is 100 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg. In still another aspect, the therapeutically effective amount of navitoclax is 300 mg. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0145] In one embodiment, a method for significantly reducing spleen volume in a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who is refractory to treatment with a JAK-2 inhibitor is provided, comprising orally administering to the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder once a day a therapeutically effective amount of navitoclax of 50 mg; wherein after at least 7 days, the therapeutically effective amount of navitoclax is increased from 50 mg to 100 mg; wherein following 24 weeks of said administering navitoclax, the spleen volume of the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder is optionally reduced by at least 35%. In one aspect, the human subject has a platelet count of at least 75 x 10^9 / L prior to increasing the therapeutically effective amount of navitoclax. In another aspect, after at least 7 days at 100 mg of navitoclax, the therapeutically effective amount of navitoclax is increased from 100 mg to 200 mg. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0146] In one embodiment, a method for significantly reducing spleen volume in a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who is refractory to treatment with a JAK-2 inhibitor is provided, comprising orally administering to the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder once a day a therapeutically effective amount of navitoclax is 100 mg; wherein after at least 7 days, the therapeutically effective amount of navitoclax is increased to 200 mg; wherein following 24 weeks of said administering navitoclax, the spleen volume of the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder is optionally reduced by at least 35%. In one aspect, the human subject has a platelet count of at least 75 x 10^9 / L prior to

increasing the therapeutically effective amount of navitoclax. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0147] In one embodiment, a method for significantly reducing spleen volume in a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who is refractory to treatment with a JAK-2 inhibitor is provided, comprising orally administering to the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder once a day a therapeutically effective amount of navitoclax is 200 mg; wherein the human subject has a platelet count of at least 150 x 10^9 / L prior to administering navitoclax a first time; wherein following 24 weeks of said administering navitoclax, the spleen volume of the human subject with myelofibrosis is optionally reduced by at least 35%. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0148] In one embodiment, a method for treatment of a human subject with is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; wherein the myelofibrosis is relapsed or refractory myelofibrosis; and wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%.

[0149] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%; wherein the therapeutically effective amount of navitoclax is administered once a day. In one aspect, the therapeutically effective amount of navitoclax is 100 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg.

[0150] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; wherein the myelofibrosis is relapsed or refractory

myelofibrosis; wherein the human subject has received at least one dose of ruxolitinib prior to administering a therapeutically effective amount of navitoclax; and wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%. In one aspect, the human subject has received at least one dose at least 10 mg of ruxolitinib prior to administering a therapeutically effective amount of navitoclax. In another aspect, the human subject has received at least one dose of 20 mg of ruxolitinib prior to administering a therapeutically effective amount of navitoclax.

[0151] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; wherein the human subject has received at least one dose of a JAK2 inhibitor prior to administering the therapeutically effective amount of navitoclax; and wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%. In one aspect, the therapeutically effective amount of navitoclax is 50 mg. In another aspect, the therapeutically effective amount of navitoclax is 100 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg. In still another aspect, the therapeutically effective amount of navitoclax is 300 mg. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0152] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; wherein the human subject has received at least one dose of ruxolitinib prior to administering the therapeutically effective amount of navitoclax; and wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%. In one aspect, the therapeutically effective amount of navitoclax is 50 mg. In another aspect, the therapeutically effective amount of navitoclax is 100 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg. In still another aspect, the therapeutically effective amount of navitoclax is 300 mg. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential

thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0153] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; wherein the human subject has received at least one dose of ruxolitinib of at least 10 mg prior to administering the therapeutically effective amount of navitoclax; and wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0154] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; wherein the human subject has received at least one dose of ruxolitinib prior to administering the therapeutically effective amount of navitoclax; wherein the dose of ruxolitinib is more than 10 mg, wherein the dose of ruxolitinib is reduced to the therapeutically effective amount of ruxolitinib of 10 mg prior to administering the therapeutically effective amount of navitoclax; and wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0155] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; wherein the human subject has received at least one dose of ruxolitinib prior to administering the therapeutically effective amount of navitoclax; and wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0156] In one embodiment, a method for treatment of a human subject with myelofibrosis is

provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; wherein the myelofibrosis is relapsed or refractory myelofibrosis; wherein the human subject has received a dose of at least 10 mg ruxolitinib twice a day for 12 weeks prior to administering a therapeutically effective amount of navitoclax; and wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%. In one aspect, the therapeutically effective amount of navitoclax is 100 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 300 mg.

[0157] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; wherein the human subject has failed to achieve a spleen volume reduction of at least 35% prior to being administered navitoclax; and wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0158] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; wherein the human subject has failed to achieve a spleen volume reduction of at least 35% prior to being administered navitoclax; wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%; wherein the therapeutically effective amount of navitoclax is administered once a day. In one aspect, the therapeutically effective amount of navitoclax is 100 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg. In still another aspect, the therapeutically effective amount of navitoclax is 300 mg. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0159] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; wherein the human subject has failed to achieve a spleen volume reduction of at least 35% prior to being administered navitoclax; wherein the human subject has received at least one dose of ruxolitinib prior to administering a therapeutically effective amount of navitoclax; and wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%. In one aspect, the human subject has received at least one dose at least 10 mg of ruxolitinib prior to administering a therapeutically effective amount of navitoclax. In another aspect, the human subject has received at least one dose of 10 mg of ruxolitinib prior to administering a therapeutically effective amount of navitoclax. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0160] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; wherein the human subject has failed to achieve a spleen volume reduction of at least 35% prior to being administered navitoclax; wherein the human subject has received a dose of at least 10 mg ruxolitinib twice a day for 12 weeks prior to administering a therapeutically effective amount of navitoclax; and wherein the treatment of the human subject optionally results in a spleen volume reduction of at least 35%. In one aspect, the therapeutically effective amount of navitoclax is 100 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 300 mg. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0161] In one embodiment, a method for improving bone marrow fibrosis grade in a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who is refractory to treatment with a JAK-2 inhibitor is provided, comprising orally administering to the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who once a day a therapeutically effective amount of navitoclax selected from the group consisting of

25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; wherein following 24 weeks of said administering navitoclax the bone marrow fibrosis grade of the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who is improved by at least one grade. In one aspect, the grade of the bone marrow fibrosis is measured according to the European Consensus grading system. In one aspect, the bone marrow fibrosis grade is improved to MF-2. In one aspect, the bone marrow fibrosis grade is improved to MF-1. In one aspect, the bone marrow fibrosis grade is improved to MF-0. In one aspect, the baseline grade of bone marrow fibrosis is ≥ 1. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0162] In one embodiment, a method for improving bone marrow fibrosis grade in a human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who is refractory to treatment with a JAK-2 inhibitor is provided, comprising orally administering to the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who once a day a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; wherein following 24 weeks of said administering navitoclax the bone marrow fibrosis grade of the human subject with myelofibrosis or a myeloproliferative neoplasm (MPN)-related disorder who is improved by at least one grade. In one aspect, the therapeutically effective amount of navitoclax is 100 mg. In one aspect, the therapeutically effective amount of navitoclax is 200 mg. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0163] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg.

[0164] In one embodiment, a method for treatment of a human subject with primary myelofibrosis is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg.

[0165] 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 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg.

[0166] In one embodiment, a method for treatment of a human subject with relapsed or refractory myelofibrosis is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg.

[0167] In one embodiment, a method for treatment of a human subject with polycythemia vera (PCV) is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg.

[0168] In one embodiment, a method for treatment of a human subject with essential thrombocytopenia (ET) is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg.

[0169] In one embodiment, a method for treatment of a human subject with chronic myelomonocytic leukemia (CMML) is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg.

[0170] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg and administering a therapeutically effective amount of ruxolitinib selected from the group consisting of 5 mg twice daily, 10 mg twice daily, 15 mg twice daily, 20 mg twice daily, and 25 mg twice daily.

[0171] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg and administering a therapeutically effective amount of ruxolitinib selected from the group consisting of 5 mg twice daily, 10 mg twice daily, 15 mg twice daily, 20 mg twice daily, and 25 mg twice daily.

[0172] In one embodiment, a method for treatment of a human subject with relapsed or refractory myelofibrosis is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg and administering a therapeutically effective amount of ruxolitinib selected from the group consisting of 5 mg twice daily, 10 mg twice daily, 15 mg twice daily, 20 mg twice daily, and 25 mg twice daily.

[0173] In one embodiment, a method for treatment of a human subject with polycythemia vera (PCV) is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg and administering a therapeutically effective amount of ruxolitinib selected from the group consisting of 5 mg twice daily, 10 mg twice daily, 15 mg twice daily, 20 mg twice daily, and 25 mg twice daily.

[0174] In one embodiment, a method for treatment of a human subject with essential thrombocytopenia (ET) is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg and administering a therapeutically effective amount of ruxolitinib selected from the group consisting of 5 mg twice daily, 10 mg twice daily, 15 mg twice daily, 20 mg twice daily, and 25 mg twice daily.

[0175] In one embodiment, a method for treatment of a human subject with chronic myelomonocytic leukemia (CMML) is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg and administering a therapeutically effective amount of ruxolitinib selected from the group consisting of 5 mg twice daily, 10 mg twice daily, 15 mg twice daily, 20 mg twice daily, and 25 mg twice daily.

[0176] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg and administering a therapeutically effective amount of ruxolitinib selected from the group consisting of 5 mg once daily, 10 mg once daily, 15 mg once daily, 20 mg once daily, and 25 mg once daily.

[0177] In one embodiment, a method for treatment of a human subject with relapsed or

refractory myelofibrosis is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg and administering a therapeutically effective amount of ruxolitinib selected from the group consisting of 5 mg once daily, 10 mg once daily, 15 mg once daily, 20 mg once daily, and 25 mg once daily.

[0178] In one embodiment, a method for treatment of a human subject with polycythemia vera (PCV) is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg and administering a therapeutically effective amount of ruxolitinib selected from the group consisting of 5 mg once daily, 10 mg once daily, 15 mg once daily, 20 mg once daily, and 25 mg once daily.

[0179] In one embodiment, a method for treatment of a human subject with essential thrombocytopenia (ET) is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg and administering a therapeutically effective amount of ruxolitinib selected from the group consisting of 5 mg once daily, 10 mg once daily, 15 mg once daily, 20 mg once daily, and 25 mg once daily.

[0180] In one embodiment, a method for treatment of a human subject with chronic myelomonocytic leukemia (CMML) is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg and administering a therapeutically effective amount of ruxolitinib selected from the group consisting of 5 mg once daily, 10 mg once daily, 15 mg once daily, 20 mg once daily, and 25 mg once daily.

[0181] In one embodiment, a method for treatment of a human subject with is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; wherein the myelofibrosis is relapsed or refractory myelofibrosis; wherein the 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; and wherein the improvement in the grade of the bone marrow fibrosis is measured according to the European consensus grading system.

[0182] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; wherein the myelofibrosis is relapsed or refractory myelofibrosis; and wherein the 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 of ≥ 1. In one aspect, the therapeutically effective amount of navitoclax is 100 mg. In yet another aspect, the therapeutically effective amount of navitoclax is 200 mg.

[0183] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective amount of navitoclax selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg; in combination with administering a therapeutically effective amount of ruxolitinib; wherein the myelofibrosis is relapsed or refractory myelofibrosis; wherein the 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 of ≥ 1; wherein the therapeutically effective amount of navitoclax is administered once a day.

[0184] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the effective amount of ruxolitinib comprises 10 mg administered twice daily; wherein if the human subject has a platelet count of $\leq 150 \times 10^9$/L the effective amount of navitoclax comprises 100 mg, optionally increased to 200 mg navitoclax after ≥ 7 days if the human subject has a platelet count $\geq 75 \times 10^9$/L. In one aspect, the method for treatment is for first line treatment of myelofibrosis. In another aspect, the human subject has not previously received treatment with a JAK-2 inhibitor. In one aspect, a maximum dose of navitoclax is 300 mg. In one aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen reduction volume of at least 35% (SVR_{35}) is measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0185] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the effective amount of ruxolitinib comprises 10 mg administered twice daily; wherein if the human subject has a platelet count of > 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg. In one aspect, the method for treatment is for first line treatment of myelofibrosis. In another aspect, the human subject has not previously received treatment with a JAK-2 inhibitor. In one aspect, a maximum dose of navitoclax comprises 300 mg. In one aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen reduction volume of at least 35% (SVR_{35}) is measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0186] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the effective amount of ruxolitinib comprises 20 mg; wherein if the human subject has a platelet count of ≤ 150 x 10^9/L the effective amount of navitoclax comprises 100 mg, optionally increased to 200 mg navitoclax after ≥ 7 days if the human subject has a platelet count ≥ 75 x 10^9/L. In one aspect, the method for treatment is for first line treatment of myelofibrosis. In another aspect, the human subject has not previously received treatment with a JAK-2 inhibitor. In one aspect, a maximum dose of navitoclax comprises 300 mg. In one aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen reduction volume of at least 35% (SVR_{35}) is measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0187] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in

combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the effective amount of ruxolitinib comprises 20 mg; wherein if the human subject has a platelet count of > 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg. In one aspect, the method for treatment is for first line treatment of myelofibrosis. In another aspect, the human subject has not previously received treatment with a JAK-2 inhibitor. In one aspect, a maximum dose of navitoclax comprises 300 mg. In one aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen reduction volume of at least 35% (SVR_{35}) is measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0188] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the effective amount of ruxolitinib comprises 20 mg; wherein (a) if the human subject has a platelet count of > 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg, (b) if the human subject has a platelet count of ≤ 150 x 10^9/L the effective amount of navitoclax comprises 100 mg, optionally increased to 200 mg navitoclax after ≥ 7 days if the human subject has a platelet count ≥ 75 x 10^9/L; and wherein if after 24 weeks the patient fails to achieve a spleen reduction volume (SVR) of at least 10%, the effective amount of navitoclax in (a) or (b) may be increased to 300 mg. In one aspect, the method for treatment is for first line treatment of myelofibrosis. In another aspect, the human subject has not previously received treatment with a JAK-2 inhibitor. In one aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen reduction volume of at least 35% (SVR_{35}) is measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0189] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in

combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the effective amount of ruxolitinib comprises 10 mg administered twice daily; wherein (a) if the human subject has a platelet count of > 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg navitoclax administered once daily, (b) if the human subject has a platelet count of ≤ 150 x 10^9/L the effective amount of navitoclax comprises 100 mg administered once daily, optionally increased to 200 mg navitoclax administered once daily after ≥ 7 days if the human subject has a platelet count ≥ 75 x 10^9/L; and wherein if after 24 weeks the patient fails to achieve a spleen reduction volume (SVR) of at least 10%, the effective amount of navitoclax in (a) or (b) may be increased to 300 mg administered once daily. In one aspect, the method for treatment is for first line treatment of myelofibrosis. In another aspect, the human subject has not previously received treatment with a JAK-2 inhibitor. In one aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen reduction volume of at least 35% (SVR_{35}) is measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0190] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the effective amount of ruxolitinib comprises 10 mg administered twice daily; wherein (a) if the human subject has a platelet count of > 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg navitoclax administered once daily, (b) if the human subject has a platelet count of ≤ 150 x 10^9/L the effective amount of navitoclax comprises 100 mg administered once daily, optionally increased to 200 mg navitoclax administered once daily after ≥ 7 days if the human subject has a platelet count ≥ 75 x 10^9/L; and wherein if after 24 weeks the patient fails to achieve a spleen reduction volume (SVR) of at least 10%, the effective amount of navitoclax in (a) or (b) may be increased to 300 mg administered once daily. In one aspect, the method for treatment is for first line treatment of myelofibrosis. In another aspect, the human subject has not previously received treatment with a JAK-2 inhibitor. In one aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human

subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen reduction volume of at least 35% (SVR_{35}) is measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0191] In one embodiment, a method for first line treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with 10 mg of ruxolitinib twice daily to the human subject; wherein (a) if the human subject has a platelet count of $> 150 \times 10^9$/L, the effective amount of navitoclax comprises 200 mg navitoclax administered once daily, (b) if the human subject has a platelet count of $\leq 150 \times 10^9$/L the effective amount of navitoclax comprises 100 mg administered once daily, optionally increased to 200 mg navitoclax administered once daily after ≥ 7 days if the human subject has a platelet count $\geq 75 \times 10^9$/L; and wherein if after 24 weeks the patient fails to achieve a spleen reduction volume (SVR) of at least 10%, the effective amount of navitoclax in (a) or (b) may be increased to 300 mg administered once daily. In one aspect, the human subject has not previously received treatment with a JAK-2 inhibitor. In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen reduction volume of at least 35% (SVR_{35}) is measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0192] In one embodiment, a method for treatment of a human subject with myelofibrosis who has not previously received therapy with a JAK-2 inhibitor is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with 10 mg of ruxolitinib twice daily to the human subject; wherein (a) if the human subject has a platelet count of $> 150 \times 10^9$/L, the effective amount of navitoclax comprises 200 mg navitoclax administered once daily, (b) if the human subject has a platelet count of $\leq 150 \times 10^9$/L the effective amount of navitoclax comprises 100 mg administered once daily, optionally increased to 200 mg navitoclax administered once daily after ≥ 7 days if the human subject has a platelet count $\geq 75 \times 10^9$/L; and wherein if after 24 weeks the patient fails to achieve a spleen reduction volume (SVR) of at least

