TREATMENT OF MEDICAL DISORDERS USING CXCR4 INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Application No. 63/553,001, filed on February 13, 2024; the entirety of which is hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to methods for treating leukocytopenia, e.g., neutropenia, such as severe chronic idiopathic neutropenia, and certain genetically defined congenital forms of neutropenia, using a compound that inhibits CXC Receptor type 4 (CXCR4) administered after a patient has fasted.

BACKGROUND OF THE INVENTION

[0003] Neutropenia is a condition characterized by an abnormally low concentration of neutrophils circulating in the blood, and defined by an absolute neutrophil count (ANC) below 1500 cells/μL. Severe neutropenia (ANC <500 cells/μL) is a risk factor for susceptibility to bacterial infection. Neutrophils make up the majority of circulating white blood cells and play an important role in the body's defenses against bacterial or fungal pathogenic infections and in shaping the host response to infection. In addition, neutrophils participate in immune system homeostasis. Neutropenia can be divided into congenital (i.e., present at birth) and acquired. Additionally, neutropenia can be "acute" (transient, or temporary, often as a response to specific events that deplete the body of neutrophils, such as radiation or chemotherapy), or "chronic" (a long-term or long-lasting effect that may be due to the presence of genetic abnormalities).

[0004] Acute or transient neutropenia can be caused by infectious agents, such as the typhoid-causing bacterium *Salmonella enterica*; and cytomegalovirus, as well as chemical agents, including propylthiouracil; levamisole; penicillamine; clozapine; valproic acid; and cancer chemotherapy.

[0005] Chronic neutropenia can be caused by genetic abnormalities (congenital neutropenia). Mutations in *ELANE* are the most common cause of congenital neutropenia. Other examples of genes that can be responsible for genetic causes of neutropenia include *HAX1*, *G6PC3*, *WAS*,

SBDS, and others. In addition, some enzyme deficiencies can be associated with neutropenia such as glycogen storage disease 1b. Other causes of neutropenia include mitochondrial diseases, such as Pearson syndrome. Some autoimmune diseases, such as systemic lupus erythematosus ("SLE" or "lupus") may be associated with neutropenia. Aplastic anemia, due to bone marrow failure, is associated with thrombocytopenia, anemia and neutropenia; Evans syndrome is characterized by autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) and/or immune neutropenia; and Felty's syndrome is characterized by rheumatoid arthritis, splenomegaly and neutropenia. Chronic neutropenia may also be the result of nutritional deficiencies, such as abnormally low levels of copper or Vitamin B12; or chronic infections, such as with human immunodeficiency virus (HIV), the agent that causes AID syndrome.

[0006] Neutropenia may be asymptomatic and often is only diagnosed fortuitously. Today, the standard treatment for severe neutropenia is administration of granulocyte colony-stimulating factor (G-CSF). Historically, neutropenia has been treated in a host of manners, including splenectomy, corticosteroids, androgens, and immunosuppressive and immune-modulating therapies. Currently, however, these treatments are generally not recommended except in cases where treatment with G-CSF is not effective. Dale et al. (2017) Curr. Opin. Hematol. 24:46-53; Sicre de Fontbrune et al. (2015) Blood 126:1643-1650. Other treatments for neutropenia can include bone marrow transportation and/or treatment with cord blood stem cells.

[0007] There remains a need for effective treatments of neutropenias, particularly severe and chronic neutropenias that result in increased risk of infections and other disorders. The present invention meets this need and provides other related advantages.

BRIEF DESCRIPTION OF THE FIGURES

[0008] **FIG. 1** shows the effect of fed and fasted states on the C_{max} of mavorixafor in healthy volunteers.

[0009] **FIG. 2** shows the effect of fed and fasted states on the $AUC_{(0\text{-}inf)}$ of mavorixafor in healthy volunteers.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

[0010] Administration of CXCR4 inhibitors, with and without G-CSF, has been shown to be useful for treating neutropenias. It has now been found that the effectiveness of CXCR4 inhibitors

may be dramatically improved by optimizing pharmacokinetic (PK) parameters such as the peak serum concentration (C_{max}). For example, administering a CXCR4 inhibitor to a patient in a fasted state provides an optimized PK profile and increased effectiveness. Accordingly, the present invention provides fasting profiles for lymphocytopenia (e.g., leukopenia or neutropenia) patients being treated with CXCR4 inhibitors.

[0011] It has now been found that the dosing regimen (e.g., fasting requirements) may be helpful in optimizing the PK profile, and therefore the efficacy, of CXCR4 inhibitors in treating neutropenia. Chronic neutropenia can be congenital or acquired and within the acquired forms there are primary and secondary neutropenias. Primary neutropenias include idiopathic (by definition, idiopathic means that all other causes have been excluded); and caused by autoimmune and alloimmune factors, etc. Secondary neutropenia is most often due to hypersplenism (overactive spleen), as well as the effects of drugs such as chemotherapies. Chronic congenital neutropenia includes certain genetically defined congenital forms of neutropenia, including those disclosed herein.

[0012] As used herein, the term "neutropenia" means that a patient has an absolute neutrophil count (ANC) that is at or below about 1500 cells per μL. Neutropenias to be treated according to the disclosed methods include mild, moderate, and severe neutropenia. "Mild neutropenia" is generally described as a patient having an ANC between 1000 and 1500 cells/μL. "Moderate neutropenia" is generally understood to refer to patients having an ANC between 500 and 1500 cells/μL. As used herein, "severe neutropenia" means that the patient has an ANC that is at or below 500 cells/μL. A beneficial treatment may comprise a treatment that significantly increases a patient's neutrophil counts, even though the patient still has an ANC <1500 cells per μL, thus remaining 'neutropenic'. For example, a patient with severe neutropenia [ANC< 500 cells/μL] may be treated using the methods of the present invention, until the patient's ANC is raised to 1000 cell/μL. In the expert judgement of the treating physician, such a result would likely be considered a successful treatment, though the patient would continue to be characterized as having mild-to-moderate neutropenia.

[0013] As used herein, the term "chronic neutropenia" is defined as neutropenia lasting for a period of at least three (3) months. The term "idiopathic" as applied herein to neutropenia means that all other causes have been excluded, for example, the patient's neutropenia is not attributable to drugs, or to a specific identified genetic, infectious, inflammatory, autoimmune or malignant

cause.

[0014] As used herein, the term "congenital neutropenia" condition includes patients who exhibit neutropenia (or severe neutropenia) due to a genetically defined mutation such as ELANE, due to mutations in the *ELANE* gene, which is one of the most common causes of congenital neutropenia, glycogen storage disease type 1b (GSD1b) due to mutations in *SLC37A4*, glucose-6-phosphatase catalytic subunit 3 (G6PC3) deficiency due to mutations in *G6PC3;* or GATA-binding protein 2 (GATA2) deficiency due to mutations in *GATA2*. Other genetically-defined conditions without myeloid maturation arrest at the myelocyte/promyelocyte stage are also included in this definition.

[0015] As used herein, the term "cyclic neutropenia" or "cyclical neutropenia" may be used interchangeably to mean that a patient has a rare hematological condition that is typically characterized by regular fluctuations in blood neutrophil counts, leading to periodic neutropenia with approximately a 21-day turnover frequency. During the cycle, severe neutropenia typically lasts for 3 to 6 days. The cycling period usually remains constant and consistent among affected individuals. In addition, abnormal levels of red blood cells (anemia), changes in levels of the blood particles that assist in clotting (platelets), presence of immature red blood cells (reticulocytes), and cyclic changes in other white blood cells can occur. An almost constant feature is an increase in blood monocytes at the lowest point in the neutrophil cycle. A diagnosis of cyclical neutropenia is made based upon a detailed patient history and thorough clinical evaluation. A diagnosis may be confirmed by monitoring an individual's neutrophil count twice or three times per week for six weeks. Individuals with cyclic neutropenia should be genetically tested for mutations in the *ELANE* gene. In some embodiments of the present invention, the patient to be treated has cyclic neutropenia. In some embodiments, the patient has an *ELANE* mutation.

Neutropenias Such as Chronic Idiopathic Neutropenia (CIN), Severe Chronic Neutropenia (SCN), Cyclical Neutropenia (CyN), and Autoimmune Neutropenia (AIN)

[0016] Chronic neutropenia is defined as neutropenia lasting for at least 3 months. The term "idiopathic" indicates that the neutropenia is not attributable to drugs or an identified genetic, infectious, inflammatory, autoimmune, or malignant causes. Thus, the diagnosis of chronic idiopathic neutropenia (CIN) is one made by exclusion of other causes. Finally, the neutropenia is "severe" when the absolute neutrophil count (ANC) is below 500 cells/μL. There is also overlap

of patients with the diagnosis of CIN and "autoimmune neutropenia" (AIN) because it is difficult to accurately detect circulating antibodies directed toward antigens present on the surface of neutrophils, and clinical interpretation of the anti-neutrophil antibody test result is also difficult. (Dale, Current Opin Hematol, 2018). The estimated adult prevalence of severe chronic idiopathic neutropenia is approximately 5 per million (Dale and Bolyard (2017) Curr. Opin. Hematol. 24:46-53). There is a female predominance of CIN (Kyle and Linman (1968) N. Engl. J. Med. 279:1015-1019). Distinct pathophysiologic mechanisms have been found, including decreased production, enhanced peripheral removal, and excessive margination of neutrophils (Greenberg et al. (1980) Blood 55:915-921). Neutrophil counts < 500 cells/μL are associated with a higher risk of infections. In one study, the bone marrow was analyzed in approximately one third of a series of 108 patients and results were normal in 34% of patients; late maturation arrest was seen in 31% of the patients; granulocytic hypoplasia was observed in 15% of the patients; and 20% of the patients had increased cellularity (Sicre de Fontbrune 2015). A randomized, controlled trial of G-CSF for treatment of severe chronic neutropenia, including 42 patients with CIN, established G-CSF as an effective therapy for this condition (Dale (1993) Blood 81:2496-2502).