10%, the effective amount of navitoclax in (a) or (b) may be increased to 300 mg administered once daily. In one aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen reduction volume of at least 35% (SVR_{35}) is measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0193] In one embodiment, a method for first line treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the effective amount of ruxolitinib comprises 10 mg administered twice daily; wherein (a) if the human subject has a platelet count of $> 150 \times 10^9$/L, the effective amount of navitoclax comprises 200 mg navitoclax administered once daily, (b) if the human subject has a platelet count of $\leq 150 \times 10^9$/L the effective amount of navitoclax comprises 100 mg administered once daily, optionally increased to 200 mg navitoclax administered once daily after ≥ 7 days if the human subject has a platelet count $\geq 75 \times 10^9$/L; and wherein if after 24 weeks the patient fails to achieve a spleen reduction volume (SVR) of at least 10%, the effective amount of navitoclax in (a) or (b) may be increased to 300 mg administered once daily. In one aspect, the human subject has not previously received treatment with a JAK-2 inhibitor. In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen reduction volume of at least 35% (SVR_{35}) is measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0194] In one embodiment, a method for treatment of a human subject with myelofibrosis who has not previously received therapy with a JAK-2 inhibitor is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the effective amount of ruxolitinib comprises 10 mg administered twice daily; wherein (a) if the human subject has a platelet count of $> 150 \times 10^9$/L, the effective amount of navitoclax comprises 200

mg navitoclax administered once daily, (b) if the human subject has a platelet count of ≤ 150 x 10^9/L the effective amount of navitoclax comprises 100 mg administered once daily, optionally increased to 200 mg navitoclax administered once daily after ≥ 7 days if the human subject has a platelet count ≥ 75 x 10^9/L; and wherein if after 24 weeks the patient fails to achieve a spleen reduction volume (SVR) of at least 10%, the effective amount of navitoclax in (a) or (b) may be increased to 300 mg administered once daily. In one aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen reduction volume of at least 35% (SVR_{35}) is measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0195] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the effective amount of ruxolitinib comprises 10 mg administered twice daily; wherein (a) if the human subject has a platelet count of > 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg navitoclax administered once daily, (b) if the human subject has a platelet count of ≤ 150 x 10^9/L the effective amount of navitoclax comprises 100 mg administered once daily, optionally increased to 200 mg navitoclax administered once daily after ≥ 7 days if the human subject has a platelet count ≥ 75 x 10^9/L; and wherein the effective amount of navitoclax in (a) or (b) may be increased to 300 mg administered once daily. In one aspect, the method for treatment is for first line treatment of myelofibrosis. In another aspect, the human subject has not previously received treatment with a JAK-2 inhibitor. In one aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen reduction volume of at least 35% (SVR_{35}) is measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0196] In one embodiment, a method for treatment of a human subject with myelofibrosis is

provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the effective amount of ruxolitinib comprises 10 mg administered twice daily; wherein (a) if the human subject has a platelet count of > 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg navitoclax administered once daily, (b) if the human subject has a platelet count of ≤ 150 x 10^9/L the effective amount of navitoclax comprises 100 mg administered once daily, optionally increased to 200 mg navitoclax administered once daily after ≥ 7 days if the human subject has a platelet count ≥ 75 x 10^9/L; and wherein after 24 weeks the effective amount of navitoclax in (a) or (b) may be increased to 300 mg administered once daily. In one aspect, the method for treatment is for first line treatment of myelofibrosis. In another aspect, the human subject has not previously received treatment with a JAK-2 inhibitor. In one aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen reduction volume of at least 35% (SVR_{35}) is measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0197] In one embodiment, a method for first line treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with 10 mg of ruxolitinib twice daily to the human subject; wherein (a) if the human subject has a platelet count of > 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg navitoclax administered once daily, (b) if the human subject has a platelet count of ≤ 150 x 10^9/L the effective amount of navitoclax comprises 100 mg administered once daily, optionally increased to 200 mg navitoclax administered once daily after ≥ 7 days if the human subject has a platelet count ≥ 75 x 10^9/L; and wherein the effective amount of navitoclax in (a) or (b) may be increased to 300 mg administered once daily. In one aspect, the human subject has not previously received treatment with a JAK-2 inhibitor. In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen reduction volume of at least 35%

(SVR_{35}) is measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0198] In one embodiment, a method for treatment of a human subject with myelofibrosis who has not previously received therapy with a JAK-2 inhibitor is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with 10 mg of ruxolitinib twice daily to the human subject; wherein (a) if the human subject has a platelet count of > 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg navitoclax administered once daily, (b) if the human subject has a platelet count of ≤ 150 x 10^9/L the effective amount of navitoclax comprises 100 mg administered once daily, optionally increased to 200 mg navitoclax administered once daily after ≥ 7 days if the human subject has a platelet count ≥ 75 x 10^9/L; and wherein the effective amount of navitoclax in (a) or (b) may be increased to 300 mg administered once daily. In one aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen reduction volume of at least 35% (SVR_{35}) is measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0199] In one embodiment, a method for treatment of a human subject with myelofibrosis who has not previously received therapy with a JAK-2 inhibitor is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with 10 mg of ruxolitinib twice daily to the human subject; wherein (a) if the human subject has a platelet count of > 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg navitoclax administered once daily, (b) if the human subject has a platelet count of ≤ 150 x 10^9/L the effective amount of navitoclax comprises 100 mg administered once daily, optionally increased to 200 mg navitoclax administered once daily after ≥ 7 days if the human subject has a platelet count ≥ 75 x 10^9/L; and wherein after 24 weeks the effective amount of navitoclax in (a) or (b) may be increased to 300 mg administered once daily. In one aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen reduction volume of at least 35% (SVR_{35}) is measured according to magnetic

resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0200] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the effective amount of ruxolitinib comprises 10 mg administered twice daily; wherein (a) if the human subject has a platelet count of > 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg navitoclax administered once daily, and (b) if the human subject has a platelet count of ≤ 150 x 10^9/L the effective amount of navitoclax comprises 100 mg administered once daily, optionally increased to 200 mg administered once daily. In one aspect, the myelofibrosis is relapsed or refractory. In one aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen reduction volume of at least 35% (SVR_{35}) is measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0201] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the effective amount of ruxolitinib comprises 10 mg administered twice daily; wherein (a) if the human subject has a platelet count of > 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg navitoclax administered once daily, (b) if the human subject has a platelet count of ≤ 150 x 10^9/L the effective amount of navitoclax comprises 100 mg administered once daily, optionally increased to 200 mg navitoclax administered once daily after ≥ 7 days if the human subject has a platelet count ≥ 75 x 10^9/L; and wherein if after 24 weeks the patient fails to achieve a spleen reduction volume (SVR) of at least 10%, the effective amount of navitoclax in (a) or (b) may be increased to 300 mg administered once daily. In one aspect, the myelofibrosis is relapsed or refractory. In one aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen

reduction volume of at least 35% (SVR_{35}) is measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0202] In one embodiment, a method for treatment of a human subject with relapsed or refractory myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the effective amount of ruxolitinib comprises 10 mg administered twice daily; wherein (a) if the human subject has a platelet count of > 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg navitoclax administered once daily, (b) if the human subject has a platelet count of ≤ 150 x 10^9/L the effective amount of navitoclax comprises 100 mg administered once daily, optionally increased to 200 mg navitoclax administered once daily after ≥ 7 days if the human subject has a platelet count ≥ 75 x 10^9/L; and wherein if after 24 weeks the patient fails to achieve a spleen reduction volume (SVR) of at least 10%, the effective amount of navitoclax in (a) or (b) may be increased to 300 mg administered once daily. In one aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen reduction volume of at least 35% (SVR_{35}) is measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0203] In one embodiment, a method for treatment of a human subject with relapsed or refractory myelofibrosis is provided, comprising administering a therapeutically effective amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the effective amount of ruxolitinib comprises 10 mg administered twice daily; wherein (a) if the human subject has a platelet count of > 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg navitoclax administered once daily, and (b) if the human subject has a platelet count of ≤ 150 x 10^9/L the effective amount of navitoclax comprises 100 mg administered once daily, optionally increased to 200 mg administered once daily. In one aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen reduction volume of at least 35%

(SVR_{35}) is measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0204] In one embodiment, a method for treatment of a human subject with relapsed or refractory myelofibrosis is provided, comprising administering a therapeutically effective amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the effective amount of ruxolitinib comprises 10 mg administered twice daily; wherein (a) if the human subject has a platelet count of $> 150 \times 10^9$/L, the effective amount of navitoclax comprises 200 mg navitoclax administered once daily, and (b) if the human subject has a platelet count of $\leq 150 \times 10^9$/L the effective amount of navitoclax comprises 100 mg administered once daily, optionally increased to 200 mg administered once daily. In one aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen reduction volume of at least 35% (SVR_{35}) is measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0205] In one embodiment, a method for treatment of a human subject with relapsed or refractory myelofibrosis is provided, comprising administering a therapeutically effective amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the effective amount of ruxolitinib comprises 10 mg administered twice daily; wherein (a) if the human subject has a platelet count of $> 150 \times 10^9$/L, the effective amount of navitoclax comprises 200 mg navitoclax administered once daily, and (b) if the human subject has a platelet count of $\leq 150 \times 10^9$/L the effective amount of navitoclax comprises 100 mg administered once daily, optionally increased to 200 mg administered once daily. In one aspect, the effective amount of navitoclax is optionally increased to 300 mg administered once daily. In one aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen reduction volume of at least 35% (SVR_{35}) is measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0206] In one embodiment, a method for treatment of a human subject with relapsed or refractory myelofibrosis is provided, comprising administering a therapeutically effective amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the effective amount of ruxolitinib comprises 10 mg administered twice daily; wherein (a) if the human subject has a platelet count of > 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg navitoclax administered once daily, and (b) if the human subject has a platelet count of ≤ 150 x 10^9/L the effective amount of navitoclax comprises 100 mg administered once daily, optionally increased to 200 mg administered once daily. In one aspect, the effective amount of navitoclax is optionally increased to 300 mg administered once daily. In one aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen reduction volume of at least 35% (SVR_{35}) is measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0207] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the effective amount of ruxolitinib comprises 20 mg; wherein (a) if the human subject has a platelet count of > 150 x 10^9/L, the effective amount of navitoclax comprises 200 mg, and (b) if the human subject has a platelet count of ≤ 150 x 10^9/L the effective amount of navitoclax comprises 100 mg, optionally increased to 200 mg. In one aspect, the myelofibrosis is relapsed or refractory. In one aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}). In another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In yet another aspect, the human subject achieves a spleen reduction volume of at least 35% (SVR_{35}) after week 24. In yet another aspect, the spleen reduction volume of at least 35% (SVR_{35}) is measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0208] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein

if the human subject has a platelet count of > 200 × 10^9/L, the effective amount of ruxolitinib comprises 20 mg twice daily, and if the human subject has a platelet count of count 100 × 10^9/L to 200 × 10^9/L, the effective amount of ruxolitinib comprises 15 mg twice daily; wherein if the human subject has a platelet count of > 150 × 10^9/L, the effective daily amount of navitoclax comprises 200 mg; wherein if the human subject has a platelet count of ≤ 150 x 10^9/L, the effective daily amount of navitoclax comprises 100 mg, optionally increased to 200 mg navitoclax after ≥ 7 days if the human subject has a platelet count ≥ 75 x 10^9/L; and wherein if the human subject fails to achieve SVR_{35} by week 24 of treatment, the navitoclax dose may be optionally increased to 300 mg once daily.

[0209] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein if the human subject has a platelet count of > 200 × 10^9/L, the effective amount of ruxolitinib comprises 20 mg twice daily, wherein if the human subject has a platelet count of count 100 × 10^9/L to 200 × 10^9/L, the effective amount of ruxolitinib comprises 15 mg twice daily; wherein if the human subject has a platelet count of > 150 × 10^9/L, the effective daily amount of navitoclax comprises 200 mg; wherein if the human subject has a platelet count of ≤ 150 x 10^9/L the effective daily amount of navitoclax comprises 100 mg, optionally increased to 200 mg navitoclax after ≥ 7 days if the human subject has a platelet count ≥ 75 x 10^9/L; and wherein if the human subject fails to achieve SVR_{35} by week 24 of treatment, the navitoclax dose may be optionally increased to 300 mg once daily.

[0210] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the dose of navitoclax may be adjusted for thrombocytopenia. In another embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the dose of navitoclax may be adjusted for thrombocytopenia, wherein if platelets ≥ 75 × 10^9/L, the current dose of navitoclax is maintained or escalated by one dose level not to exceed 200 mg once daily or 300 mg. In another embodiment, a method for treatment of a human subject with myelofibrosis is provided,

comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the dose of navitoclax may be adjusted for thrombocytopenia, wherein if platelets $\geq 75 \times 10^9$/L, the current dose of navitoclax is maintained.

[0211] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the dose of navitoclax may be adjusted for thrombocytopenia. In another embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the dose of navitoclax may be adjusted for thrombocytopenia wherein if platelets $\geq 75 \times 10^9$/L, the current dose of navitoclax is maintained or escalated by one dose level not to exceed 200 mg once daily or 300 mg. In another embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the dose of navitoclax may be adjusted for thrombocytopenia, wherein if platelets $\geq 75 \times 10^9$/L, the current dose of navitoclax is maintained. .

[0212] In another embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the dose of navitoclax may be adjusted for thrombocytopenia wherein if platelets $< 75 \times 10^9$/L - $\geq 50 \times 10^9$/L, the current navitoclax dose level is maintained or the current navitoclax dose level is reduced one dose level lower. In another embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the dose of navitoclax may be adjusted for thrombocytopenia wherein if platelets $< 75 \times 10^9$/L - $\geq 50 \times 10^9$/L, the current navitoclax dose level is maintained or the current navitoclax dose level is reduced to one dose level lower, and the dose of ruxolitinib is optionally reduced as well, wherein the platelet count is rechecked approximately every 7 days until ≥ 2 consecutive lab values indicate stable platelet count.

[0213] In another embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the dose of navitoclax may be adjusted for thrombocytopenia wherein if platelets $< 75 \times 10^9$/L - $\geq 50 \times 10^9$/L, the current navitoclax dose level is maintained or the current navitoclax dose level is reduced one dose level lower. In another embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the dose of navitoclax may be adjusted for thrombocytopenia wherein if platelets $< 75 \times 10^9$/L - $\geq 50 \times 10^9$/L, the current navitoclax dose level is maintained or the current navitoclax dose level is reduced to one dose level lower, and the dose of ruxolitinib is optionally reduced as well. In another embodiment, Platelet count should be rechecked approximately every 7 days until ≥ 2 consecutive lab values indicate stable platelet count.

[0214] In another embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the dose of navitoclax may be adjusted for thrombocytopenia wherein if platelets $< 50 \times 10^9$/L, the current navitoclax dose level is interrupted. In another embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the dose of navitoclax may be adjusted for thrombocytopenia wherein if platelets $< 50 \times 10^9$/L, the current navitoclax dose level is interrupted, and the dose of ruxolitinib is interrupted wherein the platelet count is rechecked approximately 2 – 3 days until recovery to $\geq 50 \times 10^9$/L wherein navitoclax administration is resumed at one dose level lower and ruxolitinib is optionally reduced as well and wherein platelet count should be rechecked approximately every 7 days until ≥ 2 consecutive lab values indicate stable platelet count.