[0017] In some embodiments, treatment of particular sub-populations of patients with a CXCR4 antagonist (e.g., mavorixafor, or a pharmaceutically acceptable salt thereof), is particularly effective.

[0018] In some embodiments, the patient is male. In some embodiments, the patient is female.

[0019] In some embodiments, the patient is less than 50 years old. In some embodiments, the patient is at least 50 years old.

[0020] In some embodiments, the patient has previously been treated with G-CSF. In some embodiments, the patient has previously been treated with G-CSF, but is not currently receiving G-CSF.

[0021] It should be understood that G-CSF, as used herein, may be substituted for variants of G-CSF, such as pegylated G-CSF (peg-filgrastim), or GM-CSF.

[0022] In some embodiments, the mavorixafor, or a pharmaceutically acceptable salt thereof, and the G-CSF, or another granulocyte-colony stimulating factor treatment such as those described herein, act synergistically. Synergism includes, for example, more effective treatment of the disease than with either agent alone; or a lower dose of one or both agents providing effective treatment for the disease than would be the case if either agent were used alone.

[0023] In some embodiments, mavorixafor and G-CSF act with cooperativity, either additively or synergistically.

[0024] In some embodiments treatment with a CXCR4 antagonist is effective in increasing lymphocytes. In some embodiments, treatment with a CXCR4 antagonist has beneficial effects on lymphocytes (particularly B- and T- cells). In some embodiments, treatment with the CXCR4 antagonist has beneficial effects on adaptive immunity responses. In some embodiments, treatment with a CXCR4 antagonist is effective in treating infection frequency, severity and/or infection duration.

[0025] In some embodiments, the patient has not previously been treated with G-CSF prior to commencing treatment with mavorixafor, or a pharmaceutically acceptable salt thereof.

[0026] In some embodiments, as discussed further below, the patient is currently being treated with G-CSF. In some embodiments, the dose and/or frequency of administration of G-CSF (while maintaining effectiveness of the treatment regimen) is/are reduced after treatment with mavorixafor, or a pharmaceutically acceptable salt thereof, is commenced. In some embodiments, treatment with G-CSF is completely discontinued (while maintaining effective treatment of the patient's neutropenia) after commencing treatment with mavorixafor, or a pharmaceutically acceptable salt thereof.

[0027] In some embodiments, the patient is effectively treated with a CXCR4 antagonist, such as mavorixafor, and the G-CSF dose adjustment is made while maintaining effective treatment of the patient's infection frequency, severity, and/or infection duration,

[0028] In some embodiments, the patient has idiopathic neutropenia. In some embodiments, the patient has severe idiopathic neutropenia. In some embodiments, the patient has chronic neutropenia. In some embodiments, the patient has SCN, CIN, or AIN. In some embodiments, the patient has undergone genetic testing but no diagnosis of a genetic abnormality has been made. In some embodiments, the genetic testing was inconclusive. In some embodiments, the genetic testing revealed no known genetic abnormality, or a genetic abnormality not associated with neutropenia. In some embodiments, the patient has neutropenia not due to a genetic abnormality and due to one or more of an infectious, inflammatory, autoimmune, or malignant cause. In some embodiments, the malignant cause is a cancer.

[0029] In some embodiments, the patient has severe congenital neutropenia, suspected aplastic anemia, B-cell immunodeficiency, juvenile myelodysplastic syndrome (MDS), chronic

myelomonocytic leukemia, a severe Epstein-Barr virus infection or Epstein-Barr-associated cancers, B-cell acute lymphoblastic leukemia, or unexplained bone marrow failure.

[0030] In some embodiments, the patient has undergone genetic testing and a genetic abnormality other than one associated with WHIM syndrome has been diagnosed. In some embodiments, the patient has a congenital neutropenia. In some embodiments, the patient has a genetic abnormality selected from GSD1b, G6PC3 deficiency, GATA2 deficiency, a genetically-defined condition without myeloid maturation arrest at the myelocyte/promyelocyte stage, or an undefined genetic abnormality.

[0031] In some embodiments, the patient treated with G-CSF has experienced safety and tolerability issues (such as bone pain, myalgia, etc.), and/or when a treating physician considers a patient with congenital neutropenia's risk of malignant transformation to be significant. In some embodiments, the treating clinician considers that addition of treatment with a CXCR4 antagonist, such as mavorixafor, combined with a reduction in the patient's G-CSF dose and/or frequency will result in a decrease in any of the above safety and tolerability issues.

G6PC3 Deficiency

[0032] The *G6PC3* gene encodes the ubiquitously expressed G6PC3. In 2009, Boztug showed that effective function of G6PC3 underlies a severe congenital neutropenia syndrome associated with cardiac and urogenital malformations (Boztug et al. (2009) N Engl J Med. 360:32-43).

[0033] As of 2013, 57 patients with G6PC3 deficiency have been described in the literature (Banka and Newman (2013) Orphanet J Rare Dis. 8:84). There have been 91 cases reported globally with an estimated incidence of 0.4 in 1,000,000 births and primarily of Turkish, Pakistani, and French descent. G6PC3 deficiency usually presents in the first few months of life with recurrent bacterial infections and ANC counts ranging from 120 to 550 cells/μL (McDermott et al. (2010) Blood. 116:2793-802). The first serious infection can occur at any age, ranging from immediately after birth to adulthood (Banka (2015, in Gene Reviews, Adam et al, editors. University of Washington, Seattle; 1993-2019). Reported common bacterial infections are respiratory tract infections, otitis media, stomatitis, urinary tract infections, pyelonephritis, skin abscesses, cellulitis, and sepsis. G6PC3 deficiency varies in its severity and associated clinical features. It may present as non-syndromic, with isolated severe congenital neutropenia or, more frequently, syndromic, with cardiovascular and/or urogenital features. A subset of those with

syndromic disease present a severe form (Dursun syndrome), due to the additional involvement of myeloid cells, characterized by primary pulmonary hypertension in the newborn period and minor dysmorphic features (Banka 2015). While it is estimated that nearly 10% of G6CP3 deficiency is the non-syndromic form, this could be an underestimate due to ascertainment bias (i.e., selection of more severe phenotypes for testing of G6PC3 in previous studies) (Banka 2013). It is also possible that some patients who initially present with the non-syndromic form may develop features of the classic form later in life (Banka 2015). While bone marrow analysis may show maturation arrest in the myeloid lineage, other G6PC3 deficiency patients may have hyper- or normo-cellular marrows (McDermott 2010; Banka et al. (2011) Am J Hematol. 86:235-7).

GATA2 Deficiency

[0034] GATA2 deficiency is an autosomal dominant bone marrow failure disorder with systemic features caused by heterozygous germline mutation in 1 of 2 copies of the *GATA2* gene encoding the GATA2 protein. Germline *GATA2* mutations have been detected among patients presenting with severe congenital neutropenia, suspected aplastic anemia, B-cell immunodeficiency, juvenile myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia, severe Epstein-Barr virus infections and Epstein-Barr-associated cancers, B-cell acute lymphoblastic leukemia, and other unexplained cases of bone marrow failure (Crispino and Horwitz (2017) Blood. 129:2103-10). In 2017 and 2018, 457 cases of GATA2 deficiency were reported globally. Patients presented with varying ANC levels of 1100 to 8460 cells/μL (Maciejewski-Duval et al. (2016) J Leukoc Bio. 99:1065-76) and often low lymphocyte levels from 112 to 1987 cells/μL (Vinh et al. (2010) Blood. 115:1519-29) or 490 to 2900×10^6/mL (Maciejewski-Duval 2016). The bone marrow of patients with GATA2 deficiency has been reported to range from a hypocellular marrow with normal cytogenetics to hypercellular marrow with unfavorable cytogenetics to overt AML with 85% monoblasts (Hickstein (2018) Blood. 131:1272-74). The GATA 2 deficiency phenotype ranges from immunodeficiency to aplastic anemia to MDS to leukemia (Hickstein 2018).

[0035] The diagnosis is further challenging because of the observation that while germline mutations in *GATA2* are responsible for GATA2 deficiency, acquired mutations are seen in MDS, AML, and in blast crisis transformation of chronic myeloid leukemia. In fact, GATA2 deficiency is currently the most common hereditary cause of MDS in children and adolescents. The natural

history of GATA2 deficiency is highly variable, even in individuals with identical mutations. Infectious complications are common in GATA2 deficiency and result from the selective cellular deficiency profile, namely deficiency of monocytes, natural killer cells, and B lymphocytes. Hematologic manifestations of GATA2 deficiency are mainly progressive cytopenias, with a possible progression from a normocellular marrow to hypocellular MDS or AML.

[0036] Approximately half of patients with GATA2 deficiency receive allogeneic hematopoietic stem cell transplant (Hickstein 2018), and allogeneic stem cell transplantation is the only curative therapy for GATA2 deficiency. There are no clear guidelines regarding the monitoring schedule or the ideal prophylaxis for asymptomatic *GATA2* patients. However, proposals include monitoring peripheral blood counts every 3 to 6 months and bone marrow biopsy with cytogenetics every 1 to 2 years and to transplant before the development of severe end organ damage or leukemia (Hsu et al. (2015) Curr. Opin. Allergy Clin. Immunol. 15:104-9).

[0037] CXCR4 inhibitors (e.g., mavorixafor) may prove a useful bridge to transplant because of the potential to improve both the neutropenia and the lymphopenia in these patients.

Methods for Treating Neutropenia Using a CXCR4 Inhibitor with Patient Fasting

[0038] Without wishing to be bound by theory, it is believed that fasting prior to dosing a patient with a CXCR4 inhibitor enhances the PK properties (e.g., increased C_{max}) thereof, resulting in increased efficacy (e.g., increased neutrophil count compared to administration without fasting) and/or increased duration of elevated neutrophil count ("Time Above Threshold" or "TAT-ANC"). Additionally, it is believed that such methods may result in increased lymphocyte count ("ALC") and or increased duration of elevated lymphocyte count ("Time Above Threshold" or "TAT-ALC").

[0039] In some embodiments, the TAT-ANC is about 15 hours. In some embodiments, the TAT-ANC is about 15-18 hours. In some embodiments, the TAT-ANC is about 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, or 20 hours. In some embodiments, the TAT-ANC is about 13-20, 13.5-20, 14-20, 14.5-20, 15-20, 15.5-20, 16-20, 16.5-20, 17-20, 17.5-20, 18-20, 18.5-20, 19-20, or 19.5-20 hours. In some embodiments, the TAT-ANC is about 13-19, 13.5-19, 14-19, 14.5-19, 15-19, 15.5-19, 16-19, 16.5-19, 17-19, 17.5-19, 18-19, or 18.5-19 hours. In some embodiments, the TAT-ANC is about 13-18, 13.5-18, 14-18, 14.5-18, 15-18, 15.5-18, 16-18, 16.5-18, 17-18, or 17.5-18 hours. In some embodiments, the TAT-ANC is about 13-17, 13.5-17, 14-

17, 14.5-17, 15-17, 15.5-17, 16-17, or 16.5-17 hours.

[0040] In some embodiments, the TAT-ALC is about 15 hours. In some embodiments, the TAT-ALC is about 15-18 hours. In some embodiments, the TAT-ALC is about 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, or 20 hours. In some embodiments, the TAT-ALC is about 13-20, 13.5-20, 14-20, 14.5-20, 15-20, 15.5-20, 16-20, 16.5-20, 17-20, 17.5-20, 18-20, 18.5-20, 19-20, or 19.5-20 hours. In some embodiments, the TAT-ALC is about 13-19, 13.5-19, 14-19, 14.5-19, 15-19, 15.5-19, 16-19, 16.5-19, 17-19, 17.5-19, 18-19, or 18.5-19 hours. In some embodiments, the TAT-ALC is about 13-18, 13.5-18, 14-18, 14.5-18, 15-18, 15.5-18, 16-18, 16.5-18, 17-18, or 17.5-18 hours. In some embodiments, the TAT-ALC is about 13-17, 13.5-17, 14-17, 14.5-17, 15-17, 15.5-17, 16-17, or 16.5-17 hours.

[0041] **Discussion of PK/PD Parameters**

[0042] **PK/PD Parameters:**

[0043] **Cmax** – Maximum concentration of a therapeutic (e.g., a CXCR4 inhibitor) after such therapeutic detected in plasma.

[0044] **Tmax** – Time after administration at which Cmax is observed.

[0045] **Tlast** – Time after administration at which a therapeutic is last detectable in plasma.

[0046] **Tlag** – Time lag or phase from the time of ingestion until 10%.

[0047] $T_{1/2}$ – Time after administration of a therapeutic at which the concentration of the therapeutic is equal to ½ the concentration immediately after administration (or ½ of Cmax).

[0048] **AUC** – Area Under the Curve - is the total area under the curve of the concentration of a therapeutic (or other parameter) detected in plasma over a period of time. Measures the total amount of the therapeutic (or other parameter) over a period of time after administration.

[0049] **ANC-max**

[0050] **ALC-max**

[0051] **TAT-ANC = "Time Above Threshold** – Time after administration of a therapeutic during which the measure of ANC remains above a threshold neutrophil concentration desired to be achieved.

[0052] **TAT-ALC = "Time Above Threshold"** – Time after administration of a therapeutic during which the measure of ALC remains above a threshold lymphocyte concentration desired to

be achieved.

[0053] Thus, in one aspect, the present disclosure provides a method for treating neutropenia in a patient, comprising orally administering to the patient a CXCR4 inhibitor or a pharmaceutically acceptable salt thereof, wherein the patient has fasted from all food and drink except for water for at least 7 hours prior to administration of the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof and continues to fast for at least 30 minutes after administration; and the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof is administered once per day at a dosage of about 100 mg to about 800 mg. In another aspect, the present disclosure provides a method for treating lymphocytopenia in a patient, comprising orally administering to the patient a CXCR4 inhibitor or a pharmaceutically acceptable salt thereof, wherein the patient has fasted from all food and drink except for water for at least 7 hours prior to administration of the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof and continues to fast for at least 30 minutes after administration; and the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof is administered once per day at a dosage of about 100 mg to about 800 mg.

[0054] In some embodiments, wherein the patient is young and/or of a lower weight (e.g., < about 50kg), the methods of the present invention may further comprise administering a lower dosage of the CXCR4 inhibitor. For example, for a patient aged from 6 to 11 years, a lower dose of about 50 mg to about 100 mg may be administered daily; for a patient aged from 2 to 5 years, a lower dose of about 25 mg to about 100 mg may be administered daily. For example, the daily dosage may be about 25 mg to about 50 mg, such as a daily dosage of about 25 mg, about 50 mg, about 75 mg, or about 100 mg.

[0055] In some embodiments, the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof is mavorixafor or a pharmaceutically acceptable salt thereof. It should be understood that, in any of the methods described herein, the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof may be a CXCR4 inhibitor other than mavorixafor or a pharmaceutically acceptable salt thereof. CXCR4 inhibitors include those described herein.

[0056] In some embodiments, the present disclosure provides a method for treating neutropenia in a patient, comprising orally administering to the patient mavorixafor or a pharmaceutically acceptable salt thereof, wherein the patient has fasted from all food and drink except for water for at least 7 hours prior to administration of the mavorixafor or a pharmaceutically acceptable salt thereof and continues to fast for at least 30 minutes after

administration; and the mavorixafor or a pharmaceutically acceptable salt thereof is administered once per day at a dosage of about 100 mg to about 800 mg. In cases where a patient is of young age or body weight less than about 50 kg, the mavorixafor or a pharmaceutically acceptable salt thereof is administered once per day at a dosage of about 25 mg to about 100 mg.

[0057] In some embodiments, the mavorixafor or a pharmaceutically acceptable salt thereof is administered once per day at a dosage of about 100 mg to about 800 mg; about 100 mg to about 700 mg; about 100 mg to about 600 mg; about 100 mg to about 500 mg; about 100 mg to about 400 mg; about 100 mg to about 300 mg; about 100 mg to about 200 mg; 200 mg to about 800 mg; about 200 mg to about 700 mg; about 200 mg to about 600 mg; about 200 mg to about 500 mg; about 200 mg to about 400 mg; about 200 mg to about 300 mg; 300 mg to about 800 mg; about 300 mg to about 700 mg; about 300 mg to about 600 mg; about 300 mg to about 500 mg; about 300 mg to about 400 mg; about 400 mg to about 800 mg; about 400 mg to about 700 mg; about 400 mg to about 600 mg; about 400 mg to about 500 mg; about 500 mg to about 800 mg; about 500 mg to about 700 mg; about 500 mg to about 600 mg; about 600 mg to about 800 mg; about 600 mg to about 700 mg; or about 700 mg to about 800 mg. In some embodiments, the mavorixafor is administered once per day at a dosage of about 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, or 800 mg.

[0058] In the methods described herein, the dosage of mavorixafor may be dependent upon the age and/or weight of the patient. For instance, in some embodiments, the patient is at least 18 years old. In some embodiments, the patient is 12 to 17 years old and weighing at least 50 kg. In some embodiments, the patient is 12 to 17 years old and weighing under 50 kg. In some embodiments, the patient is 6 to 11 years of age, or 6 to 12 years of age. In some embodiments, the patient is 2 to 5 years of age, or 2 to 6 years of age.