[0215] In another embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human

subject; wherein the dose of navitoclax may be adjusted for thrombocytopenia wherein if platelets < 50×10^9/L, the current navitoclax dose level is interrupted or discontinued. In another embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein the dose of navitoclax may be adjusted for thrombocytopenia wherein if platelets < 50×10^9/L, the current navitoclax dose level is interrupted, wherein the platelet count is rechecked approximately 2 – 3 days until recovery to ≥ 50×10^9/L wherein navitoclax administration is resumed at one dose level lower and wherein platelet count should be rechecked approximately every 7 days until ≥ 2 consecutive lab values indicate stable platelet count.

[0216] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein if the human subject has a platelet count of > 150×10^9/L, the effective daily amount of navitoclax comprises 200 mg; wherein if the human subject has a platelet count of ≤ 150 x 10^9/L, the effective daily amount of navitoclax comprises 100 mg, wherein the effective daily amount of navitoclax is optionally increased to 200 mg navitoclax, if 100 mg dose is tolerable; wherein the dose may be increased to 300 mg once daily for subjects with sub-optimal spleen response defined as failure to achieve a spleen volume reduction of at least 10% after 24 weeks.

[0217] In one embodiment, a method for treatment of a human subject with myelofibrosis is provided, comprising administering a therapeutically effective of amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib to the human subject; wherein human subjects receiving ruxolitinib continue at a current stable dose of ≥ 10 mg twice daily, wherein subjects not receiving ruxolitinib receive ruxolitinib at a dose of 10 mg twice daily; and wherein ruxolitinib dose adjustment in subjects with hepatic or renal impairment is optionally adjusted.

[0218] In one embodiment, a method for treatment of a human subject with myelofibrosis or MPN (myeloproliferative neoplasms)-related disorders is provided comprising administering a therapeutically effective amount of navitoclax. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0219] In one embodiment, a method for treatment of a human subject with myelofibrosis or MPN (myeloproliferative neoplasms)-related disorders who have failed, are intolerant to, or refuse standard therapy is provided comprising administering a therapeutically effective amount of navitoclax. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0220] In one embodiment, a method for treatment of a human subject with myelofibrosis or MPN (myeloproliferative neoplasms)-related disorders who have failed, are intolerant to, or refuse standard therapy is provided, comprising administering a therapeutically effective amount of navitoclax wherein based on individual tolerability including platelet counts, the dose of navitoclax may be increased weekly in a stepwise fashion. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0221] In one embodiment, a method for treatment of a human subject with myelofibrosis or MPN (myeloproliferative neoplasms)-related disorders who have failed, are intolerant to, or refuse standard therapy is provided, comprising administering a therapeutically effective amount of navitoclax wherein based on individual tolerability including platelet counts, the dose of navitoclax may be increased weekly in a stepwise fashion, wherein the dose of navitoclax may be increased every $\geq$ 7 days to the next dose level up to a maximum dose of navitoclax 300 mg once daily.

[0222] In one embodiment, a method for treatment of a human subject with myelofibrosis or MPN (myeloproliferative neoplasms)-related disorders who have failed, are intolerant to, or refuse standard therapy is provided, comprising administering a therapeutically effective amount of navitoclax wherein based on individual tolerability including platelet counts, the dose of navitoclax may be increased weekly in a stepwise fashion, wherein the dose of navitoclax may be increased every $\geq$ 7 days to the next dose level up to a maximum dose of navitoclax 300 mg once daily, provided the platelet count is $> 100 \times 10^9$/L. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0223] In one embodiment, a method for treatment of a human subject with myelofibrosis or MPN (myeloproliferative neoplasms)-related disorders who have failed, are intolerant to, or refuse standard therapy is provided, comprising administering 50 mg of navitoclax once daily

wherein based on individual tolerability including platelet counts, the dose of navitoclax may be increased weekly in a stepwise fashion, wherein the dose of navitoclax may be increased every ≥ 7 days to the next dose level up to a maximum dose of navitoclax 300 mg once daily, provided the platelet count is > 100×10^9/L. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0224] In one embodiment, a method for treatment of a human subject with myelofibrosis or MPN (myeloproliferative neoplasms)-related disorders is provided, comprising administering a therapeutically effective amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib. In some embodiments, the MPN-related disorder comprises polycythemia vera (PCV), essential thrombocytopenia (ET), or chronic myelomonocytic leukemia (CMML).

[0225] In one embodiment, a method for treatment of a human subject with primary myelofibrosis (PMF) or secondary myelofibrosis (SMF), is provided, comprising administering a therapeutically effective amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib.

[0226] In one embodiment, a method for treatment of a human subject with primary myelofibrosis (PMF) or secondary myelofibrosis (SMF), is provided, comprising administering a therapeutically effective amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib wherein the human subject has received ruxolitinib therapy for at least 12 weeks prior to starting navitoclax.

[0227] In one embodiment, a method for treatment of a human subject with primary myelofibrosis (PMF) or secondary myelofibrosis (SMF), is provided, comprising administering a therapeutically effective amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib wherein the human subjects has received ruxolitinib therapy for at least 12 weeks prior to starting navitoclax, wherein the human subject is currently on a stable dose of ≥ 10 mg of ruxolitinib twice daily.

[0228] In one embodiment, a method for treatment of a human subject with primary myelofibrosis (PMF) or secondary myelofibrosis (SMF), is provided, comprising administering a therapeutically effective amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib wherein the human subject has received ruxolitinib therapy for at least 12 weeks prior to starting navitoclax, wherein the human subject is currently on a stable dose of ≥

10 mg of ruxolitinib twice daily.

[0229] In one embodiment, a method for treatment of a human subject with primary myelofibrosis (PMF) or secondary myelofibrosis (SMF), is provided, comprising administering a therapeutically effective amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib wherein the human subject has received ruxolitinib therapy for at least 12 weeks prior to starting navitoclax, wherein the human subject is currently on a stable dose of ≥ 10 mg of ruxolitinib twice daily, comprising administering a therapeutically effective amount of navitoclax; wherein based on individual tolerability including platelet counts, the dose of navitoclax is increased in a stepwise fashion until at least 300 mg. navitoclax is administered once daily.

[0230] In one embodiment, a method for treatment of a human subject with primarily myelofibrosis (PMF) or secondary myelofibrosis (SMF), is provided, comprising administering a therapeutically effective amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib wherein the human subject has received ruxolitinib therapy for at least 12 weeks prior to starting navitoclax, wherein the human subject is currently on a stable dose of ≥ 10 mg of ruxolitinib twice daily, comprising administering a therapeutically effective amount of navitoclax wherein based on individual tolerability including platelet counts, the dose of navitoclax is increased weekly in a stepwise fashion wherein the dose of navitoclax is increased every ≥ 7 days up to a maximum dose of navitoclax 300 mg administered once daily.

[0231] In one embodiment, a method for treatment of a human subject with primarily myelofibrosis (PMF) or secondary myelofibrosis (SMF), is provided, comprising administering a therapeutically effective amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib wherein the human subject has received ruxolitinib therapy for at least 12 weeks prior to starting navitoclax, wherein the human subject is currently on a stable dose of ≥ 10 mg of ruxolitinib twice daily, comprising administering a therapeutically effective amount of navitoclax wherein based on individual tolerability including platelet counts, the dose of navitoclax may be increased weekly in a stepwise fashion wherein the dose of navitoclax is increased every ≥ 7 days up to a maximum dose of navitoclax 300 mg QD, provided the platelet count of the human subject is $> 100 \times 10^9$/L.

[0232] In one embodiment, a method for treatment of a human subject with primary myelofibrosis (PMF) or secondary myelofibrosis (SMF), is provided, comprising administering a

therapeutically effective amount of navitoclax in combination with a therapeutically effective amount of ruxolitinib wherein the human subject has received ruxolitinib therapy for at least 12 weeks prior to starting navitoclax, wherein the human subject is currently on a stable dose of ≥ 10 mg of ruxolitinib twice daily, comprising administering 50 mg of navitoclax once daily wherein based on individual tolerability including platelet counts, the dose of navitoclax is increased weekly in a stepwise fashion wherein the dose of navitoclax is increased every ≥ 7 days up to a maximum dose of navitoclax 300 mg once daily, provided the platelet count of the human subject is $> 100 \times 10^9$/L.

[0233] In one embodiment, a method for treatment of a human subject having CMML (chronic myelomonocytic leukemia) is provided, comprising administering a therapeutically effective amount of navitoclax.

[0234] In one embodiment, a method for treatment of a human subject having CMML (chronic myelomonocytic leukemia) is provided, comprising administering a therapeutically effective amount of navitoclax, optionally with a therapeutic amount of ruxolitinib.

[0235] In one embodiment, a method for treatment of a human subject CMML (chronic myelomonocytic leukemia) is provided, comprising administering one of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg of navitoclax.

[0236] In one embodiment, a method for treatment of a human subject CMML (chronic myelomonocytic leukemia) is provided, comprising administering one of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg of navitoclax once daily.

[0237] In one embodiment, a method for treatment of a human subject having CMML (chronic myelomonocytic leukemia) is provided, comprising administering one of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mgof navitoclax once daily, optionally with a therapeutically effective amount of ruxolitinib.

[0238] In one embodiment, a method for treatment of a human subject having CMML (chronic myelomonocytic leukemia) is provided, comprising administering one of 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, or 300 mg of navitoclax once daily, optionally with a therapeutically effective amount of ruxolitinib.

[0239] In one embodiment, a method for treatment of a human subject having CMML (chronic myelomonocytic leukemia) is provided, comprising administering one of 25 mg, 50 mg,

75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg of navitoclax once daily, optionally with a therapeutically effective amount of ruxolitinib selected from the group consisting of 5 mg twice daily, 10 mg twice daily, 15 mg twice daily, 20 mg twice daily, and 25 mg twice daily.

[0240] In one embodiment, a method for treatment of a human subject having CMML (chronic myelomonocytic leukemia) is provided, comprising administering one of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg of navitoclax once daily, optionally with a therapeutically effective amount of ruxolitinib selected from the group consisting of 5 mg once daily, 10 mg once daily, 15 mg once daily, 20 mg once daily, and 25 mg once daily.

[0241] In one embodiment, a method for treatment of a human subject having polycythemia vera (PCV) is provided, comprising administering a therapeutically effective amount of navitoclax.

[0242] In one embodiment, a method for treatment of a human subject having polycythemia vera (PCV) is provided, comprising administering a therapeutically effective amount of navitoclax, optionally with a therapeutic amount of ruxolitinib.

[0243] In one embodiment, a method for treatment of a human subject having polycythemia vera (PCV) is provided, comprising administering one of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg of navitoclax.

[0244] In one embodiment, a method for treatment of a human subject having polycythemia vera (PCV) is provided, comprising administering one of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg of navitoclax once daily.

[0245] In one embodiment, a method for treatment of a human subject having polycythemia vera (PCV) is provided, comprising administering one of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg of navitoclax once daily, optionally with a therapeutically effective amount of ruxolitinib.

[0246] In one embodiment, a method for treatment of a human subject having polycythemia vera (PCV) is provided, comprising administering one of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg of navitoclax once daily, optionally with a therapeutically effective amount of ruxolitinib.

[0247] In one embodiment, a method for treatment of a human subject having polycythemia

vera (PCV) is provided, comprising administering one of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg of navitoclax once daily, optionally with a therapeutically effective amount of ruxolitinib selected from the group consisting of 5 mg twice daily, 10 mg twice daily, 15 mg twice daily, 20 mg twice daily, and 25 mg twice daily.

[0248] In one embodiment, a method for treatment of a human subject having polycythemia vera (PCV) is provided, comprising administering one of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg of navitoclax once daily, optionally with a therapeutically effective amount of ruxolitinib selected from the group consisting of 5 mg once daily, 10 mg once daily, 15 mg once daily, 20 mg once daily, and 25 mg once daily.

[0249] In one embodiment, a method for treatment of a human subject having essential thrombocytopenia (ET) is provided, comprising administering a therapeutically effective amount of navitoclax.

[0250] In one embodiment, a method for treatment of a human subject having essential thrombocytopenia (ET) is provided, comprising administering a therapeutically effective amount of navitoclax, optionally with a therapeutic amount of ruxolitinib.

[0251] In one embodiment, a method for treatment of a human subject having essential thrombocytopenia (ET) is provided, comprising administering one of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg of navitoclax.

[0252] In one embodiment, a method for treatment of a human subject having essential thrombocytopenia (ET) is provided, comprising administering one of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg of navitoclax once daily.

[0253] In one embodiment, a method for treatment of a human subject having essential thrombocytopenia (ET) is provided, comprising administering one of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg of navitoclax once daily, optionally with a therapeutically effective amount of ruxolitinib.

[0254] In one embodiment, a method for treatment of a human subject having essential thrombocytopenia (ET) is provided, comprising administering one of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg of navitoclax once

daily, optionally with a therapeutically effective amount of ruxolitinib.

[0255] In one embodiment, a method for treatment of a human subject having essential thrombocytopenia (ET) is provided, comprising administering one of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg of navitoclax once daily, optionally with a therapeutically effective amount of ruxolitinib selected from the group consisting of 5 mg twice daily, 10 mg twice daily, 15 mg twice daily, 20 mg twice daily, and 25 mg twice daily.

[0256] In one embodiment, a method for treatment of a human subject having essential thrombocytopenia (ET) is provided, comprising administering one of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, and 300 mg of navitoclax once daily, optionally with a therapeutically effective amount of ruxolitinib selected from the group consisting of 5 mg once daily, 10 mg once daily, 15 mg once daily, 20 mg once daily, and 25 mg once daily.

[0257] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 25 mg.

[0258] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 50 mg.

[0259] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 75 mg.

[0260] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 100 mg.

[0261] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 125 mg.

[0262] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 150 mg.

[0263] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 175 mg.

[0264] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 200 mg.

[0265] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 225 mg.

[0266] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 250 mg.

[0267] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 275 mg.

[0268] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 300 mg.

[0269] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise more than 300 mg. In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 50 mg administered once daily.

[0270] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 75 mg administered once daily.

[0271] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 100 mg administered once daily.

[0272] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 125 mg administered once daily.

[0273] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 150 mg administered once daily.

[0274] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 175 mg administered once daily.

[0275] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 200 mg administered once daily.

[0276] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 225 mg administered once daily.

[0277] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 250 mg administered once daily.

[0278] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 275 mg administered once daily.

[0279] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 300 mg administered once daily.

[0280] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise more than 300 mg administered once daily.

[0281] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 50 mg administered once daily, optionally increased to 100 mg administered once daily.

[0282] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 100 mg administered once daily, optionally increased to 150 mg administered once daily.

[0283] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 100 mg administered once daily, optionally increased to 200 mg administered once daily.

[0284] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 150 mg administered once daily, optionally increased to 200 mg administered once daily.

[0285] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 150 mg administered once daily, optionally increased to 250 mg administered once daily.

[0286] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 150 mg administered once daily, optionally increased to 200 mg administered once daily.

[0287] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 150 mg administered once daily, optionally increased to 250 mg administered once daily.

[0288] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 200 mg administered once daily, optionally increased to 250 mg administered once daily.

[0289] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 200 mg administered once daily, optionally increased to 300 mg administered once daily.

[0290] In any of the embodiments disclosed herein, the effective amount of navitoclax can comprise 100 mg administered once daily, optionally increased to 200 mg administered once daily after $\geq$ 7 days if the human subject has a platelet count $\geq$ 75 x 10^9/L.

[0291] In any of the embodiments disclosed herein, the effective amount of navitoclax can

be increased to 300 mg administered once daily.

[0292] In any of the embodiments disclosed herein, the effective amount of navitoclax can be increased to 300 mg administered once daily, if after 24 weeks the patient fails to achieve a spleen reduction volume (SVR) of at least 10%.

[0293] In any of the embodiments disclosed herein, the effective amount of ruxolitinib can comprise 5 mg administered once daily.

[0294] In any of the embodiments disclosed herein, the effective amount of ruxolitinib can comprise 10 mg administered once daily.

[0295] In any of the embodiments disclosed herein, the effective amount of ruxolitinib can comprise 15 mg administered once daily.

[0296] In any of the embodiments disclosed herein, the effective amount of ruxolitinib can comprise 20 mg administered once daily.

[0297] In any of the embodiments disclosed herein, the effective amount of ruxolitinib can comprise 25 mg administered once daily.

[0298] In any of the embodiments disclosed herein, the effective amount of ruxolitinib can comprise more than 25 mg administered once daily.