[0059] In some embodiments, the patient receives about 400 mg mavorixafor or a pharmaceutically acceptable salt thereof per day if the patient is at least 18 years old; or the patient receives about 400 mg mavorixafor or a pharmaceutically acceptable salt thereof per day if the patient is 12 to 17 years old and weighing at least 50 kg; or the patient receives about 200 mg mavorixafor or a pharmaceutically acceptable salt thereof per day if the patient is 12 to 17 years old and weighing under 50 kg.

[0060] In some embodiments, the patient is at least 12 years old. In some embodiments, the patient is at least 18 years old. In some embodiments, the patient is between 12 and 17 years old.

In some embodiments, the patient is between 18 and 30 years old, between 18 and 40 years old, between 18 and 50 years old, between 18 and 60 years old, between 18 and 70 years old, between 30 and 40 years old, between 30 and 50 years old, between 30 and 60 years old, between 30 and 70 years old, between 40 and 50 years old, between 40 and 60 years old, between 40 and 70 years old, between 50 and 60 years old, between 50 and 70 years old, between 60 and 70 years old. In some embodiments, the patient is older than 70 years old.

[0061] Additionally, in any of the methods described herein, the fasting period prior to, or after, administration of the CXCR4 inhibitor (e.g., mavorixafor) may be increased or decreased depending on the patient.

[0062] In some embodiments, the patient has fasted for at least 8 hours prior to administration of the mavorixafor or a pharmaceutically acceptable salt thereof. In some embodiments, the patient has fasted for at least 6 hours, at least 7 hours, at least 8 hours, at least 9 hours, at least 10 hours, at least 11 hours, at least 12 hours, at least 13 hours, at least 14 hours, at least 15 hours, or at least 16 hours prior to administration of the mavorixafor or a pharmaceutically acceptable salt thereof.

[0063] In some embodiments, the patient has fasted for 7-16 hours prior to administration of the mavorixafor or a pharmaceutically acceptable salt thereof. In certain embodiments, the patient has fasted for 7-14, 7-12, 7-10, 7-9, 8-16, 8-14, 8-12, 8-10, 10-16, 10-14, 10-12, 12-16, 12-14, or 14-16 hours prior to administration of the mavorixafor or a pharmaceutically acceptable salt thereof.

[0064] In any of the methods described herein, it may be advantageous for the patient to continue fasting after administration of the CXCR4 inhibitor (e.g., mavorixafor). For instance, in some embodiments, the patient continues to fast for at least 30 minutes, at least 45 minutes, at least 1 hour, at least 1.5 hours, or at least 2 hours after administration. In certain embodiments, the patient continues to fast for 30 minutes to 4 hours after administration. In some embodiments, the patient continues to fast for 30 minutes to 4 hours, 30 minutes to 3.5 hours, 30 minutes to 3 hours, 30 minutes to 2.5 hours, 30 minutes to 2 hours, 30 minutes to 1.5 hours, 30 minutes to 1 hour; 1 hour to 4 hours, 1 hour to 3.5 hours, 1 hour to 3 hours, 1 hour to 2.5 hours, 1 hour to 2 hours, 1 hour to 1.5 hours, 1.5 hours to 4 hours, 1.5 hours to 3.5 hours, 1.5 hours to 3 hours, 1.5 hours to 2.5 hours, 1.5 hours to 2 hours, 2 hours to 4 hours, 2 hours to 3.5 hours, 2 hours to 3 hours, 2 hours to 2.5 hours, 2.5 hours to 4 hours, 2.5 hours to 3.5 hours, 2.5 hours to 3 hours, 3 hours to 4 hours, 3 hours to 3.5 hours, or 3.5 hours to 4 hours.

[0065] In some embodiments, the first meal eaten post-administration of the CXCR4 inhibitor is a high fat meal (e.g., 40-60% fat content, such as about 50% fat content; in some embodiments the high fat meal is also high-calorie, defined as consisting of about 800 to about 1000 calories). In some embodiments, the high fat meal derives approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. In some embodiments, the first meal eaten post-administration of the CXCR4 inhibitor is a moderate fat meal (e.g., 30-40% fat content, such as about 35% fat content; in some embodiments, the moderate fat meal is about 600 to <800 calories). In some embodiments, the first meal eaten post-administration of the CXCR4 inhibitor is a low fat meal (e.g., 10 to <30% fat content, such as about 20% fat; in some embodiments, the low fat meal is about 300 to <600 calories).

[0066] As described above, neutropenia may be characterized by a patient's absolute neutrophil count (ANC) prior to treatment. In some embodiments of the methods disclosed herein, the patient has an absolute neutrophil count (ANC) less than 1500 cells/μL prior to beginning treatment with mavorixafor or a pharmaceutically acceptable salt thereof that has persisted for at least 3 months. In some embodiments, the patient has an absolute neutrophil count (ANC) less than 1000 cells/μL prior to beginning treatment with mavorixafor or a pharmaceutically acceptable salt thereof that has persisted for at least 3 months. In some embodiments, the patient has an absolute neutrophil count (ANC) less than 600 cells/μL prior to beginning treatment with mavorixafor or a pharmaceutically acceptable salt thereof that has persisted for at least 3 months. In some embodiments, the patient has an absolute neutrophil count (ANC) less than 500 cells/μL prior to beginning treatment with mavorixafor or a pharmaceutically acceptable salt thereof. In some embodiments, the patient has an absolute neutrophil count (ANC) less than 400 cells/μL prior to beginning treatment with mavorixafor or a pharmaceutically acceptable salt thereof.

[0067] In some embodiments, the patient has an ANC less than 300 cells/μL, less than 200 cells/μL, or less than 100 cells/μL prior to beginning treatment. In some embodiments, the patient has an ANC of between about 100-1500 cells/μL, about 100-1000 cells/μL, about 100-600 cells/μL, about 100-500 cells/μL, about 500-1500 cells/μL, about 500-1000 cells/μL, about 500-600 cells/μL, about 600-1500 cells/μL, about 600-1000 cells/μL, or about 1000-1500 cells/μL, prior to beginning treatment.

[0068] In some embodiments, the patient has had neutropenia for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 9 months, at least 1 year, at least 1.5 years, at

least 2 years, at least 2.5 years, or at least 3 years prior to beginning treatment. In some embodiments, the patient has previously been treated for neutropenia. In some embodiments, the patient is currently undergoing treatment for neutropenia. In some embodiments, the patient has not previously been treated for neutropenia. In some embodiments, the patient is not currently undergoing treatment for neutropenia.

[0069] The methods described herein may be suitable for treating patients with any severity of neutropenia. For instance, in some embodiments, the patient has mild neutropenia (e.g., ANC $\geq$ 1000 - < 1500 cells/μL). In some embodiments, the patient has moderate neutropenia (e.g., ANC $\geq$ 500 - < 1,000 cells/μL). In some embodiments, the patient has severe neutropenia (e.g., ANC < 500 cells/μL). In some embodiments, the patient has chronic neutropenia (e.g., ANC < 1500 cells/μL persisting for 3 months or greater).

[0070] As described above, there are multiple etiologies for neutropenia. The methods described herein may be useful for treating neutropenia of various origins, including those specifically described herein. In some embodiments, the patient has congenital neutropenia. In some embodiments, the patient has acquired neutropenia. In some embodiments, the patient has ELANE-associated congenital neutropenia. In some embodiments, the patient has CSF3R-associated congenital neutropenia. In some embodiments, the patient has HAX1-associated congenital neutropenia. In some embodiments, the patient has CXCR4-associated congenital neutropenia. In some embodiments, the neutropenia is associated with extra-hematological manifestations manifestation selected from Barth syndrome, Cohen syndrome, G6PC3, and Kostmann disease; or is associated with glycogen storage disease 1b (GSD1b). In some embodiments, the neutropenia is associated with one or more metabolic disorders. In some embodiments, the neutropenia is associated with Shwachman-Diamond syndrome. In some embodiments, the neutropenia is associated with Cohen Syndrome. In some embodiments, the neutropenia is associated with GSD1b/Von Gierke disease. In some embodiments, the neutropenia is associated with Pearson syndrome. In some embodiments, the neutropenia is associated with Schimke immune-osseus dysplasia. In some embodiments, the neutropenia is associated with Specific Granule Deficiency. In some embodiments, the neutropenia is associated with Wolcott-Rallison syndrome. In some embodiments, the neutropenia is a cyclic neutropenia.

[0071] In some embodiments, the patient has severe congenital neutropenia (SCN) prior to beginning treatment with mavorixafor or a pharmaceutically acceptable salt thereof. In some

embodiments, the patient has chronic idiopathic neutropenia (CIN) prior to beginning treatment with mavorixafor or a pharmaceutically acceptable salt thereof.

[0072] In some embodiments, the neutropenia is an SCN associated with ELANE, CSF3R, CXCR2, or WAS mutation.

[0073] In some embodiments, the patient has GATA2 deficiency. In some embodiments, the patient has a genetically-defined condition without myeloid maturation arrest at the myelocyte/promyelocyte stage.

[0074] In some embodiments, the patient has a genetically-defined chronic neutropenia associated with a gene selected from AK2, AP3B1, CD40LG, CEBPE, CLPB, CSF3R, CXCR2, EIF2AK, ELANE/ELA2*, G6PC3, GATA2, GFI1, HAX1, JAGN1, LAMTOR2, LCP1, LYST, RAB27A, RMRP, SARCAL1, SEC61A1, SLC37A4, SMARCD2, SRP54, STK4, TAZ, TCIRG1, TCN2, VPS13B, VPS45, or WAS. It should be understood that the neutropenia could be associated with any number of genetic variants including combinations of any of the foregoing.

[0075] In some embodiments, the patients has a congenital neutropenia or an acquired primary autoimmune or chronic idiopathic neutropenia prior to beginning treatment with mavorixafor or a pharmaceutically acceptable salt thereof. In some embodiments, the patient has a congenital neutropenia. In some embodiments, the patient has a primary acquired neutropenia. In some embodiments, the primary acquired neutropenia is a primary autoimmune neutropenia. In some embodiments, the primary acquired neutropenia is idiopathic.

[0076] In some embodiments, the neutropenia is not attributable to medications the patient is or was taking. In some embodiments, the neutropenia is not attributable to active or recent infections. In some embodiments, the neutropenia is not attributable to a malignancy.

[0077] In some embodiments, the patient has an elevated risk of an infection selected from respiratory tract infections, otitis media, stomatitis, urinary tract infections, pyelonephritis, skin abscesses, cellulitis, and sepsis prior to beginning treatment.

[0078] In some embodiments, the patient has had at least 7 infections over the past year. In some embodiments, the patient has had at least 2 infections requiring hospitalization over the past year. In some embodiments, the patient has had at least 7 infections over the past year and at least 2 infections requiring hospitalization over the past year.

[0079] The methods described herein may be useful for improving the outcome of infections. For instance, in some embodiments, the methods produce an improvement in the frequency,

severity, duration of infections or time to next infection; the emergence and/or clearance of oral ulcers; the appearance and/or clearance of gingivitis; or any combination of the foregoing.

[0080] As described above, the methods disclosed herein are useful for increasing the patient's absolute neutrophil count (ANC) or absolute leukocyte count (ALC) compared to before treatment. For instance, in some embodiments, the method achieves an ANC of at least 500 cells/μL and/or an absolute leukocyte count ALC of at least 1000 cells/μL. In some embodiments, the method achieves an ANC of about 500 cells/μL to 3000 cells/μL; about 1000 cells/μL to 3000 cells/μL; about 1500 cells/μL to 3000 cells/μL; about 2000 cells/μL to 3000 cells/μL; about 2500 cells/μL to 3000 cells/μL; about 500 cells/μL to 2500 cells/μL; about 1000 cells/μL to 2500 cells/μL; about 1500 cells/μL to 2500 cells/μL; about 2000 cells/μL to 2500 cells/μL; about 500 cells/μL to 2000 cells/μL; about 1000 cells/μL to 2000 cells/μL; about 1500 cells/μL to 2000 cells/μL; about 500 cells/μL to 1500 cells/μL; about 1000 cells/μL to 1500 cells/μL; or about 500 cells/μL to 1000 cells/μL.

[0081] In some embodiments, the method achieves an ALC of about 1000 cells/μL to 3000 cells/μL; about 1500 cells/μL to 3000 cells/μL; about 2000 cells/μL to 3000 cells/μL; about 2500 cells/μL to 3000 cells/μL; 1000 cells/μL to 2500 cells/μL; about 1500 cells/μL to 2500 cells/μL; about 2000 cells/μL to 2500 cells/μL; 1000 cells/μL to 2000 cells/μL; about 1500 cells/μL to 2000 cells/μL; or about 1500 cells/μL to 2000 cells/μL.

[0082] In some embodiments, the method achieves an ANC of about 500 cells/μL to 3,000 cells/μL and an absolute leukocyte count ALC of about 1,000 to 3,000 cells/μL, or any combination of the foregoing ranges.

[0083] In some embodiments, the methods described herein achieve an ANC of at least 1500 cells/μL or, if the patient has an ANC level prior to treatment of 500 or less cells/μL, an increase in ANC of at least 2-fold.

[0084] In some embodiments, the methods described herein achieve on at least 60% of assessments, an ANC of at least 1500 cells/μL or, if the patient has an ANC level prior to treatment of 500 or less cells/μL, an increase in ANC of at least 2-fold.

[0085] In some embodiments, the methods described herein achieve on at least 65% of assessments, an ANC of at least 1500 cells/μL or, if the patient has an ANC level prior to treatment of 500 or less cells/μL, an increase in ANC of at least 2-fold.

[0086] In some embodiments, the methods described herein achieve on at least 70% of

assessments, an ANC of at least 1500 cells/μL or, if the patient has an ANC level prior to treatment of 500 or less cells/μL, an increase in ANC of at least 2-fold.

[0087] In some embodiments, the methods described herein achieve on at least 80% of assessments, an ANC of at least 1500 cells/μL or, if the patient has an ANC level prior to treatment of 500 or less cells/μL, an increase in ANC of at least 2-fold.

[0088] In some embodiments, the methods described herein achieve on at least 50%, at least 55%, at least 60%, at least 65%, at least 75%, at least 85%, at least 90%, or at least 95% of assessments, or achieve on about 50% to about 75%, about 50% to about 65%, about 60% to about 80%, or about 70% to about 90% of assessments, an ANC of at least 1500 cells/μL or, if the patient has an ANC level prior to treatment of 500 or less cells/μL, an increase in ANC of at least 2-fold.

[0089] In some embodiments, the methods described herein achieve an ANC of at least 2000 cells/μL or, if the patient has an ANC level prior to treatment of 500 or less cells/μL, an increase in ANC of at least 2.5-fold.

[0090] In some embodiments, the methods described herein achieve on at least 50%, at least 55%, at least 60%, at least 65%, at least 75%, at least 85%, at least 90%, or at least 95% of assessments, or achieve on about 50% to about 75%, about 50% to about 65%, about 60% to about 80%, or about 70% to about 90% of assessments, an ANC of at least 2000 cells/μL or, if the patient has an ANC level prior to treatment of 500 or less cells/μL, an increase in ANC of at least 2.5-fold.

[0091] In some embodiments, the methods described herein achieve an ANC of at least 2500 cells/μL or, if the patient has an ANC level prior to treatment of 500 or less cells/μL, an increase in ANC of at least 3-fold.

[0092] In some embodiments, the methods described herein achieve on at least 50%, at least 55%, at least 60%, at least 65%, at least 75%, at least 85%, at least 90%, or at least 95% of assessments, or achieve on about 50% to about 75%, about 50% to about 65%, about 60% to about 80%, or about 70% to about 90% of assessments, an ANC of at least 2500 cells/μL or, if the patient has an ANC level prior to treatment of 500 or less cells/μL, an increase in ANC of at least 3-fold.

[0093] As described above, patients being treated for neutropenia may also receive treatment with G-CSF, GM-CSF, or a variant of either.

[0094] The methods described herein may increase or decrease absolute neutrophil count (ANC) and/or increase absolute lymphocyte count (ALC) in the patient, for example in the

patient's blood. In some embodiments, the ANC and/or ALC is increased or decreased in the patient by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45% or at least 50% of that of the pre-treatment baseline counts.

[0095] In some embodiments, the methods described herein increase absolute neutrophil count (ANC) to a level greater than or equal to 500/μL and/or increase absolute lymphocyte count (ALC) to a level greater than or equal to 1000/μL.

[0096] In some embodiments, said patient originally exhibits ANC less than 600/μL and/or ALC less than 1000/μL before treatment. In some embodiments, said patient originally exhibits ANC less than 500/μL and/or ALC less than 650/μL before.

[0097] In some embodiments, a method described herein results in an increase in ANC levels to at least about 500/μL, at least about 600/μL, at least about 700/μL, at least about 800/μL, at least about 900/μL, at least about 1000/μL, at least about 1,100/μL, at least about 1,200/μL, at least about 1,300/μL, at least about 1,400/μL, at least about 1,500/μL, or to about that of a human with a normally-functioning immune system, on at least 85% of assessments.

[0098] In some embodiments, a method described herein results in and increase in ALC to at least about 1000/μL, about 1,200/μL, or about 1,500/μL, or to about that of a human with a normally-functioning immune system, on at least 85% of assessments.

[0099] In some embodiments, a method described herein results in a lowered frequency of infections in the patient, such as at least 10%; at least 25%; or at least 50% less infections. In some embodiments, the method reduces the frequency of a respiratory tract infection. In some embodiments, a method described herein results in lowered severity and/or duration of infections.