[0299] In any of the embodiments disclosed herein, the effective amount of ruxolitinib can comprise 5 mg administered twice daily.

[0300] In any of the embodiments disclosed herein, the effective amount of ruxolitinib can comprise 10 mg administered twice daily.

[0301] In any of the embodiments disclosed herein, the effective amount of ruxolitinib can comprise 15 mg administered twice daily.

[0302] In any of the embodiments disclosed herein, the effective amount of ruxolitinib can comprise 20 mg administered twice daily.

[0303] In any of the embodiments disclosed herein, the effective amount of ruxolitinib can comprise 25 mg administered twice daily.

[0304] In any of the embodiments disclosed herein, the effective amount of ruxolitinib can comprise more than 25 mg administered twice daily.

[0305] In any of the embodiments disclosed herein, the effective amount of ruxolitinib can comprise 5 mg.

[0306] In any of the embodiments disclosed herein, the effective amount of ruxolitinib can

comprise 10 mg.

[0307] In any of the embodiments disclosed herein, the effective amount of ruxolitinib can comprise 15 mg.

[0308] In any of the embodiments disclosed herein, the effective amount of ruxolitinib can comprise 20 mg.

[0309] In any of the embodiments disclosed herein, the effective amount of ruxolitinib can comprise 25 mg.

[0310] In any of the embodiments disclosed herein, the effective amount of ruxolitinib can comprise 30 mg.

[0311] In any of the embodiments disclosed herein, the effective amount of ruxolitinib can comprise 40 mg.

[0312] In any of the embodiments disclosed herein, the effective amount of ruxolitinib can comprise 50 mg.

[0313] In any of the embodiments disclosed herein, the effective amount of ruxolitinib can comprise more than 50 mg.

[0314] In any of the embodiments disclosed herein, the administration of navitoclax can comprise oral administration.

[0315] In any of the embodiments disclosed herein, the administration of ruxolitinib can comprise oral administration.

[0316] In any of the embodiments disclosed herein, the administration of navitoclax can comprise oral administration and the administration of ruxolitinib can comprise oral administration.

[0317] In any of the embodiments disclosed herein, the human subject can achieve a spleen reduction volume of at least 35% (SVR_{35}). In any of the foregoing embodiments, the human subject can achieve a spleen reduction volume of at least 35% (SVR_{35}) by week 24. In any of the foregoing embodiments, the human subject can achieve a spleen reduction volume of at least 35% (SVR_{35}) after week 24.

[0318] In any of the embodiments disclosed herein, the spleen reduction volume of at least 35% (SVR_{35}) can be measured according to magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

[0319] In any of the embodiments disclosed herein, if the human subject has a platelet count

of > 150 × 10^9/L, the effective amount of ruxolitinib can comprise 20 mg twice daily.

[0320] In any of the embodiments disclosed herein, if the human subject has a platelet count of > 200 × 10^9/L, the effective amount of ruxolitinib can comprise 20 mg twice daily.

[0321] In any of the embodiments disclosed herein, if the human subject has a platelet count of 100 × 10^9/L to 200 × 10^9/L, the effective amount of ruxolitinib can comprise 15 mg twice daily.

[0322] In any of the embodiments disclosed herein, if the human subject has a platelet count of > 150 × 10^9/L, the effective daily amount of navitoclax can comprise 200 mg.

[0323] In any of the embodiments disclosed herein, if the human subject has a platelet count of ≤ 150 x 10^9/L, the effective daily amount of navitoclax can comprise 100 mg, optionally increased to 200 mg navitoclax after ≥ 7 days if the human subject has a platelet count ≥ 75 x 10^9/L.

[0324] In any of the embodiments disclosed herein, the navitoclax dose may be increased to 300 mg once daily based on platelet count for subjects with sub-optimal spleen response, defined as failure to achieve a spleen volume reduction of at least 10%.

[0325] In any of the embodiments disclosed herein, if the human subject has a platelet count of ≥ 75 × 10^9/L, the current dose of navitoclax can be maintained.

[0326] In any of the embodiments disclosed herein, if the human subject has a platelet count of ≥ 75 × 10^9/L, the current dose of navitoclax can be escalated to 200 mg or optionally 300 mg once daily.

[0327] In any of the embodiments disclosed herein, if the human subject has a platelet count of ≥ 75 × 10^9/L, the current dose of navitoclax can be maintained, wherein, the dose of navitoclax may be adjusted for thrombocytopenia.

[0328] In any of the embodiments disclosed herein, if the human subject has a platelet count of < 75 × 10^9/L - ≥ 50 × 10^9/L, the current navitoclax dose level can be maintained or reduced.

[0329] In any of the embodiments disclosed herein, if the human subject has a platelet count of < 50 × 10^9/L, the current navitoclax dose level can be interrupted, wherein the platelet count is rechecked approximately 2 – 3 days until recovery to ≥ 50 × 10^9/L wherein navitoclax administration can be resumed, optionally at a lower dose level.

[0330] In any of the embodiments disclosed herein, the dose of navitoclax can only be escalated if current dose of navitoclax has been administered for at least 7 days, wherein platelet

count can be rechecked approximately 7 days after navitoclax dose escalation.

[0331] In any of the embodiments disclosed herein, the daily therapeutically effective amount of navitoclax administered to the human subject if the human subject has a platelet count of $>150 \times 10^9$/L can comprise 200 mg.

[0332] In any of the embodiments disclosed herein, the daily therapeutically effective amount of navitoclax administered to the human subject if the human subject has a platelet count of ≤ 150 x 10^9/L can comprise 100 mg.

[0333] In any of the embodiments disclosed herein, the daily therapeutically effective amount of navitoclax administered to the human subject if the human subject has a platelet count of $>150 \times 10^9$/L can comprise 300 mg.

[0334] In any of the embodiments disclosed herein, the daily therapeutically effective amount of navitoclax administered to the human subject if the human subject has a platelet count of ≤ 150 x 10^9/L can comprise 200 mg.

[0335] In any of the embodiments disclosed herein, the daily therapeutically effective amount of navitoclax administered to the human subject if the human subject has a platelet count of $>200 \times 10^9$/L can comprise 200 mg.

[0336] In any of the embodiments disclosed herein, the daily therapeutically effective amount of navitoclax administered to the human subject if the human subject has a platelet count of ≤ 200 x 10^9/L can comprise 100 mg.

[0337] In any of the embodiments disclosed herein, the daily therapeutically effective amount of navitoclax administered to the human subject if the human subject has a platelet count of $>200 \times 10^9$/L can comprise 300 mg.

[0338] In any of the embodiments disclosed herein, the daily therapeutically effective amount of navitoclax administered to the human subject if the human subject has a platelet count of ≤ 200 x 10^9/L can comprise 200 mg..

[0339] In any of the embodiments disclosed herein, human subjects receiving ruxolitinib at Screening can continue at the current stable dose of $\geq$ 10 mg twice daily.

[0340] In any of the embodiments disclosed herein, human wherein subjects not receiving ruxolitinib before starting navitoclax can receive ruxolitinib at a dose of 10 mg twice daily.

[0341] In any of the embodiments disclosed herein, the ruxolitinib dose can be adjusted in subjects with hepatic or renal impairment.

[0342] In any of the embodiments disclosed herein, the navitoclax dose can be adjusted in subjects with hepatic or renal impairment.

[0343] In any of the embodiments disclosed herein, the ruxolitinib dose can be adjusted, modified, or discontinued temporarily or permanently in subjects receiving treatment with a CYP3A substrate or CYP3A inhibitor.

[0344] In any of the embodiments disclosed herein, the navitoclax dose can be adjusted, modified, or discontinued temporarily or permanently in subjects receiving treatment with a CYP3A substrate or CYP3A inhibitor.

[0345] In any of the embodiments disclosed herein, the ruxolitinib dose can be adjusted, modified, or discontinued temporarily or permanently in subjects with abnormal hemoglobin levels.

[0346] In any of the embodiments disclosed herein, the ruxolitinib dose can be adjusted, modified, or discontinued temporarily or permanently in subjects with abnormal platelet levels.

[0347] In any of the embodiments disclosed herein, the navitoclax dose can be adjusted, modified, or discontinued temporarily or permanently in subjects with abnormal platelet levels.

[0348] In any of the embodiments disclosed herein, the ruxolitinib dose can be adjusted, modified, or discontinued temporarily or permanently in subjects with abnormal absolute neutrophil count (ANC).

[0349] In any of the embodiments disclosed herein, the myelofibrosis can comprise relapsed/refractory (R/R) myelofibrosis.

[0350] In any of the embodiments disclosed herein, the myelofibrosis can comprise intermediate or intermediate-risk primary myelofibrosis.

[0351] In any of the embodiments disclosed herein, the myelofibrosis can comprise high-risk primary myelofibrosis.

[0352] In any of the embodiments disclosed herein, the myelofibrosis can comprise intermediate or intermediate-risk secondary myelofibrosis.

[0353] In any of the embodiments disclosed herein, the myelofibrosis can comprise high-risk secondary myelofibrosis.

[0354] In any of the embodiments disclosed herein, the myelofibrosis can comprise post-polycythemia vera (post-PCV) myelofibrosis.

[0355] In any of the embodiments disclosed herein, the myelofibrosis can comprise post-

essential thrombocytopenia (post-ET) myelofibrosis.

[0356] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in this application, including but not limited to patents, patent applications, articles, books, and treatises, are hereby expressly incorporated by reference in their entirety for any purpose. To the extent documents incorporated by reference contradict the disclosure contained in the specification; the specification will supersede any contradictory material.

[0357] Generally, nomenclatures used in connection with cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well-known and commonly used in the art. The nomenclatures used in connection with analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in the art unless otherwise indicated.

[0358] So that the disclosure may be more readily understood, select terms are defined below.

Definitions

[0359] As used in the specification and the appended claims, unless specified to the contrary, the following terms have the meaning indicated:

[0360] The term "ANC" as used herein refers to absolute neutrophil count.

[0361] The term "aPTT" as used herein refers to activated partial thromboplastin time.

[0362] The term "ALT" as used herein refers to alanine aminotransferase.

[0363] The term "AST" as used herein refers to aspartate aminotransferase.

[0364] The term "BID" as used herein refers to twice a day.

[0365] The term "CYP3A" as used herein refers to Cytochrome P450 3A.

[0366] The term "CT" as used herein refers to computed tomography, as in CT scan.

[0367] The term "ECOG" as used herein refers to Eastern Cooperative Oncology Group.

[0368] The term "INR" as used herein refers to International Normalized Ratio.

[0369] The term "IWG" as used herein refers to International Working Group, as in IWG criteria for myelofibrosis, described in Tefferi *et al.*, Blood, 22 August 2013, Vol. 122, Number 8, hereby incorporated by reference in its entirety.

[0370] The term "JAK2" or "JAK-2" as used herein refers to Janus Kinase 2.

[0371] The term "LMWH" as used herein refers to low-molecular-weight heparin.

[0372] The term "MF" as used herein refers to myelofibrosis.

[0373] The term "MRI" as used herein refers to magnetic resonance imaging.

[0374] The term "PET-MF" as used herein refers to post-essential thrombocythemia myelofibrosis.

[0375] The term "PPV-MF" as used herein refers to post-polycythemia vera myelofibrosis.

[0376] The term "QD" as used herein refers to once a day.

[0377] The term "SVR" as used herein refers to spleen volume reduction.

[0378] The term "ULN" as used herein refers upper normal limit.

[0379] The term "relapsed" refers to disease that reappears or grows again after a period of remission.

[0380] The term "refractory" is used to describe when the disease does not respond to treatment (meaning that the cancer cells continue to grow) or when the response to treatment does not last very long.

[0381] The term "therapeutically effective amount" or "effective amount" as used herein refers to a sufficient amount of the compound to treat disorders, at a reasonable benefit/risk ratio applicable to any medical treatment within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient can depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound(s) employed; and like factors n in the medical arts.

[0382] The term "in combination" means that the drugs administered are given either simultaneously or sequentially. If given sequentially, one of the two compounds is usually detectable in the serum of the subject at the onset of administration of the other compound.

[0383] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

[0384] The use of the terms "a" and "an" and "the" and similar referents in the context of

describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to,") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[0385] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

EXAMPLES

[0386] In order that the invention described herein may be more fully understood, the following examples are set forth.

EXAMPLE 1

Phase 2 Study of Navitoclax in Combination with Ruxolitinib in Subjects with

Primary or Secondary Myelofibrosis

Methods

[0387] This Phase 2 single-arm, multicenter, open-label study assessed the efficacy and safety of navitoclax combined with ruxolitinib in subjects with myelofibrosis (MF). Eligible subjects (≥18 years old, diagnosis of primary myelofibrosis, post-essential thrombocythemia (PET-MF), or post-polycythemia vera myelofibrosis (PPV-MF), Eastern Cooperative Oncology Group Performance Status (ECOG) 0–2, receiving at least 12 weeks of continuous ruxolitinib therapy prior to study treatment initiation) received a starting dose of 50 mg navitoclax once-daily combined with the current stable dose of ruxolitinib (≥10 mg twice a day (BID)). Weekly intra-subject dose-escalation of navitoclax was allowed based on tolerability and platelet count, first from 50 mg to 100 mg, then to 200 mg, up to a maximum daily dose of 300 mg. Treatment continued until the end of clinical benefit, unacceptable toxicity, or discontinuation. The primary efficacy endpoint was percentage reduction in splenic volume from baseline. Secondary endpoints included effect on total symptom score (TSS), overall response rate, rate of anemia response, improvement in bone marrow fibrosis, and safety profile.

Subject Inclusion Criteria

[0388] For this study, inclusion criteria included the following:

1. Subject must be ≥ 18 years of age.
2. Subject has documented diagnosis of Intermediate or High-Risk Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis (PPV-MF), or Post-Essential Thrombocythemia Myelofibrosis (PET-MF) as defined by the World Health Organization classification.
3. Subject must be ineligible or unwilling to undergo stem cell transplantation at time of study entry.
4. Subject must have an Eastern Cooperative Oncology Group (ECOG) Performance Score of 0, 1, or 2.
5. Cohort 1a only: Subject must have received ruxolitinib therapy for at least 12 weeks and be currently on a stable dose of ≥ 10 mg BID of ruxolitinib for ≥ 8 weeks prior to the 1st dose of navitoclax.
6. Cohort 1b only: Subject must have received prior treatment with JAK-2 inhibitor therapy for at least 12 weeks

7. Cohort 2 only: Subject must have received prior treatment with JAK-2 inhibitor therapy and meet one of the following criteria (a or b):
    a. Prior treatment with JAK-2 inhibitor for at least 12 weeks
    b. Prior treatment with JAK-2 inhibitor for at least 28 days complicated by any of the following:
        i. Development of red blood cell transfusion requirement (at least 2 units/month for 2 months,

        OR

        ii. Grade ≥ 3 adverse events of thrombocytopenia, anemia, hematoma and/or hemorrhage while on JAK-2 inhibitor treatment
8. Cohort 3 only: Subject must not have received prior treatment with a JAK-2 inhibitor.
9. Subject has splenomegaly defined as spleen palpation measurement ≥ 5 cm below costal margin or spleen volume ≥ 450 cm^3 as assessed by MRI.
10. Subject must meet the following laboratory parameters per local laboratory reference range at Screening:
    - Adequate bone marrow reserves; in the absence of growth factors, thrombopoietic factors, or platelet transfusions for at least 14 days:
        - Platelet count ≥ 100 × 10^9 /L (Cohorts 1a, 1b or 3)
        - Platelet count ≥ 75 × 10^9 /L (Cohort 2)
        - ANC ≥ 1 × 10^9 /L
    - Renal function: calculated creatinine clearance ≥ 30 mL/minute.
    - Hepatic function and enzymes:
        - AST and ALT ≤ 3.0 × the upper normal limit (ULN)
        - Total Bilirubin ≤ 1.5 × ULN (exception: subjects with Gilbert's Syndrome may have a Bilirubin > 1.5 × ULN)
    - Coagulation: aPTT and INR ≤ 1.5 × ULN

Key Exclusion Criteria

1. Splenic irradiation within 6 months prior to screening, or prior splenectomy.
2. Leukemic transformation (> 10% blasts in peripheral blood or bone marrow biopsy).
3. Subject is currently on medications that interfere with coagulation (including

warfarin) or platelet function with the exception of low dose aspirin (up to 100 mg) and low-molecular-weight heparin (LMWH).

4. Prior therapy with a BH3 mimetic compound.
5. Subject has received strong or moderate CYP3A inhibitors (e.g., ketoconazole, clarithromycin and fluconazole) within 14 days prior to the administration of the first dose of navitoclax.

Table 13: Bone Marrow Grading of Myelofibrosis

Grading	Description
MF-0	Scattered linear reticulin with no intersections (cross-overs) corresponding to normal bone marrow
MF-1	Loose network of reticulin with many intersections, especially in perivascular areas
MF-2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis
MF-3	Diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis.

*Fiber density should be assessed in hematopoietic (cellular) areas. (Thiele J, Kvasnicka HM, Facchetti F, et al. European Consensus on Grading Bone Marrow Fibrosis and Assessment of Cellularity. Haematologica.2005;90(8):1128-32.)

Results

[0389] Thirty-four subjects (primary myelofibrosis, n = 16; PET-MF, n = 5; PPV-MF, n = 13) had received ≥1 dose of navitoclax in combination with ruxolitinib. Median age was 68 years old (range was 42 years old – 86 years old), 68% were male, and 9 subjects (26%) had ≥3 prior lines of myelofibrosis therapy.

[0390] Subjects needed to have received ruxolitinib therapy for at least 12 weeks prior to study enrollment without interruption, have splenomegaly as defined by a spleen palpable ≥ 5 cm below costal margin and be currently on a stable dose of ≥ 10 mg BID of ruxolitinib. The median duration of prior ruxolitinib exposure was 745 days (range was 134 – 4549 days). Of the 34 subjects enrolled, 27 (79%) had *JAK-2* and 7 subjects (21%) had *CALR* mutations. There were no subjects enrolled with triple-negative myelofibrosis. Of 33 subjects with available baseline

testing, 17 (52%) had high molecular risk, defined by mutations within *ASXL1*, *EZH2*, *IDH1/2*, *SRSF2*, or *U2AF1*. The mean baseline platelet count was 231 x 10^9/L (range was 99-706). The mean baseline hemoglobin (Hgb) was 10.8 g/dL. Nineteen (56%) subjects had elevated white blood cell count (WBC) at baseline (>1.5× ULN (upper limit of normal)).

[0391] Navitoclax was administered at a starting dose of 50 mg oral QD. Based on individual tolerability including platelet counts, the dose of navitoclax was increased weekly to a maximum dose of 300 mg QD. Of the 34 patients enrolled, maximal navitoclax dose of 300 mg was achieved in 23 subjects (68%). As shown in Table 14, 83% (19/23) of patients subsequently dose reduced navitoclax with the primary reason for dose reduction being thrombocytopenia (47.8%). Hence, an optimal dose of 200 mg navitoclax was chosen.

Table 14: Navitoclax Dose Reduction

Navitoclax QD Dosing	**n [a] (%)**
Dose Reduction	
No Dose Reduction	4 (17.4)
Only One Dose Reduction	10 (43.5)
More Than One Dose Reduction	9 (39.1)
All Reasons for Dose Reduction	
Adverse Events	17 (73.9)
Thrombocytopenia	11 (47.8)
Diarrhea	2 (8.7)
Anemia	4 (17.4)
Other	7 (30.4)
Logistics/Schedule/Surgery Conflicts	0
Other	4 (17.4)
Dose Delay / Interruption	
No Interruption	8 (34.8)
Only One Interruption	6 (26.1)

More Than One Interruption	9 (39.1)
All Reasons for Dose Delay / Interruption	
Adverse Events	12 (52.2)
Thrombocytopenia	8 (34.8)
Diarrhea	1 (4.3)
Anemia	1 (4.3)
Other	4 (17.4)
Logistics/Schedule/Surgery Conflicts	0
Other	7 (30.4)

[a] n = number of subjects

[0392] Of the 25 (74%) subjects that enrolled on ruxolitinib doses >10 mg BID, 22 (88%) subsequently had the dose of ruxolitinib reduced to 10 mg BID. At the time of this analysis, 24 subjects were evaluable for efficacy, with 20 subjects completing ≥24 weeks on study and 4 subjects with treatment discontinuations prior to 24 weeks. **Figure 1** shows a waterfall plot of spleen volume change from baseline at week 24.

[0393] Efficacy data are shown in Table 15. At week 24 of treatment with the combination of navitoclax and ruxolitinib, 7 of 24 subjects (29%) achieved a spleen volume reduction of ≥35% (SVR_{35}) from baseline by MRI (magnetic resonance imaging) as determined by prespecified central review and 54% of subjects achieved >50% reduction of the spleen length (cm, below costal margin) as assessed by palpation. Additionally, spleen responses deepened beyond 24 weeks of treatment and the best overall SVR_{35} at any time on study was achieved in 10 subjects (42%), with 79% of subjects achieving reductions in spleen length by palpation of >50%. Reductions in driver mutation allelic burden of >5% were observed in 10 subjects (42%); 6 subjects (25%) had bone marrow fibrosis (BMF) improvement of ≥1 grade, suggesting that the combination of navitoclax and ruxolitinib is disease modifying.

Table 15: Best Response Rates in Efficacy Evaluable Population

Navitoclax QD + Ruxolitinib BID (N^a = 24)[b]	**N^a (%)**

SVR_{35}[c] at week 24	7 (29)
SVR_{35}[c] Best On-Study	10 (42)
Reduction in Bone Marrow Fibrosis of ≥ 1 Grade	6 (25)
Reduction > 5% from Baseline in Allelic Frequency	10 (42)

[a] N = number of subjects

[b] Four subjects discontinued treatment prior to Week 24, considered non-responders for analysis purpose

[c] SVR_{35} = spleen volume reduction of 35%

[0394] Of the 13 subjects with total symptom score (TSS) data available at baseline and Week 24, 54% of subjects report a reduction in TSS with 3 patients (23%) achieving ≥50% TSS reduction from baseline with the addition of navitoclax. The median TSS at week 24 was 7.4 (range: 0–23), a 20.4% improvement from baseline. All patients (N=34) receiving navitoclax and ruxolitinib combination therapy experienced at least 1 treatment-emergent adverse event (TEAE). The most common (≥20%) were thrombocytopenia (82%), diarrhea (62%), fatigue (53%), anemia (27%), nausea (27%), contusion (24%), and vomiting (21%). TEAE Grade ≥3 TEAEs occurred in 26 subjects (77%); most common were thrombocytopenia (n=15, 44%; Grade 4 n=1, 3%) and anemia (n=8, 24%; no Grade 4). Five subjects (15%) experienced serious adverse events that resolved including anemia, upper abdominal pain, vomiting, chest pain, increased C-reactive protein, and abnormal liver function test (3% each). One subject (4%) had an anemia response; the mean Hgb at week 24 was slightly improved over baseline at 11.3 g/dL. Of the 19 subjects with elevated baseline white blood cell count, 16 (84%) reduced to within normal limits during treatment, with a median white blood cell count (WBC) reduction of 17.7 × 10^9/L. Notably, there were no significant episodes of bleeding and no TEAE-related deaths.

[0395] The Phase 2 clinical data demonstrate, for the first time in human patients, that the combination therapy of navitoclax and ruxolitinib, particularly for patients who are refractory to ruxolitinib monotherapy, led to a clinically meaningful reduction in spleen volume, allelic burden reductions, Total Symptom Score improvements and, importantly, encouraging improvements in bone marrow fibrosis (BMF) in subjects with myelofibrosis who have received prior treatment with ruxolitinib, with a manageable safety profile. Weekly navitoclax dose escalation from 50

mg once daily to 300 mg once daily in combination with ruxolitinib at ≥ 10 mg, was generally safe without clinically relevant thrombocytopenia-related bleeding. In addition, 83% of subjects experienced a dose reduction of navitoclax during study treatment with the primary reason being thrombocytopenia. Of the subjects with navitoclax dose reductions for thrombocytopenia, 60% received 300 mg of navitoclax. Therefore, doses of navitoclax < 300 mg once daily seem to be better tolerated in patients with myelofibrosis.

EXAMPLE 2

Dose Selection of Navitoclax and Ruxolitinib in Phase 3 Studies in Subjects with Myelofibrosis

Selection of Navitoclax Dose using Exposure-Platelet Response Modeling

Exposure-Platelet Response Model

[0396] A mechanistic model evaluating the effect of navitoclax and ruxolitinib on platelets counts was developed to guide navitoclax dose selection in Phase 3 studies (Examples 4 and 5 *supra*) in combination with ruxolitinib in MF. The model was based on established models described in the literature (Kaefer, A., Yang, J., Noertersheuser, P. et al. Cancer Chemother Pharmacol (2014) 74: 593. doi:10.1007/s00280-014-2530-2530; and Friberg, Lena E., et al. "Model of chemotherapy-induced myelosuppression with parameter consistency across drugs. "*Journal of clinical oncology* 20.24 (2002): 4713-4721, both references hereby incorporated by reference in their entireties). The model was also used to perform simulations of the add-on effects of navitoclax at stable ruxolitinib dose. **Figure 2** shows the model scheme utilized wherein

[0397] Ka is first-order absorption rate constant,

[0398] ALAG1is absorption lag time of navitoclax,

[0399] ALAG2 is absorption lag time of ruxolitinib,

[0400] kel is first order elimination rate constant,

[0401] kcp and kpc are first-order intercompartmental rate constants between central and peripheral PK compartments,

[0402] Proliferation is progenitor cell compartment,

[0403] Maturation 1, Maturation 2, and Maturation 3 are transit compartments representing maturation of the progenitor cells,

[0404] Platelet 1 + Platelet 2 are circulating platelets relative to baseline,

[0405] k_{in} and k_{in2} are zero-order platelet proliferation rate constants,

[0406] k_{trans} is rate constant describing the transfer between the different transit compartments,

[0407] k_{out}, is rate constant describing loss of the circulating cells in blood,

[0408] γ is power term on the feedback mechanism,

[0409] POOL is initial size of the progenitor cell compartment,

[0410] Eff_{NAV} and Eff_{RUX} are effect of navitoclax and ruxolitinib, respectively on platelets;,

[0411] $EC50_{NAV}$ and $EC50_{RUX}$, are navitoclax and ruxolitinib concentrations, respectively at which half-maximal drug effect is obtained,

[0412] $Emax_{NAV}$ and $Emax_{RUX}$ are maximum effect of navitoclax and ruxolitinib, respectively on platelets, and

[0413] $Conc_{NAV,c}$ and $Conc_{RUX,c}$ are navitoclax and ruxolitinib concentration in the central plasma compartment, respectively.

[0414] The mechanistic model was fitted in NONMEM® (Version 7.4.3, 3) to individual concentration (navitoclax and ruxolitinib) and platelet response data from 34 subjects receiving oral navitoclax starting at 50 mg QD with step-wise weekly dose escalation to 100 mg QD, 200 mg QD and 300 mg QD and ruxolitinib at ≥ 10 mg BID (Data from Example 1 *infra*).

[0415] The navitoclax pharmacokinetic (PK) model was a two-compartmental model with a lag-time in absorption (Equations 1a through 1c). PK model for ruxolitinib was described by a two-compartment model with a lag-time in absorption (Equations 2a through 2c).

[0416] Subsequently, the relationship between navitoclax and ruxolitinib exposure and longitudinal platelet response was analyzed. The time course of platelet response was modeled using a semi-physiological model that comprised a progenitor cell compartment, three transition compartments representing the maturation chain in the bone marrow and a peripheral blood compartment (*see* **Figure 2**). A feedback system was used in this model to describe the increase in the maturation rate in bone marrow when the platelet level in the blood compartment is below baseline and decrease in the maturation rate when the platelet level in blood is above baseline. The model also included a progenitor cell "POOL" which describes a large pool of platelet progenitor cells at the beginning of navitoclax and ruxolitinib treatment. Navitoclax effect was modeled to increase the elimination of the circulating platelets (increasing elimination of

platelets). Due to insufficient data to estimate ruxolitinib effect and observed difference in the effect of ruxolitinib on platelets compared to navitoclax (owing to longer exposure to ruxolitinib prior to navitoclax introduction), ruxolitinib effect on platelets was described based on an available model (4) and was assumed to inhibit proliferation of platelets. The drug effect was incorporated as an E_{max}-EC_{50} inhibitory model based on navitoclax and ruxolitinib concentrations. Equations 3 to 9 represent the PD model.

Navitoclax PK Model

$$\frac{dGut}{dt} = -k_a \times Gut \quad \text{Equation 1a}$$

$$\frac{dConc_{NAV,c}}{dt} \times V_c = k_a \times Gut - k_{el} \times Conc_{NAV,c} \times V_{NAV,c} - k_{cp} \times Conc_{NAV,c} \times V_{NAV,c} + k_{pc} \times Conc_{NAV,p} \times V_{NAV,p} \quad \text{Equation 1b}$$

$$\frac{dConc_{NAV,p}}{dt} \times V_p = k_{cp} \times Conc_{NAV,c} \times V_{NAV,c} - k_{pc} \times Conc_{NAV,p} \times V_{NAV,p} \quad \text{Equation 1c}$$

Ruxolitinib PK Model

$$\frac{dGut}{dt} = -k_a \times Gut \quad \text{Equation 2a}$$

$$\frac{dConc_{RUX,c}}{dt} \times V_c = k_a \times Gut - k_{el} \times Conc_{RUX,c} \times V_{RUX,c} - k_{cp} \times Conc_{RUX,c} \times V_{RUX,c} + k_{pc} \times Conc_{RUX,p} \times V_{RUX,p} \quad \text{Equation 2b}$$

$$\frac{dConc_{RUX,p}}{dt} \times V_p = k_{cp} \times Conc_{RUX,c} \times V_{RUX,c} - k_{pc} \times Conc_{RUX,p} \times V_{RUX,p} \quad \text{Equation 2c}$$

Pharmacodynamic (PD) Model

$$Feedback = k_{in} - \frac{k_{trans}}{POOL} \times \left(\frac{1}{PLT1+PLT2}\right)^{\gamma} \quad \text{Equation 3}$$

$$\frac{dPROLIF}{dt} = k_{in} - \frac{k_{trans}}{POOL} \times PROLIF \times Feedback \quad \text{Equation 4}$$

$$\frac{dMAT1}{dt} = \frac{k_{trans}}{POOL} \times PROLIF \times Feedback - k_{trans} \times \text{MAT1} \quad \text{Equation 5}$$

$$\frac{dMAT2}{dt} = k_{trans} \times MAT1 - k_{trans} \times MAT2 \quad \text{Equation 6}$$

$$\frac{dMAT3}{dt} = k_{trans} \times MAT2 - k_{trans} \times MAT3 \quad \text{Equation 7}$$

$$\frac{dPLT1}{dt} = k_{trans} \times MAT3 - k_{out} \times PLT1 \times (1 + \frac{Emax_{NAV} \times Conc_{NAV,c}}{EC50_{NAV} + Conc_{NAV,c}}) \quad \text{Equation 8}$$

$$\frac{dPLT2}{dt} = k_{in2} \times PLT2 \times \left(1 - \frac{Emax_{RUX} \times Conc_{RUX,c}}{EC50_{RUX} + Conc_{RUX,c}}\right) - k_{out2} \times PLT2 \quad \text{Equation 9}$$

[0417] In the PK model, the term(s)

[0418] "Gut" is the amount of navitoclax or ruxolitinib remaining to be absorbed from the gut

[0419] "k_a" represents a first-order absorption rate constant

[0420] "$Conc_{NAV,c}$" and "$Conc_{RUX,c}$" represent navitoclax and ruxolitinib concentration in the central plasma compartment, respectively,

[0421] "$Conc_{NAV,p}$" and "$Conc_{RUX,p}$" represent navitoclax and ruxolitinib concentration in the peripheral compartment, respectively,

[0422] "$V_{NAV,c}$" and "$V_{RUX,c}$" represent navitoclax and ruxolitinib central volumes of distribution, respectively,

[0423] "$V_{NAV,p}$" and "$V_{RUX,p}$" represent navitoclax and ruxolitinib peripheral volumes of distribution, respectively,

[0424] "k_{cp}" and "k_{pc}" represent first-order intercompartmental rate constants between central and peripheral PK compartments, and

[0425] "k_{el}" represents a first-order elimination rate constant.