[00100] In some embodiments, a method described herein results in increased levels of total circulating WBC, neutrophils, and/or lymphocytes. In some embodiments, cell counts of WBC, neutrophils, and/or lymphocytes increase to approximately 1.4x baseline. In some embodiments, cell counts of WBC, neutrophils, and/or lymphocytes increase to approximately 1.6x baseline, 1.8x baseline, or 2.0x baseline. In some embodiments, cell counts of WBC, neutrophils, and/or lymphocytes increase to approximately 2.9x baseline. In some embodiments, cell counts of lymphocytes increase to approximately 2.9x baseline. In some embodiments, cell counts of neutrophils increase to approximately 2.7x baseline and lymphocytes to approximately 1.9x baseline.

[00101] In some embodiments, the method provides an increased maximum plasma

concentration of mavorixafor (Cmax) and/or Area Under the Curve (AUC) as compared to mavorixafor administered to the patient in an un-fasted state. In some embodiments, the patient in an un-fasted state has fasted for less than 7 hours, for example less than 6, 5, 4, 3, or 2 hours. In some embodiments, the patient in an un-fasted state has fasted for an hour or less.

[00102] In some embodiments, the method provides a maximum plasma concentration of mavorixafor (Cmax) of at least 3700 μg/mL and/or an Area Under the Curve over 24 hours (AUC0-24) of at least 16,000 μg/mL.

[00103] In some embodiments, the method provides a maximum plasma concentration of mavorixafor (Cmax) of at least 4000 μg/mL and/or an Area Under the Curve over 24 hours (AUC0-24) of at least 17,000 μg/mL.

[00104] In some embodiments, the method provides a maximum plasma concentration of mavorixafor (Cmax) of at least 4200 μg/mL and/or an Area Under the Curve over 24 hours (AUC0-24) of at least 18,000 μg/mL.

[00105] In some embodiments, the method provides a maximum plasma concentration of mavorixafor (Cmax) of about 3700 to about 7500 μg/mL and/or an Area Under the Curve over 24 hours (AUC0-24) of about 16,000 to 25,000 μg/mL.

[00106] In some embodiments, the method provides a mean maximum plasma concentration of mavorixafor (Cmax) in a group of 2 or more patients of about 3700 to about 7500 μg/mL and/or a mean Area Under the Curve over 24 hours (AUC_{0-24}) of about 16,000 to 25,000 μg/mL.

[00107] In some embodiments, the method provides a mean maximum plasma concentration of mavorixafor (C_{max}) in a group of 2 or more patients that is about 15% to 30% greater than that in a comparable group of 2 or more patients administered mavorixafor in a non-fasted state; and/or the method provides a mean Area Under the Curve over 24 hours (AUC_{0-24}) in a group of 2 or more patients that is about 15% to 30% greater than that in a comparable group of 2 or more patients administered mavorixafor in a non-fasted state. In some embodiments, the method provides a mean maximum plasma concentration of mavorixafor (C_{max}) in a group of 2 or more patients that is about 20% greater than that in a comparable group of 2 or more patients administered mavorixafor in a non-fasted state; and/or the method provides a mean Area Under the Curve over 24 hours (AUC_{0-24}) in a group of 2 or more patients that is about 20% greater than that in a comparable group of 2 or more patients administered mavorixafor in a non-fasted state. In some embodiments, the method provides a mean maximum plasma concentration of

mavorixafor (C_{max}) in a group of 2 or more patients that is about 30% greater than that in a comparable group of 2 or more patients administered mavorixafor in a non-fasted state; and/or the method provides a mean Area Under the Curve over 24 hours (AUC_{0-24}) in a group of 2 or more patients that is about 30% greater than that in a comparable group of 2 or more patients administered mavorixafor in a non-fasted state. In some embodiments, the method provides a mean maximum plasma concentration of mavorixafor (C_{max}) in a group of 2 or more patients that is about 30% to about 50% greater than that in a comparable group of 2 or more patients administered mavorixafor in a non-fasted state; and/or the method provides a mean Area Under the Curve over 24 hours (AUC_{0-24}) in a group of 2 or more patients that is about 30% to about 50% greater than that in a comparable group of 2 or more patients administered mavorixafor in a non-fasted state. In some embodiments, the method provides a mean maximum plasma concentration of mavorixafor (C_{max}) in a group of 2 or more patients that is at least 30% greater than that in a comparable group of 2 or more patients administered mavorixafor in a non-fasted state; and/or the method provides a mean Area Under the Curve over 24 hours (AUC_{0-24}) in a group of 2 or more patients that is at least 30% greater than that in a comparable group of 2 or more patients administered mavorixafor in a non-fasted state. In some embodiments, the patients in an un-fasted state have fasted for less than 7 hours, for example less than 6, 5, 4, 3, or 2 hours. In some embodiments, the patients in an un-fasted state have fasted for an hour or less.

[00108] Because neutropenic patients may have variable endogenous G-CSF levels, administering additional G-CSF may be ineffective or even dangerous (e.g., in patients with high levels of endogenous G-CSF). The methods described herein may be modified accordingly to account for a patient's endogenous G-CSF. In some embodiments of any of the method described herein, the patient has an endogenous G-CSF concentration of about 10^2 pg/mL or lower. In some embodiments, the patient has an endogenous G-CSF concentration of between about 10^2 pg/mL and 10^3 pg/mL. In some embodiments, the patient has an endogenous G-CSF concentration of between about 10^2 pg/mL and 10^4 pg/mL. In some embodiments, the patient has an endogenous G-CSF concentration of between about 10^2 pg/mL and 10^5 pg/mL. In some embodiments, the patient has an endogenous G-CSF concentration of between about 10^3 pg/mL and 10^4 pg/mL. In some embodiments, the patient has an endogenous G-CSF concentration of between about 10^3 pg/mL and 10^5 pg/mL. In some embodiments, the patient has an endogenous G-CSF concentration of between about 10^4 pg/mL and 10^5 pg/mL. In some embodiments, the patient has an endogenous

G-CSF concentration of about 10^5 pg/mL or greater. In some embodiments, the patient has an endogenous G-CSF concentration of about 10 pg/mL or lower, about 10^2 pg/mL, about 10^3 pg/mL, about 10^4 pg/mL, about 10^5 pg/mL, about 10^6 pg/mL, or higher.

[00109] In some embodiments of the methods described herein, the patient is receiving a first dose of G-CSF, GM-CSF, or a variant of either, once daily.

[00110] In some embodiments, the patient is receiving a first dose of G-CSF, GM-CSF, or a variant of either of 0.1 mcg/kg, 0.2 mcg/kg, 0.2 mcg/kg, 0.3 mcg/kg, 0.4 mcg/kg, 0.5 mcg/kg, 0.6 mcg/kg, 0.7 mcg/kg, 0.8 mcg/kg, 0.9 mcg/kg, 1.0 mcg/kg, 1.1 mcg/kg, 1.2 mcg/kg, 1.3 mcg/kg, 1.4 mcg/kg, 1.5 mcg/kg, 1.6 mcg/kg, 1.7 mcg/kg, 1.8 mcg/kg, 1.9 mcg/kg, 2.0 mcg/kg, 2.1 mcg/kg, 2.2 mcg/kg, 2.3 mcg/kg, 2.4 mcg/kg, 2.5 mcg/kg, 2.6 mcg/kg, 2.7 mcg/kg, 2.8 mcg/kg, 2.9 mcg/kg, 3.0 mcg/kg, 3.1 mcg/kg, 3.2 mcg/kg, 3.3 mcg/kg, 3.4 mcg/kg, 3.5 mcg/kg, 3.6 mcg/kg, 3.7 mcg/kg, 3.8 mcg/kg, 3.9 mcg/kg, 4.0 mcg/kg, 4.1 mcg/kg, 4.2 mcg/kg, 4.3 mcg/kg, 4.4 mcg/kg, 4.5 mcg/kg, 4.6 mcg/kg, 4.7 mcg/kg, 4.8 mcg/kg, 4.9 mcg/kg, 5.0 mcg/kg, 5.1 mcg/kg, 5.2 mcg/kg, 5.3 mcg/kg, 5.4 mcg/kg, 5.5 mcg/kg, 5.6 mcg/kg, 5.7 mcg/kg, 5.8 mcg/kg, 5.9 mcg/kg, or 6.0 mcg/kg, once or twice daily, every other day, every third day, weekly, every 2 weeks, monthly, or as otherwise prescribed by a treating physician.

Methods for Treatment of Chronic Neutropenia Using Combinations of a CXCR4 Inhibitor and G-CSF

[00111] Granulocyte colony-stimulating factor is currently the standard of care for severe chronic neutropenia (SCN). Indeed, in patients diagnosed with chronic neutropenia, particularly those with severe neutropenia with ANC < 500 cells/μL, daily (or multiple times a week) injections of G-CSF are commonly given to increase the ANC and reduce the risk of infections. The efficacy of G-CSF in this indication was proven by a placebo-controlled clinical trial that demonstrated G-CSF safety and efficacy in reducing the risk of infection in patients with SCN of various etiologies (Dale et al. (1993) Blood. 81:2496-502).

[00112] A number of literature reports indicate that G-CSF alone was not effective in reducing mortality in patients with pneumonia (Cheng et al. (2004) Cochrane Database of Systematic Reviews, CD004400); and that long-term G-CSF therapy may present elevated risk of transformation to MDS/AML or mortality due to sepsis (Rosenberg et al. (2006) Blood, 107:4628-4635).