[0426] In the pharmacodynamic (PD) model, the term(s)

[0427] "PROLIF" represents the progenitor cell compartment that undergoes active proliferation,

[0428] "MAT1", "MAT2", "MAT3" are the transit compartments representing maturation of the progenitor cells,

[0429] "PLT1" and "PLT2" together represent circulating platelets relative to baseline,

[0430] "k_{in}" and "k_{in2}" represent zero-order platelet proliferation rate constant,

[0431] "k_{trans}" is the rate constant describing the transfer between the different transit compartments,

[0432] "k_{out}" is the rate constant describing loss of the circulating cells in blood,

[0433] "γ" is the power term on the feedback mechanism,

[0434] "POOL" represents the initial size of the progenitor cell compartment,

[0435] "$EC50_{NAV}$" and "$EC50_{RUX}$" represent the navitoclax and ruxolitinib concentrations,

respectively at which half-maximal drug effect is obtained, and

[0436] $Emax_{NAV}$ and $Emax_{RUX}$ represent the maximum effect of navitoclax and ruxolitinib, respectively on platelets.

[0437] The model is initialized at 0 for the PK related compartments, at POOL for the PROLIF compartment, and at 1 for the maturation and circulation compartments. The platelet prediction is obtained by $(Baseline\ Platelets) \times PLT1 \times PLT2$. The rates of the Platelet1 model are set to be the same $k_{trans}=k_{in}= k_{out}$ due to a steady state assumption without treatment interference.

[0438] Some of the parameters were fixed to values published in the literature. k_{out} was fixed to 0.521 1/day, γ was fixed to 0.667, E_{max} of navitoclax was fixed to 5 based on Kaefer *et al.* (Kaefer, A., Yang, J., Noertersheuser, P. et al. Cancer Chemother Pharmacol (2014) 74: 593. doi:10.1007/s00280-014-2530-2530), hereby incorporated by reference in its entirety. EC50 values of ruxolitinib was fixed to published value of 0.08248 mg/L, k_{out2} was fixed to 0.0312 1/day and E_{max} value of ruxolitinib was assumed to be 1 (US Drug Approval Package for JAKAFI® (ruxolitinib) Tablets. CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S); APPLICATION NUMBER: 202192Orig1s000), hereby incorporated by reference in its entirety.

[0439] To account for the ruxolitinib experienced nature of subjects, platelets at the initiation of Navitoclax (baseline) were assumed to be ruxolitinib treatment challenged. A factor was included on the baseline platelet count such that

$$baseline(t = -84\ days) = factor \times baseline(t = 0\ days)$$

[0440] where t=0 is the time of initiation of navitoclax. This yields a relative pseudo baseline at initiation of ruxolitinib (referred to as 'ruxolitinib factor' on baseline platelet count). Thus, the model was run for 84 days before the start of navitoclax (with ruxolitinib administered in monotherapy) to account for ruxolitinib effect in the 12 weeks prior to administration of navitoclax. However, data before initiation of navitoclax was not fitted due to incomplete history of individual ruxolitinib treatment before start of the study. The first 56 days of data were fitted to avoid influence of long-term disease effects on the model.

[0441] EC50 for navitoclax, the POOL size and the ruxolitinib factor for pseudo baseline were the only parameters that were estimated. Inter-individual variability was incorporated on navitoclax EC50 and the residual variability was characterized using combined proportional and

additive error model. No inter-individual variability was estimated on ruxolitinib EC50 since limited data precluded its appropriate estimation.

Results

[0442] The estimated model parameters are listed in Table 16. All parameters were estimated with good precision.

[0443] As the observed baseline at initiation is assumed to be lower than at the initiation of ruxolitinib, a factor was estimated that yields the relative pseudo baseline at initiation of ruxolitinib. This factor was estimated to be 1.53-fold, thus, ruxolitinib was estimated to cause a ~36% drop in platelet count (from 1.53 to 1) at average ruxolitinib concentration. This estimate is aligned with the observed decline published in the US FDA clinical pharmacology review of ruxolitinib (Drug Approval Package for JAKAFI® (ruxolitinib) Tablets. CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S); APPLICATION NUMBER: 202192Orig1s000) and by Verstovsek et al (Verstovsek S, Gotlib J, Gupta V, Atallah E, Mascarenhas J, Quintas-Cardama A, Sun W, Sarlis NJ, Sandor V, Levy RS, Kantarjian HM, Mesa RA. Management of cytopenias in patients with myelofibrosis treated with ruxolitinib and effect of dose modifications on efficacy outcomes. Onco Targets Ther. 2013 Dec 17;7:13-21. doi: 10.2147/OTT.S53348. PMID: 24368888; PMCID: PMC3869911), all references hereby incorporated by reference in their entireties.

Table 16. Parameter Estimates of the Exposure-Platelet Response Model for the Combination of Navitoclax and Ruxolitinib

Parameter	Estimate and 95% Confidence Interval	Inter individual variablity (OMEGA)
k_{out} (1/day)	0.521 fixed	
Gamma	0.667 fixed	
POOL size	15.8 (8.12; 31.0)	
BaselineFactor	1.53 (1.41; 1.65)	
Navitoclax EC_{50} (mg/L)	3.61 (1.97; 6.58)	1.03 (134% CV)
Navitoclax E_{max}	5 fixed	
k_{out2} (1/day)	0.0312 fixed	
Ruxolitinib EC_{50} (mg/L)	0.0825 fixed	

Ruxolitinib E_{max}	1 fixed

Simulations

[0444] Platelet count simulations were conducted considering two dosing regimens corresponding to R/R MF population and naive MF (no prior treatment for MF) population enrolling 100 subjects for each scenario. Within each of these scenarios, simulations were conducted at different navitoclax doses in combination with 10 mg BID ruxolitinib:

[0445] R/R MF subjects: In R/R MF subjects currently on ruxolitinib treatment of 10 mg BID, different doses navitoclax were simulated as follows:

- Flat starting doses of navitoclax (100 mg QD, 200 mg QD, 300 mg QD)
- Starting navitoclax at 100 mg QD with a weekly ramp-up to 200 mg QD.

[0446] Naive MF: In naive MF subjects, different doses navitoclax in combination with 10 mg BID ruxolitinib were simulated as follows:

- Flat starting doses of navitoclax (100 mg QD, 200 mg QD, 300 mg QD)
- Starting navitoclax at 100 mg QD with a weekly ramp-up to 200 mg QD.

[0447] The impact of adaptive dosing was explored using a regimen with platelet count dependent dose escalation from 100 mg QD to 200 mg QD navitoclax after two weeks of treatment (only if platelet count >=100 x 10^9 cells/L).

[0448] 100 subjects were simulated for each regimen and scenario. 250 replicates of the simulations were run and summarized. Overall, 12 weeks of various navitoclax daily doses plus continuous 10 mg BID treatment of ruxolitinib were administered. Continuous dosing of navitoclax and ruxolitinib without any dose reductions or interruptions was assumed.

[0449] All simulations were conducted using the model estimated for 34 subjects from Example 1. For the simulation, the inter individual variability for ruxolitinib EC50 was assumed to be 98.2% based on the available model (4). Only subjects with a platelet count between 100 and 500 at the initiation of navitoclax were allowed in the simulation. For R/R the observed baseline from Example 1 was used (~200 x 10^9 cells/L), with CV of 51%) and adjusted with the estimated baseline factor. The R/R population was treated with ruxolitinib for 12 weeks before administration of the first navitoclax dose. For the naïve population, the baseline factor was not

used, but a slightly higher baseline based on the available model was used (276 x 10^9 cells/L, CV of 57%) (Drug Approval Package for JAKAFI® (ruxolitinib) Tablets. CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S); APPLICATION NUMBER: 202192Orig1s000), hereby incorporated by reference in its entirety. Baseline platelet count was assumed to be lognormally distributed.

[0450] Mean percent subjects with Grade 3/4 thrombocytopenia were calculated using all replicates. Based on these percentages, confidence intervals were derived using a binomial distribution assumption. Table 17 shows the allocation of subjects to baseline groups was used (resulting from the baseline distribution as defined above).

Table 17. Allocation of Subjects to Different Baseline Groups in the Simulations

Baseline group (x 10^9 cells/L)	Naive MF	R/R MF
100-150	22	12
150-300	59	52
300-500	19	36
Total	100	100

Simulation Results

[0451] Based on the simulations, maximum decreases in platelets and incidences of Grade 3/4 thrombocytopenia during weekly ramp-up from 100 mg to 200 mg QD were either similar to or slightly lower than those predicted at a flat starting dose of 200 mg (<6% difference for baseline platelet >150 × 10^9/L and ≤150 × 10^9/L) in both R/R and Naive MF (**Figure 3**, Table 18).

Table 18. Simulated Mean (90% CI) Percent Changes from Baseline, Percent Incidence of Grade 3/4 Thrombocytopenia for Combination of Navitoclax and Ruxolitinib (10 mg BID) in Naïve MF and R/R MF

Cohort	Baseline Platelet Count (x 10^9 Cells/L)	Regimen	Grade 3	Grade 4
Naive MF	100-150	100 mg	76.0% (59.1; 90.9)	17.9% (4.5; 31.8)
	100-150	200 mg	87.2% (72.7; 95.5)	33.2% (18.2; 50.0)
	100-150	300 mg	92.7% (81.8; 100.0)	45.0% (27.3; 63.6)
	100-150	100->200 mg	82.2% (68.2; 95.5)	21.2% (9.1; 36.4)
	>150-300	100 mg	31.0% (22.0; 40.7)	4.2% (0.0; 8.5)
	>150-300	200 mg	47.8% (37.3; 57.6)	8.4% (3.4; 15.3)
	>150-300	300 mg	58.1% (47.5; 67.8)	12.8% (6.8; 20.3)
	>150-300	100->200 mg	44.7% (33.9; 55.9)	6.7% (1.7; 11.9)
	>300-500	100 mg	6.4% (0.0; 15.8)	0.6% (0.0; 5.3)
	>300-500	200 mg	12.9% (0.0; 26.3)	1.3% (0.0; 5.3)
	>300-500	300 mg	18.9% (5.3; 36.8)	2.0% (0.0; 10.5)
	>300-500	100->200 mg	12.6% (0.0; 26.3)	1.2% (0.0; 5.3)
R/R MF	100-150	100 mg	78.7% (58.3; 100.0)	19.4% (0.0; 41.7)
	100-150	200 mg	88.5% (75.0; 100.0)	32.6% (8.3; 58.3)
	100-150	300 mg	93.7% (83.3; 100.0)	45.5% (25.0; 66.7)
	100-150	100->200 mg	82.4% (66.7; 100.0)	20.1% (0.0; 41.7)
	>150-300	100 mg	33.4% (23.1; 44.2)	4.4% (0.0; 9.6)
	>150-300	200 mg	49.7% (38.5; 61.5)	9.6% (3.8; 17.3)
	>150-300	300 mg	60.9% (50.0; 71.2)	13.7% (5.8; 21.2)
	>150-300	100->200 mg	43.8% (32.7; 55.8)	6.0% (1.9; 11.5)
	>300-500	100 mg	8.3% (2.8; 16.7)	0.9% (0.0; 2.8)
	>300-500	200 mg	15.6% (5.6; 25.0)	1.6% (0.0; 5.6)
	>300-500	300 mg	22.3% (11.1; 33.3)	2.3% (0.0; 8.3)
	>300-500	100->200 mg	14.7% (5.6; 25.0)	1.4% (0.0; 5.6)

[0452] Using this model-based approach, a flat starting dose of navitoclax was proposed at 200 mg QD in subjects with baseline platelet >150 × 10^9/L and a conservative dose of 100 mg QD in subjects with baseline platelet ≤150 × 10^9/L to minimize the risk of clinically relevant thrombocytopenia in combination with ruxolitinib.

Selection of Ruxolitinib Dose in R/R MF using Exposure-Spleen Volume Response Modeling

[0453] Example 1 allowed subjects who were on stable ruxolitinib dose of ≥ 10 mg BID for at least 8 weeks. Ruxolitinib dose reductions have occurred in 22 of the 25 subjects that began study on doses >10 mg twice daily primarily due to thrombocytopenia (86.4%) and anemia (18.2%). By 12 weeks, the average daily dose of ruxolitinib was around 10 mg BID. Exposure-spleen volume response analysis was conducted to evaluate if >10 mg BID ruxolitinib would be more efficacious in combination with navitoclax in R/R MF subjects.

Exposure-Spleen Volume Response Model

[0454] The effect of navitoclax and ruxolitinib on spleen volume was evaluated using data from cohort 1a of Example 1 in patients with relapsed/refractory MF. An indirect response model incorporating inhibitory effects of both navitoclax and ruxolitinib on spleen volume best described the data from Example 1. The model was also used to perform simulations of combination of navitoclax and ruxolitinib at different dose levels. **Figure 4** shows the model scheme.

[0455] The PK/PD model was fitted in NONMEM® (Version 7.4.3, 3) to individual concentration (navitoclax and ruxolitinib) and spleen volume data from 34 subjects receiving oral navitoclax starting at 50 mg QD with step-wise weekly dose escalation to 100 mg QD, 200 mg QD and 300 mg QD and ruxolitinib at ≥ 10 mg BID (data from Example 1).

[0456] The navitoclax and ruxolitinib PK models were already described above (Equations 1a through 2c). The relationship between navitoclax and ruxolitinib exposure and longitudinal spleen volume was analyzed. The time course of spleen volume was modeled using an indirect response model represented by a single spleen compartment linked to navitoclax and ruxolitinib central compartments with inhibitory effects of navitoclax and ruxolitinib on spleen volume (*see* **Figure 3** and Equation 10). The drug effect was incorporated as an E_{max}-EC_{50} model based on navitoclax and ruxolitinib concentrations.

PD Model

$$\frac{dSV}{dt} = k_{in} \times (1 - \frac{Emax_{NAV} \times Conc_{NAV,c}}{EC50_{NAV} + Conc_{NAV,c}}) \times (1 + E_{plc} - \frac{Emax_{RUX} \times Conc_{RUX,c}}{EC50_{RUX} + Conc_{RUX,c}}) - k_{out} \times SV \quad \text{Equation 10}$$

[0457] where the term "SV" represents the spleen volume,

[0458] "k_{in}" represents zero-order spleen growth rate constant,

[0459] "k_{out}" represents first-order spleen volume loss rate constant,

[0460] "E_{prog}" is the disease progression effect introduced on "k_{in}",

[0461] "$EC50_{NAV}$" and "$EC50_{RUX}$" represent the navitoclax and ruxolitinib concentrations, respectively at which half-maximal drug effect is obtained, and

[0462] $Emax_{NAV}$ and $Emax_{RUX}$ represent the maximum effect of navitoclax and ruxolitinib, respectively on spleen volume.

[0463] Spleen volume data up to only week 40 was used in the model to improve model predictability. Emax of Navitoclax was fixed to 1 while Emax of ruxolitinib was fixed to a published value of 0.765 (4). Inter-individual variability with full correlation matrix was incorporated on estimated baseline spleen volume, k_{out}, $EC50_{NAV}$ and $EC50_{RUX}$ using exponential function and the residual variability was characterized using combined proportional and additive error model.

[0464] At baseline, the rates of the spleen volume model are set to be the same k_{in}= k_{out} due to a theoretical steady state assumption without treatment interference. This leads to an initial condition for the SV compartment of 1, where SV predictions are derived by multiplying this compartment with baseline. Disease progression was included in the model with the factor "E_{prog}" on "k_{in}".

Results

[0465] The estimated model parameters are listed in Table 19. Due to the large %CV of the model estimates, a full covariance matrix was used during the modeling to account for correlations in the variability and thus reducing the overall variability. The shrinkage (statistical measure for overestimation of variability) of the inter-individual variability was acceptably low with a range of 12% to 39%.

Table 19. Parameter Estimates of the Spleen Volume Inhibition Model for Navitoclax and Ruxolitinib Combination

Parameter	Estimate	95% Confidence Interval	Inter-individual Variability
k_{in}, k_{out} (1/day)	0.000222	0.0000533, 0.000924	3.54 (579 %CV)
E_{prog} (cm^3/day)	0.0594	0.00394, 0.897	5.75 (1700 %CV)
Navitoclax EC_{50} (mg/L)	4.37	0.114, 167.2	2.89 (412 %CV)
Navitoclax E_{max}	1 fixed		
Ruxolitinib EC_{50} (mg/L)	0.0144	0.00047, 1.08550	1.20 (152 %CV)
Ruxolitinib E_{max}	0.765 fixed		

Simulations

[0466] Simulations were conducted at different doses of navitoclax at 100 mg QD, 200 mg QD and 300 mg QD in combination with different doses of ruxolitinib at 10 mg BID, 15 mg BID, and 20 mg BID. 5000 subjects/dose group were simulated. Key assumptions or the simulations included continuous dosing scenarios without any dose reductions or interruptions and baseline spleen volume (median 1.63) with interindividual variability (68.7 %CV) was estimated from observed data (limited to 0.35 – 5.5 cm^3).

Simulation Results

[0467] Simulations suggested moderate dose dependent decrease in percent change from baseline spleen volume for both navitoclax and ruxolitinib (**Figure 5**).

[0468] Percent of subjects with at least 35% of reduction in spleen volume (referred to as SVR35) at week 24, which is the primary end point of the study, was also simulated. Predicted SVR35 at week 24 was 33% which was consistent with the observed SVR rate of 30%. Percent of subjects with SVR35 were predicted to be higher for higher doses of navitoclax and ruxolitinib. Specifically, a 10% higher SVR_{35} was predicted with ruxolitinib dose of 20 mg BID compared to 10 mg BID at week 24 in combination with navitoclax at 200 mg QD (**Figure 6**).

[0469] Thus, simulation of spleen volume response at different navitoclax and ruxolitinib dose combinations suggested that safety permitting, higher ruxolitinib doses are likely to provide better spleen volume response in patients with R/R MF.

[0470] Using model-based approach, it was proposed that subjects on a stable dose of

ruxolitinib at the time of study entry can continue at that dose in combination with navitoclax (at 100 mg QD or 200 mg QD based on baseline platelet count). Furthermore, the dose reduction strategy established in Phase 3 trials and safety and tolerability data from Example 1 support starting ruxolitinib at >10 mg BID, e.g. 200 mg QD or 100 mg QD Navitoclax and 10, 15, or 20 mg ruxolitinib BID, depending on baseline platelet counts. For subjects who have not been on a stable dose of ruxolitinib at time of study entry were proposed to start ruxolitinib therapy at 10 mg BID in combination with navitoclax.

EXAMPLE 3

Extended Phase 2 Open-Label Study Evaluating Tolerability and Efficacy of Navitoclax Alone or in Combination with Ruxolitinib in Subjects with Myelofibrosis

Objective(s)

[0471] Building off Example 1, the primary objective of this study is to evaluate the effect of navitoclax alone or in combination with ruxolitinib on spleen volume reduction.

[0472] The secondary objectives of the study are: to assess the effect of navitoclax alone or in combination with ruxolitinib on total symptom score (TSS) as assessed by the Myelofibrosis Symptom Assessment Form (MFSAF) version 4.0 diary, to evaluate the effect of navitoclax alone or in combination with ruxolitinib on bone marrow fibrosis, to determine the rate of anemia response associated with navitoclax alone or in combination with ruxolitinib, and to describe the safety profile and PK profile observed with navitoclax alone or in combination with ruxolitinib.

[0473] The exploratory objectives of the study include but are not limited to the evaluation of the duration of disease response including effects on spleen and anemia, survival, impact on quality of life and translational biomarkers.

Study Population

[0474] Approximately 164 subjects with primary or secondary (post-polycythemia vera MF [PPV-MF]), post-essential thrombocythemia [PET-MF]) myelofibrosis who have received prior treatment with ruxolitinib or another JAK-2 inhibitor (Cohorts 1a, 1b and 2) or who have not received prior treatment with a JAK-2 inhibitor or BET inhibitor (Cohort 3).

Methodology

[0475] This extended Phase 2, multicenter, open-label study (**Figure 7**) evaluates the

tolerability and efficacy of navitoclax alone or in combination with ruxolitinib in subjects with primary or secondary myelofibrosis. For Cohort 1a, subjects must have received ruxolitinib therapy for at least 12 weeks and currently be on a stable dose of ≥ 10 mg twice daily of ruxolitinib. For Cohorts 1b or 2, subjects must have received prior treatment with a JAK-2 inhibitor. For Cohort 3, subjects must not have received prior treatment with a JAK-2 inhibitor or BET inhibitor. Navitoclax will be administered at a starting dose of 50 mg once daily (Cohort 1a) or at 100 or 200 mg once daily (Cohorts 1b, 2 and 3).

Navitoclax Dose

Cohort 1a

[0476] The dose of navitoclax may be increased after approximately 7 or more days to the next dose level provided the platelet count is ≥ 75×10^9/L up to a maximum dose of navitoclax 300 mg once daily.

Cohorts 1b, 2 or 3

[0477] Baseline Platelet Count >150×10^9/L: 200 mg once daily navitoclax starting dose.

[0478] Baseline platelet count ≤ 150×10^9/L: 100 mg once daily navitoclax starting dose. The dose of navitoclax may be increased to 200 mg once daily after 7 days provided the platelet count is ≥ 75×10^9/L.

[0479] The dose of navitoclax should not exceed 200 mg once daily for the first 24 weeks of treatment.

[0480] After the Week 24 disease assessment, the dose of navitoclax may be increased to 300 mg once daily for subjects with sub-optimal spleen response defined as failure to achieve spleen volume reduction of at least 10% as assessed by imaging.

Ruxolitinib Dose

Cohorts 1a and 1b

[0481] Subjects receive ruxolitinib administered orally twice daily at either the current stable dose of ≥ 10 mg twice daily or at a dose of 10 mg twice daily if not currently taking ruxolitinib at the time of screening.

Cohort 3

[0482] Subjects receive ruxolitinib administered orally twice daily at the individualized starting dose based on baseline platelet count as per the local approved ruxolitinib label, e.g. the FDA-approved JAKAFI® label in the US.

Cohort 2

[0483] Subjects receive Navitoclax monotherapy.

Diagnosis and Main Criteria for Inclusion/Exclusion

Key Inclusion

[0484] Subjects ≥ 18 years of age

[0485] Subjects with documented diagnosis of Primary MF, PPV-MF or PETMF as defined by the World Health Organization classification.

[0486] Subjects classified as intermediate-2 or high-risk MF, as defined by the Dynamic International Prognostic Scoring System (DIPSS.)

[0487] Subject must be ineligible or unwilling to undergo stem cell transplantation at time of study entry.

[0488] ECOG 0, 1, or 2.

[0489] **Cohort 1a only**

[0490] Subject must have received ruxolitinib therapy for at least 12 weeks and be currently on a stable dose of ≥ 10 mg twice daily of ruxolitinib for ≥ 8 weeks prior to the 1st dose of navitoclax. (Subjects with ruxolitinib dose reductions within 8 weeks prior to study enrollment may be considered on a stable dose if stable at that decreased dose of ruxolitinib for ≥ 2 weeks prior to the 1st dose of navitoclax. If the dose reduction was due to thrombocytopenia, the platelets must be confirmed to be stable by a repeat laboratory test).

[0491] **Cohort 1b only**

[0492] Subject must have received prior treatment with JAK-2 inhibitor therapy and meet one of the following criteria:

[0493] Prior treatment with JAK-2 inhibitor for ≥ 24 weeks that was stopped for lack of efficacy or intolerance,

[0494] Prior treatment with JAK-2 inhibitor for < 24 weeks with documented disease progression while on JAK-2 inhibitor therapy as defined by any of the following:

a. Appearance of new splenomegaly that is palpable to at least 5 cm below the left costal margin (LCM) in subjects with no evidence of splenomegaly prior to the initiation of JAK-2 inhibitor.
b. A ≥ 100% increase in the palpable distance below the LCM in subjects with measurable spleen distance 5 to 10 cm prior to the initiation of JAK-2 inhibitor.

c. A ≥ 50% increase in the palpable distance below the LCM in subjects with measurable spleen distance > 10 cm prior to the initiation of JAK-2 inhibitor.

d. A spleen volume increase of ≥ 25% (as assessed by MRI or CT scan) in subjects with a spleen volume assessment prior to the initiation of JAK-2 inhibitor.

[0495] Prior treatment with JAK-2 inhibitor for ≥ 28 days complicated by i or ii while receiving a total daily ruxolitinib dose of ≥ 30 mg but unable to reduce dose further due to lack of efficacy.

[0496] i. Development of RBC transfusion requirement (at least 2 units/month for 2 months), or

[0497] ii. Grade ≥ 3 adverse events of neutropenia and/or anemia while on JAK-2 inhibitor treatment.

[0498] **Cohort 2 only**

[0499] Subject must have received prior treatment with JAK-2 inhibitor therapy and meet one of the following criteria (a or b):

a. Prior treatment with JAK-2 inhibitor for at least 12 weeks

b. Prior treatment with JAK-2 inhibitor for at least 28 days complicated by any of the following:

i. Development of red blood cell transfusion requirement (at least 2 units/month for 2 months) or

ii. Grade ≥ 3 adverse events of thrombocytopenia, anemia, hematoma and/or hemorrhage while on JAK-2 inhibitor treatment

[0500] **Cohort 3 only**

[0501] Subject must not have received prior treatment with a JAK-2 or BET inhibitor.

[0502] Subject has splenomegaly defined as spleen palpation measurement ≥ 5 cm below costal margin or spleen volume ≥ 450 cm^3 as assessed by MRI/CT,

[0503] **Cohorts 1b and 3 only**

[0504] Subject has at least 2 symptoms each with a score ≥ 3 or a total score of ≥ 12, as measured by the MFSAF v4.0.

[0505] Subject must meet the following laboratory parameters per local laboratory reference range at Screening:

[0506] Adequate bone marrow reserves; in the absence of growth factors, thrombopoietic

factors, or platelet transfusions for at least 14 days:

a. Platelet count $\geq 100 \times 10^9$/L (Cohorts 1a, 1b or 3)

b. Platelet count $\geq 75 \times 10^9$/L (Cohort 2)

c. ANC $\geq 1 \times 10^9$/L

[0507] Renal function:

a. calculated creatinine clearance $\geq$ 30 mL/min

[0508] Hepatic function and enzymes:

a. AST and ALT $\leq 3.0 \times$ the upper normal limit (ULN)

b. Total Bilirubin $\leq 1.5 \times$ ULN (exception: subjects with Gilbert's Syndrome may have a Bilirubin $> 1.5 \times$ ULN)

[0509] Coagulation:

a. aPTT and INR $\leq 1.5 \times$ ULN

Key Exclusions

[0510] Splenic irradiation within 6 months prior to Screening, or prior splenectomy

[0511] Leukemic transformation (> 10% blasts in peripheral blood or bone marrow biopsy)

[0512] Subject is currently on medications that interfere with coagulation (including warfarin) or platelet function with the exception of low dose aspirin (up to 100 mg) and low-molecular-weight heparin (LMWH).

[0513] Prior therapy with a BH3 mimetic compound.

[0514] Cohort 1b Drug-Drug Interaction (DDI) sub-study subjects only: Subject has received strong or moderate CYP3A inhibitors (e.g., ketoconazole, clarithromycin and fluconazole) within 14 days prior to the administration of the first dose of navitoclax.

Cohort 1a Planned Navitoclax Dose(s) (Mode of Administration: Oral)

[0515] Dose Level –1: 25 mg once daily

[0516] Dose Level 1 (Starting Dose): 50 mg once daily

[0517] Dose Level 2: 100 mg once daily

[0518] Dose Level 3: 200 mg once daily

[0519] Dose Level 4: 300 mg once daily

Cohorts 1b, 2 and 3 Planned Navitoclax Dose(s) (Mode of Administration: Oral)

[0520] Dose Level –3: 25 mg once daily

[0521] Dose Level –2: 50 mg once daily

[0522] Dose Level –1: 100 mg once daily (Starting dose; baseline platelet count $\leq 150 \times 10^9$/L)

[0523] Dose Level 1: 200 mg once daily (Starting dose; baseline platelet count $> 150 \times 10^9$/L)

[0524] Dose Level 2: 300 mg once daily (after Week 24 for inadequate response)

All Cohorts Planned Ruxolitinib Dose(s) (Mode of Administration: Oral)

[0525] $\geq$ 10 mg twice daily

[0526] Dose reductions to 5 mg twice daily is permissible during study, if needed for management of toxicities.

Duration of Treatment

[0527] Until end of clinical benefit or occurrence of unacceptable toxicity or discontinuation criteria have been met.

Toxicity Management for Thrombocytopenia

[0528] Navitoclax accelerates apoptosis of circulating mature platelets whether endogenous or transfused. This mechanism of toxicity differs from the thrombocytopenia caused by ruxolitinib and other conventional chemotherapy (i.e., toxicity to platelet progenitors in the bone marrow) and should, therefore, be managed according to the guidelines below.

Dose Adjustment Guidelines for Thrombocytopenia

[0529] If platelets $\geq 75 \times 10^9$/L, maintain current dose of navitoclax OR escalate navitoclax dose by one dose level not to exceed 200 mg once daily (Cohorts 1b, 2 or 3) or 300 mg once daily (Cohort 1a and after the Week 24 disease assessment for Cohorts 1b, 2 or 3). The dose of navitoclax should only be escalated if current dose of navitoclax has been administered for at least 7 days. If applicable, modify the ruxolitinib dose according to the approved local label for ruxolitinib. Platelet count should be rechecked approximately 7 days after navitoclax dose escalation.

[0530] If platelets $< 75 \times 10^9$/L - $\geq 50 \times 10^9$/L, maintain current navitoclax dose level or consider navitoclax dose reduction to one dose level lower. If applicable, reduce the dose ruxolitinib per the approved local label guidance. Platelet count should be rechecked approximately every 7 days until $\geq$ 2 consecutive lab values indicate stable platelet count.

[0531] If platelets $< 50 \times 10^9$/L, for Cohorts 1a, 1b and 3, interrupt ruxolitinib and navitoclax. Recheck platelets every 2 – 3 days until recovery to $\geq 50 \times 10^9$/L. Then resume

navitoclax at one dose level lower and ruxolitinib per the approved local label guidance. Platelet count should be rechecked approximately every 7 days until ≥ 2 consecutive lab values indicate stable platelet count.

[0532] If platelets < 50×10^9/L, for Cohort 2, interrupt navitoclax. Recheck platelets every 2 – 3 days until recovery of platelets to ≥ 50×10^9/L and then resume navitoclax at one dose level lower. Platelet count should be rechecked approximately every 7 days until ≥ 2 consecutive lab values indicate stable platelet count.

Criteria for Evaluation

Efficacy

[0533] To determine initial disease status, MRI, bone marrow biopsy and aspirate are obtained at screening for all subjects. The local bone marrow evaluation includes staining for fibrosis and cytogenetics. To assess for efficacy, bone marrow biopsy, aspirate, MRI, MFSAF and laboratory tests are performed at designated timepoints throughout until disease progression is documented.

[0534] Efficacy is assessed according to International Working Group-Myeloproliferative Neoplasms Research and European LeukemiaNet (IWG-MRT/ELN).

[0535] Transfusion requirements are documented during the time period of 12 weeks before the start of navitoclax on Day 1.

Statistical Methods

Primary Efficacy Endpoint

[0536] At least 35% reduction from baseline in spleen volume at Week 24 (SVR_{35w24}) as measured by MRI/CT.

Secondary Efficacy Endpoints

[0537] At least 50% reduction in total symptom score (TSS) at Week 24 from baseline as measured by MFSAF v4.

[0538] Anemia Response.

[0539] Change in grade of bone marrow fibrosis.

Sample Size

[0540] For Cohort 1a, approximately 34 subjects are enrolled; For Cohort 1b, approximately 70 subjects are enrolled; For Cohorts 2 and 3, approximately 30 subjects are enrolled into each cohort.

[0541] Table 20 provides point estimate of SVR_{35w24} Rate and corresponding 95% confidence interval (CI) assuming different response rate scenarios given proposed sample sizes.

Table 20.

Cohort	Sample size	Number of Subjects with SVR_{35w24}	Point Estimate SVR_{35w24} Rate (%)	Exact 95% CI		Half Width of CI
				Lower Limit (%)	Upper Limit (%)	
1a	34	16	47.06	29.78	64.87	17.55
1a	34	18	52.94	35.13	70.22	17.55
1a	34	20	58.82	40.70	75.35	17.33
1a	34	22	64.71	46.49	80.25	16.88
1b	70	32	45.71	33.74	58.06	12.16
1b	70	34	48.57	36.44	60.83	12.19
1b	70	36	51.43	39.17	63.56	12.19
1b	70	38	54.29	41.94	66.26	12.16
2 or 3	30	12	40.00	22.66	59.40	18.37
2 or 3	30	14	46.67	28.34	65.67	18.67
2 or 3	30	16	53.33	34.33	71.66	18.67
2 or 3	30	18	60.00	40.60	77.34	18.37

[0542] Based on the table above, this study with proposed sample sizes provides a reasonable precise estimate of the proportion of subjects with SVR_{35w24} for each cohort. Also, if true probability of experiencing a serious adverse event (SAE) due to the study drug is 10%, then the probability of observing at least one SAE in 34 subjects is more than 97% in Cohort 1a; the probability of observing at least one SAE in 70 subjects is more than 99% in Cohort 1b; and the probability of observing at least one SAE in 30 subjects is more than 95% in either Cohort 2 or 3. Therefore, from safety assessment prospective the proposed sample sizes are adequate.