[00113] G-CSF has a number of variants, including: lenograstim (Granocyte®) filgrastim (Neupogen®, Zarzio®, Nivestim®, Accofil®) long acting (pegylated) filgrastim (pegfilgrastim, Neulasta®, Pelmeg®, Ziextenco®) and lipegfilgrastim (Lonquex®). GM-CSF (sargramostim, Leukine®) is a distinct hematopoietic cytokine that has been approved for use to shorten the time for neutrophil and or myeloid recovery in various therapeutic contexts.

[00114] For treatment of severe, chronic neutropenia, Neupogen® (filgrastim or G-CSF) is indicated at a starting dosage 6 mcg/kg as a twice daily subcutaneous injection (congenital neutropenia); or 5 mcg/kg as a single daily subcutaneous injection (idiopathic or cyclic neutropenia). It is further indicated that the starting dosage by followed by chronic daily administration in order to maintain clinical benefits. The indicated chronic daily administration is in the amount of 6 mcg/kg (congenital neutropenia); 2.1 mcg/kg (cyclic neutropenia); and 1.2 mcg/kg (idiopathic neutropenia). Neulasta® (pegfilgrastim or pegylated G-CSF) is not presently approved for treatment of severe, chronic neutropenia other than in patients receiving myelosuppressive chemotherapy or radiation. It is available in a 6 mg/0.6 mL single-dose prefilled syringe, which may be administered once per chemotherapy cycle, or in two doses of 6 mg each, one week apart, for subjects who have been exposed to radiation levels in excess of 2 gray (Gy). Neulasta® is also available for use with the "on-body injector" or OBI, which is co-packaged with a prefilled syringe, and which administers the Neulasta® dose over a period of approximately 45 minutes, beginning approximately 27 hours after the OBI is applied to the subject's skin.

[00115] While the below-stated doses are currently FDA-approved doses for single therapy, in certain embodiments, the present invention comprises the use of a lower starting dosage of filgrastim. In certain embodiments, the starting dosage of filgrastim may be lower than the below-stated starting dosages by at least 10%, 15%, 20%, 25%, 30%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%,80%, 85%, 90%, or 95% of the above stated dosages.

[00116] Bone pain experienced with administration of G-CSF has commonly been treated with acetaminophen and nonsteroidal anti-inflammatory agents as first line therapy, while antihistamines, such as loratidine (10 mg oral); or combinations of famotidine and loratadine; opioids; and dose reduction of G-CSFs are considered as second line therapy (Lambertini et al. (2014) Crit. Rev. Oncol. Hematol. 89:112-128).

[00117] Without wishing to be bound by theory, it is believed that G-CSF's effect on the bone marrow release of neutrophils is mediated in part by interfering with CXCL12 availability at the

level of the CXCR4 receptor, with minimal effects on other hematopoietic cell types.

[00118] Granulocyte-colony stimulating factor treatment induces a decrease in CXCL12 expression in the bone marrow (Semerad et al. (2002) Immunity. 17:413-23; Levesque et al. (2003) J Clin Invest. 111:187-96), and G-CSF leads to decreased surface expression of CXCR4 on neutrophils (Kim et al. (2006) Blood. 108:812-20). In fact, G-CSF does not stimulate neutrophil release from the bone marrow in the absence of CXCR4 signals (Eash et al. (2009) Blood. 113:4711-19).

[00119] Without wishing to be bound by any particular theory, it is believed that certain patient populations having neutropenia could be treated effectively with a combination of specific CXCR4 inhibitors, such as mavorixafor, and G-CSF, or a variant thereof; or with a CXCR4 inhibitor, such as mavorixafor, alone. It is further believed that such treatment produces a significant increase in patient baseline ANC. It is also believed that subjects with neutropenia (or severe neutropenia) who are currently treated with G-CSF, including those subjects who experience bone pain or other serious adverse effects of receiving G-CSF, could be treated with a CXCR4 inhibitor, such as mavorixafor, and that treatment with CXCR4 inhibitor allows for a reduction in the dosage and/or frequency of treatment with G-CSF, or even elimination of the need for treatment with G-CSF, while still maintaining an ANC above a minimum threshold (e.g., ANC of at least 500/μL) to prevent infections and other manifestations of neutropenia (e.g., oral ulcers).

[00120] Similarly, without wishing to be bound by any particular theory, the inventors similarly believe that certain patients having neutropenia (with or without accompanying lymphopenia) can be treated effectively using a combination of specific CXCR4 inhibitors, such as mavorixafor, and G-CSF, or a variant thereof; or with a CXCR4 inhibitor, such as mavorixafor, alone. It is further believed that such treatment produces a significant increase in patient baseline ANC, while also maintaining acceptable levels of absolute lymphocyte counts (ALC).

[00121] For instance, administration of a CXCR4 inhibitor (e.g., mavorixafor) will permit adjusting the dose or frequency of dose of G-CSF, GM-CSF, or a variant of either, during treatment. In some embodiments, administration of the CXCR4 inhibitor will permit reduction or discontinuation of the G-CSF for at least some patients. In some cases, this reduces the risk of G-CSF associated malignancy and myelofibrosis, and reduces G-CSF associated bone pain while maintaining protection from infection. In some cases, adjusting the dose or frequency of dose of G-CSF may prevent or improve the extent and/or duration and/or emergence of bone pain,

myalgia, splenomegaly, thrombocytopenia, interstitial pneumonitis, MDS (Myeloid Dysplastic Syndrome) AML, fibrosis, periodontitis, fatigue, or combinations of any of the foregoing.

[00122] Thus, in one aspect, the present disclosure provides a method for treating neutropenia, comprising administering to the patient an effective amount of a CXCR4 inhibitor and a starting dosage of G-CSF, GM-CSF, or a variant of either, for a first treatment period; and adjusting the starting dosage of G-CSF, GM-CSF, or variant of either to a second dosage of G-CSF, GM-CSF, or a variant of either, for a second treatment period, wherein the patient has fasted from all food and drink except for water for at least 7 hours (e.g., at least 10 hours, e.g., about 10 hours) prior to administration of the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof and continues to fast for at least 30 minutes after administration; and the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof is administered once per day at a dosage of about 100 mg to about 800 mg.

[00123] In some embodiments, the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof is mavorixafor or a pharmaceutically acceptable salt thereof. It should be understood that, in any of the methods described herein, the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof may be a CXCR4 inhibitor other than mavorixafor or a pharmaceutically acceptable salt thereof.

[00124] In some embodiments, the first treatment period and the second treatment period do not overlap.

[00125] Any of the methods described herein may be useful for treating congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia. In some embodiments, the neutropenia is congenital neutropenia. In some embodiments, the neutropenia is cyclic neutropenia. In some embodiments, the neutropenia is idiopathic neutropenia.

[00126] Likewise, any of the methods described herein may be useful for patients who have a CXCR4 mutation. In some embodiments, the patient has a WHIM, ELANE, HAX1, G6PC3, GSD1b, GATA2, WAS, or SBDS mutation.

[00127] As described above, patients who begin treatment with G-CSF and a CXCR4 inhibitor may experience side-effects associated with such a treatment. Therefore, in some embodiments of the methods described herein, the patient has an infection, oral ulcers, gingivitis, bone pain, myalgia, splenomegaly, interstitial pneumonitis, fibrosis, periodontitis, fatigue, a bone marrow failure disease, a pancytopenia (cytopenia of leukocytes and/or erythrocytes and/or thrombocytes), a panleukocytopenia (cytopenia of neutrophils and/or monocytes and/or lymphocytes such as B-

cells, T-cells and/or NK cells), or any combination of the foregoing.

[00128] Thus, in patients being administered an effective amount of a CXCR4 inhibitor and a starting dosage of G-CSF for a first treatment period, the starting dosage of G-CSF may be adjusted to a second dosage of G-CSF to reduce a side effect, including those mentioned above.

[00129] In some embodiments, the second dosage of G-CSF, GM-CSF, or a variant of either, is reduced by about 1% to 100% relative to the starting dosage of G-CSF, GM-CSF, or a variant of either. In some embodiments, the second dosage is reduced by about 25-75% relative to the starting dosage. In some embodiments, the second dosage is reduced by about 25-50%, or 50-75% relative to the starting dosage. In some embodiments, the second dosage is reduced by about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 99% relative to the starting dose.

[00130] Likewise, it may be useful to increase the dosage of G-CSF after a first treatment period. In some embodiments, the second dosage of G-CSF, GM-CSF, or a variant of either, is increased by about 1% to 500%, or greater, relative to the starting dosage of G-CSF, GM-CSF, or a variant of either. In some embodiments, the second dosage is increased by about 25-75% relative to the starting dosage. In some embodiments, the second dosage is increased by about 25-50%, 25-100%, 50-75%, or 50-100% relative to the starting dosage. In some embodiments, the second dosage is increased by about 75-100%, 100-200%, 200-300%, 300-400%, or 400-500%. In some embodiments, the second dosage is increased by about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 100%, about 200%, about 300%, about 400%, or about 500% or higher relative to the starting dose. Starting dosages of both a CXCR4 inhibitor and G-CSF, GM-CSF, or a variant of either, are described further below.