EXAMPLE 4

Phase 3 Study Design of Navitoclax in Combination with Ruxolitinib in Subjects with Primary or Secondary Myelofibrosis

M16-191: A Randomized, Open-Label, Phase 3 Study of Navitoclax in Combination with Ruxolitinib Versus Ruxolitinib Alone in Subjects with Myelofibrosis

Objectives

[0543] The primary objective is to evaluate the effect of navitoclax in combination with ruxolitinib on splenomegaly response when compared to ruxolitinib alone in subjects with MF.

[0544] The secondary objectives are to evaluate the effect of navitoclax in combination with ruxolitinib on the onset, magnitude, and duration of disease response, including Total Symptom Score (TSS), effects on spleen, bone marrow fibrosis, and anemia, to evaluate the effect of navitoclax in combination with ruxolitinib on measures of health-related quality of life (HRQoL), including fatigue, and physical functioning, and to evaluate the effect of navitoclax in combination with ruxolitinib on overall survival (OS) and leukemia-free survival (LFS).

[0545] The exploratory objectives are to evaluate responses to navitoclax and ruxolitinib versus ruxolitinib in subjects with high molecular risk (HMR) mutations, to evaluate the effect of navitoclax in combination with ruxolitinib on progression-free survival (PFS), to evaluate the effect of navitoclax in combination with ruxolitinib on the frequency of mutated alleles, exploration of biomarkers predictive of navitoclax activity and response may be performed. Potential analysis may include, but will not be limited to, the evaluation of: BCL-2 family profiling, inflammatory cytokine reduction, and/or mutational status.

Endpoints

[0546] **Primary Efficacy Endpoint**

[0547] At least 35% reduction in spleen volume from baseline at Week 24 (SVR_{35W24}) as measured by magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

Secondary Efficacy Endpoints

[0548] At least 50% reduction in total symptom score (TSS) at Week 24 from baseline as measured by Myelofibrosis Symptom Assessment Form (MFSAF) v4.0

[0549] At least 35% reduction in spleen volume from baseline (SVR_{35}) as measured by MRI or CT scan, per IWG criteria

[0550] Duration of SVR_{35}

[0551] Change in fatigue from baseline as measured by the PROMIS Fatigue SF 7a

[0552] Time to deterioration of physical functioning, as measured by the physical functioning domain of the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30

[0553] Anemia response per IWG criteria

[0554] Overall survival

[0555] Leukemia-free survival

[0556] Overall response and composite response per IWG criteria.

[0557] Reduction in grade of bone marrow fibrosis from baseline as measured by the European consensus grading system

Exploratory Endpoints

[0558] At least 50% reduction in palpable splenomegaly from baseline per IWG criteria

[0559] Red blood cell (RBC) transfusion during study drug treatment

[0560] Change in quality of life from baseline as measured by the global health status/quality of life domain of the EORTC-QLQ-C30

[0561] Change from baseline in the summary score for the EORTC QLQ-C30

[0562] Progression-free survival per IWG criteria

[0563] Change in frequency of allelic mutations from baseline

[0564] Translational biomarkers

[0565] Response in subjects with high molecular risk (HMR) mutations.

[0566] Change in EQ-5D-5L from baseline

[0567] Change in impacts associated with fatigue from baseline as assessed by the PROMIS Fatigue 7a impact items

[0568] Change in fatigue-related symptoms from baseline as assessed by the PROMIS Fatigue 7a symptom items

Safety Endpoints

[0569] Safety endpoints will be based on the following evaluations: adverse event (AE) monitoring, physical examinations, vital sign measurements, electrocardiogram (ECG) variables, and clinical laboratory testing (hematology and chemistry).

Study Population

[0570] Approximately 230 adult subjects with intermediate-2, or high-risk MF that have not been previously treated with JAK-2 inhibitor therapy

Investigational Plan

[0571] Approximately 230 subjects will receive either navitoclax once daily and ruxolitinib twice daily (Arm A), or placebo once daily and ruxolitinib twice daily (Arm B, control) until end of clinical benefit or occurrence of unacceptable toxicity or discontinuation criteria have been met. Stratification will be based on intermediate-2 versus high risk (Dynamic International Prognostic Scoring System Plus [DIPSS+]) and platelet count $\leq 200 \times 10^9$/L versus $> 200 \times 10^9$/L.

Subject Inclusion Criteria

[0572] Subject $\geq$ 18 years of age.

[0573] Subject with a documented diagnosis of primary MF or secondary MF (post polycythemia vera [PPV] -MF or post essential thrombocythemia [PET] – MF) as defined by the World Health Organization classification.

[0574] Subject must be able to complete the MFSAF v4.0 on at least 4 out of 7 days prior to Week 1 Day 1.

[0575] Subject has at least 2 symptoms with a score $\geq$ 3 or a total score of $\geq$ 12, as measured by the MFSAF v4.0.

[0576] Subject classified as intermediate-2 or high-risk MF as defined by the Dynamic International Prognostic Scoring System.

[0577] Subject must not have received prior treatment with a JAK-2 inhibitor.

[0578] Subject must not have received prior treatment with a BH3-mimetic compound or bromodomain and extra-terminal motif (BET) inhibitor.

[0579] Subject has splenomegaly defined as spleen palpation measurement $\geq$ 5 cm below costal margin or spleen volume $\geq$ 450 cm_3 as assessed centrally by MRI or CT scan.

[0580] Subject must be ineligible for stem cell transplantation at time of study entry.

[0581] Subject with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

[0582] Subject must not receive medication that interferes with coagulation or platelet function except for low dose aspirin (up to 100 mg daily) and low molecular weight heparin (LMWH) within 3 days prior to the first dose of study drug or during the study treatment period.

Study Drug and Duration of Treatment

[0583] Navitoclax is provided as film-coated tablets (25 mg and 100 mg) for oral administration.

[0584] **Arm A - Experimental group:** navitoclax + ruxolitinib

[0585] **Arm B - Control group:** placebo to match navitoclax plus ruxolitinib

Dosing of study drug:

[0586] Navitoclax/placebo:

[0587] Platelet count > 150×10^9/L: 200 mg once daily starting dose

[0588] Platelet count ≤ 150×10^9/L: 100 mg once daily starting dose; escalate to 200 mg once daily after ≥ 7 days, if tolerable (platelets ≥ 75×10^9/L).

[0589] After the Week 25 Day 1 visit, dose may be increased to 300 mg once daily at the discretion of the investigator based on platelet count for subjects with sub-optimal spleen response defined as failure to achieve a spleen volume reduction of at least 10%.

Dosing of Ruxolitinib (administered per USPI/SmPC/local prescribing guidance):

[0590] Platelet count > 200×10^9/L: 20 mg twice daily starting dose

[0591] Platelet count 100×10^9/L to 200×10^9/L: 15 mg twice daily starting dose.

[0592] Ruxolitinib dose adjustment in subjects with hepatic or renal impairment should be determined per local label/prescribing guidance.

[0593] Treatment continues until end of clinical benefit or occurrence of unacceptable toxicity or discontinuation criteria have been met.

EXAMPLE 5

Phase 3 Study Design of Navitoclax in Combination with Ruxolitinib in Subjects with Relapsed or Refractory Myelofibrosis

M20-178: A Randomized, Open-Label, Phase 3 Study of Navitoclax in Combination with Ruxolitinib versus Best Available Therapy in Subjects with Relapsed/Refractory Myelofibrosis

Objectives

[0594] The primary objective is to evaluate the effect of navitoclax in combination with ruxolitinib compared to BAT on splenomegaly response in subjects with relapsed/refractory MF.

[0595] The secondary objectives are: to evaluate the effect of navitoclax in combination

with ruxolitinib compared to BAT on measures of health-related quality of life (HRQoL) including total symptom score, fatigue, and physical functioning, to evaluate the effect of navitoclax in combination with ruxolitinib compared to BAT on the onset, magnitude, and duration of disease response, including effects on spleen, bone marrow fibrosis, and anemia, and to evaluate the effect of navitoclax in combination with ruxolitinib compared to BAT on overall survival (OS) and leukemia-free survival (LFS).

[0596] The exploratory objectives are to evaluate responses to navitoclax in combination with ruxolitinib versus BAT in subjects with high molecular risk (HMR) mutations, to evaluate the effect of navitoclax in combination with ruxolitinib on progression-free survival, to evaluate the effect of navitoclax in combination with ruxolitinib compared to BAT on the frequency of mutated alleles, and exploration of biomarkers predictive of navitoclax activity and response may be performed, where potential analysis may include, but will not be limited to: to evaluate BCL-2 family profiling; to evaluate inflammatory cytokine reduction; and to evaluate mutational status.

Endpoints

Primary Efficacy Endpoint

[0597] At least 35% reduction in spleen volume from baseline at Week 24 (SVR_{35W24}) as measured by magnetic resonance imaging (MRI) or computed tomography (CT) scan, per International Working Group (IWG) criteria.

Secondary Efficacy Endpoints

[0598] At least 50% reduction in total symptom score (TSS) at Week 24 from baseline as measured by Myelofibrosis Symptom Assessment Form (MFSAF) v4.0

[0599] At least 35% reduction in spleen volume from baseline (SVR_{35}) as measured by MRI or CT scan, per IWG criteria

[0600] Duration of SVR_{35}

[0601] Change in fatigue from baseline as measured by the PROMIS Fatigue SF 7a

[0602] Time to deterioration of physical functioning as measured by the physical functioning domain of the EORTC QLQ-C30

[0603] Anemia response per IWG criteria

[0604] Overall survival

[0605] Leukemia-free survival

[0606] Overall response and composite response per IWG criteria

[0607] Reduction in grade of bone marrow fibrosis from baseline as measured by the European consensus grading system

Exploratory Endpoints

[0608] At least 50% reduction in palpable splenomegaly from baseline per IWG criteria

[0609] Red blood cell (RBC) transfusion during study treatment

[0610] Change in quality of life from baseline as measured by the global health status/quality of life domain of the EORTC-QLQ-C30

[0611] Change from baseline in the summary score for the EORTC QLQ-C30

[0612] Progression-free survival time per IWG criteria

[0613] Change in frequency of allelic mutations from baseline

[0614] Translational biomarkers

[0615] Response in subjects with high molecular risk (HMR) mutations

[0616] Change in EQ-5D-5L from baseline

[0617] Change in fatigue-related symptoms from baseline as assessed by the PROMIS Fatigue 7a symptom items

[0618] Change in impacts associated with fatigue from baseline as assessed by the PROMIS Fatigue 7a impact items

Safety Endpoints

[0619] Safety endpoints will be based on the following evaluations:

[0620] Adverse event monitoring

[0621] Physical examinations

[0622] Vital sign measurements

[0623] Electrocardiogram (ECG) variables

[0624] Clinical laboratory testing (hematology and chemistry).

Study Population

[0625] Approximately 330 adult subjects with relapsed or refractory MF who have previously been treated with a JAK-2 inhibitor, have measurable splenomegaly, and are not candidates for allogeneic stem cell transplantation.

Investigational Plan

[0626] This is a Phase 3, open-label, randomized, 2-arm study evaluating the efficacy and

safety of the combination of navitoclax and ruxolitinib compared to BAT, in subjects with intermediate-2 or high-risk MF.

[0627] Approximately 330 subjects will be randomized to receive either navitoclax once daily and ruxolitinib twice daily (Arm A) or BAT (Arm B, control). Stratification will be based on region (US versus Japan versus Europe versus Rest of World), Dynamic International Scoring System Plus (DIPSS+; intermediate-2 versus high risk), JAK-2 inhibitor therapy at time of randomization (on stable ruxolitinib versus not on ruxolitinib/JAK-2 inhibitor).

Subject Inclusion Criteria

[0628] Subject ≥ 18 years of age.

[0629] Subject must be able to complete the MFSAF v4.0 on at least 4 out of 7 days prior to randomization.

[0630] Subject has at least 2 symptoms with a score ≥ 3 or a total score of ≥ 12, as measured by the MFSAF v4.0.

[0631] Subject with a documented diagnosis of primary MF, post polycythemia vera (PPV)-MF, or post essential thrombocythemia (PET)–MF as defined by the World Health Organization classification.

[0632] Subject classified as intermediate-2 or high-risk MF, as defined by the Dynamic International Prognostic Scoring System (DIPSS).

[0633] Subject must have received prior treatment with a single JAK-2 inhibitor and meet one of the following criteria (in addition to the minimum splenomegaly and symptom burden also required for eligibility):

a. Prior treatment with JAK-2 inhibitor for ≥ 24 weeks that was stopped due to lack of spleen response (refractory), or loss of spleen response or symptom control after a previous response (relapsed), or was continued despite relapsed/refractory status
b. Prior treatment with JAK-2 inhibitor for < 24 weeks with documented disease progression while on JAK-2 inhibitor therapy as defined by any of the following:
    i. Appearance of new splenomegaly that is palpable to at least 5 cm below the left costal margin (LCM) in subjects with no evidence of splenomegaly prior to the initiation of JAK-2 inhibitor.
    ii. A ≥ 100% increase in the palpable distance below the LCM in subjects

with measurable spleen distance 5 to 10 cm prior to the initiation of JAK-2 inhibitor.

iii. A ≥ 50% increase in the palpable distance below the LCM in subjects with measurable spleen distance > 10 cm prior to the initiation of JAK-2 inhibitor.

iv. A spleen volume increase of ≥ 25% (as assessed by MRI or CT scan) in subjects with a spleen volume assessment prior to the initiation of JAK-2 inhibitor.

[0634] Subject must not have received prior treatment with a BH3-mimetic compound or prior use of > 1 JAK-2 inhibitor.

[0635] Subject has splenomegaly defined as spleen palpation measurement ≥ 5 cm below costal margin or spleen volume ≥ 450 cm^3 as assessed centrally by MRI or CT scan.

[0636] Subject has a baseline platelet count ≥ 100 × 10^9/L.

[0637] Subject must not receive medication that interferes with coagulation or platelet function except for low dose aspirin (up to 100 mg daily) and low molecular weight heparin (LMWH) within 3 days prior to the first dose of study drug or during the study treatment period.

[0638] Subject must not receive anticancer therapy including chemotherapy, radiation therapy, hormonal therapy (with the exception of hormones for thyroid conditions or estrogen replacement therapy) within 30 days prior to first dose of study drug, and during the study treatment period (other than any overlapping therapy as part of the selected BAT).

Study Drug and Duration of Treatment

[0639] Navitoclax is provided as film-coated tablets (25 mg and 100 mg) for oral administration.

Arm A - Experimental group: navitoclax + ruxolitinib

Navitoclax Dosing

[0640] Platelet count > 150 × 10^9/L: 200 mg once daily

[0641] Platelet count ≤ 150 × 10^9/L: 100 mg once daily; if tolerable, may increase to 200 mg once daily

[0642] After the Week 25 Day 1 visit, dose may be increased to 300 mg once daily at the discretion of the investigator based on platelet count for subjects with sub-optimal spleen response defined as failure to achieve a spleen volume reduction of at least 10%.

Ruxolitinib Dosing

[0643] Subjects receiving ruxolitinib at Screening will continue at the current stable dose of ≥ 10 mg twice daily

[0644] Subjects not receiving ruxolitinib at Screening will receive ruxolitinib at a dose of 10 mg twice daily.

[0645] Ruxolitinib dose adjustment in subjects with hepatic or renal impairment is determined per local label/prescribing guidance.

Arm B – Control group: best available therapy

[0646] The investigator identifies one of the following treatment options for each subject pre-randomization: ruxolitinib, hydroxyurea, PEG-interferon-α2 or danazol additional options where BAT is sourced locally include other locally available formulations of interferon and fedratinib, where approved for relapsed/refractory MF.

[0647] Treatment continues until end of clinical benefit, occurrence of unacceptable toxicity, or discontinuation criteria have been met.