[00131] In some embodiments of the methods described herein, a first treatment period may have a duration of about one week to about 12 months or longer. In some embodiments, the first treatment period has a duration of about 1-12 months. In some embodiments, the first treatment period has a duration of about 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 2-12, 2-11, 2-10, 2-9, 2-8, 2-7, 2-6, 2-5, 2-4, 2-3, 3-12, 3-11, 3-10, 3-9, 3-8, 3-7, 3-6, 3-5, 3-4, 4-12, 4-11, 4-10, 4-9, 4-8, 4-7, 4-6, 4-5, 5-12, 5-11, 5-10, 5-9, 5-8, 5-7, 5-6, 6-12, 6-11, 6-10, 6-9, 6-8, 6-7, 7-12, 7-

11, 7-10, 7-9, 7-8, 8-12, 8-11, 8-10, 8-9, 9-12, 9-11, 9-10, 10-12, 10-11, or 11-12 months. In some embodiments, the first treatment period has a duration of about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, or about 12 months or greater.

[00132] Because adjusting the starting dosage to a second dosage of G-CSF, GM-CSF, or a variant of either, may not result in the desired outcome (e.g., elimination of side-effects, improvement in ANC or ALC), further adjustments may be made. For instance, the second dosage of G-CSF, GM-CSF, or a variant of either, in a second treatment period is further reduced or increased as needed in a subsequent treatment period. In some embodiments, the second dosage is further reduced or increased to arrive at a third dosage for a third treatment period. In some embodiments, the third dosage is further reduced or increased to arrive at a fourth dosage for a fourth treatment period. In some embodiments, the fourth dosage is further reduced or increased to arrive at a fifth dosage for a fifth treatment period. The methods described herein are not limited by the number of subsequent dosages and correspond treatment periods.

[00133] In some embodiments, the subsequent adjustment to dosages (e.g., third, fourth, fifth, sixth, seventh, or beyond) are the same as described above for the second dosage of G-CSF, GM-CSF, or a variant of either. In some embodiments, the subsequent treatment periods (e.g., second, third, fourth, fifth, sixth, seventh, or beyond) are the same as described above for the first treatment period.

[00134] In some embodiments of the methods described herein, the starting dosage is adjusted (e.g., increased or decreased) at a certain rate. For instance, in some embodiments the starting dosage is decreased by about 10-100% a month. In some embodiments, the starting dosage is decreased by about 10-90%, 10-80%, 10-70%, 10-60%, 10-50%, 10-40%, 10-30%, 10-20%, 20-100%, 20-90%, 20-80%, 20-70%, 20-60%, 20-50%, 20-40%, 20-30%, 30-100%, 30-90%, 30-80%, 30-70%, 30-60%, 30-50%, 30-40%, 40-100%, 40-90%, 40-80%, 40-70%, 40-60%, 40-50%, 50-100%, 50-90%, 50-80%, 50-70%, 50-60%, 60-100%, 60-90%, 60-80%, 60-70%, 70-100%, 70-90%, 70-80%, 80-100%, 80-90%, or 80-100% a month. In some embodiments, the starting dosage is decreased by about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or about 100% a month. In some embodiments, the starting dosage is increased by any of these amounts.

[00135] In some embodiments, the starting dosage is adjusted on a per-week or per-year basis by any of the per-month amounts provided above. It should also be understood that any subsequent

dosage (e.g., second, third, fourth, fifth, sixth, seventh, or beyond) may be adjusted (e.g., increased or decreased) by any of the monthly amounts provided above, on a monthly, weekly, or annual basis.

[00136] In some embodiments of the methods described herein, dosing with G-CSF, GM-CSF, or any variant of either, is terminated. In some embodiments, dosing with G-CSF, GM-CSF, or a variant of either, is stopped after the first, second, third, fourth, fifth, sixth, seventh (or beyond) treatment period. In some embodiments, dosing is stopped after the second treatment period.

[00137] In addition to adjusting the amount of G-CSF, GM-CSF, or a variant of either, it may be useful to instead, or additionally, adjust the frequency of dosing. In some embodiments of the methods described herein, dosing of G-CSF, GM-CSF, or a variant of either, is daily. In some embodiments, the frequency of dosing is decreased from daily in the second and/or subsequent treatment periods. In some embodiments, the frequency of dosing is decreased to every other day, once per week, once per month, once every other month, once every 6 months, once every year, or any frequency captured therein.

[00138] It should be understood that the dosing frequency can also be increased by any of the amounts described above.

[00139] It should be understood that dosing with G-CSF, GM-CSF, or a variant of either, may be stopped at any point as part of any of the methods described herein. For instance, in some embodiments, dosing is stopped between about 1-12 months after beginning treatment. In some embodiments, dosing with G-CSF, GM-CSF, or a variant of either, is stopped between about 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 2-12, 2-11, 2-10, 2-9, 2-8, 2-7, 2-6, 2-5, 2-4, 2-3, 3-12, 3-11, 3-10, 3-9, 3-8, 3-7, 3-6, 3-5, 3-4, 4-12, 4-11, 4-10, 4-9, 4-8, 4-7, 4-6, 4-5, 5-12, 5-11, 5-10, 5-9, 5-8, 5-7, 5-6, 6-12, 6-11, 6-10, 6-9, 6-8, 6-7, 7-12, 7-11, 7-10, 7-9, 7-8, 8-12, 8-11, 8-10, 8-9, 9-12, 9-11, 9-10, 10-12, 10-11, or 11-12 months after beginning treatment. In some embodiments, dosing is stopped about 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 12 months or greater after beginning treatment.

[00140] It may also be beneficial to begin administering G-CSF after a patient is already being treated with a CXCR4 inhibitor.

[00141] Thus, in another aspect, the present disclosure provides a method for treating neutropenia in a patient in need thereof, comprising administering to the patient an effective

amount of a CXCR4 inhibitor for a first treatment period, and administering to the patient a starting dosage of G-CSF, GM-CSF, or a variant of either, for a second treatment period, wherein the patient has fasted from all food and drink except for water for at least 7 hours (e.g., at least 10 hours, e.g., about 10 hours) prior to administration of the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof and continues to fast for at least 30 minutes after administration; and the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof is administered once per day at a dosage of about 100 mg to about 800 mg.

[00142] In some embodiments, the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof is mavorixafor or a pharmaceutically acceptable salt thereof. It should be understood that, in any of the methods described herein, the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof may be a CXCR4 inhibitor other than mavorixafor or a pharmaceutically acceptable salt thereof. CXCR4 inhibitors include those described herein.

[00143] It may also be beneficial to treat a patient with a CXCR4 inhibitor who is already being treated with G-CSF, GM-CSF, or a variant of either.

[00144] Thus, in another aspect, the present disclosure provides a method for treating neutropenia, comprising: administering to a patient who is receiving treatment with G-CSF, GM-CSF, or a variant of either, an effective amount of a CXCR4 inhibitor, or a pharmaceutically acceptable salt thereof, wherein the dose amount and/or dosing frequency of the G-CSF, GM-CSF, or a variant of either, necessary for treatment is reduced after the patient has received the CXCR4 inhibitor for a period of time.

[00145] In some embodiments, the dose amount and/or dosing frequency of the G-CSF, GM-CSF, or a variant of either, necessary for treatment is reduced after the patient has received the CXCR4 inhibitor for at least a day. In some embodiments, the amount and/or dosing frequency of the G-CSF, GM-CSF, or a variant of either, necessary for treatment is reduced after the patient has received the CXCR4 inhibitor for at least about a day, at least about a week, at least about one month, at least about two months, at least about three months, at least about four months, at least about five months, at least about six months, at least about seven months, at least about eight months, at least about nine months, at least about ten months, at least about 11 months, at least about 12 months or longer. In some embodiments, the patient has received the CXCR4 treatment for about one to four months, about one to three months, about one to two months, about two to four months, about two to three months, or about three to four months.

[00146] In another aspect, the present disclosure provides a method of correcting an imbalance of an immune cell population in a subject, comprising administering to the subject an effective amount of a CXCR4 inhibitor, wherein the patient has fasted from all food and drink except for water for at least 7 hours (e.g., at least 7 hours, e.g., about 10 hours) prior to administration of the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof and continues to fast for at least 30 minutes after administration; and the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof is administered once per day at a dosage of about 100 mg to about 800 mg.

[00147] In some embodiments, the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof is mavorixafor or a pharmaceutically acceptable salt thereof. It should be understood that, in any of the methods described herein, the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof may be a CXCR4 inhibitor other than mavorixafor or a pharmaceutically acceptable salt thereof. CXCR4 inhibitors include those described herein.

[00148] In some embodiments, the present disclosure provides a method of correcting an imbalance in absolute neutrophil count (ANC) and/or absolute leukocyte count (ALC) in a patient, the method comprising administering to the patient an effective amount of a CXCR4 inhibitor, wherein the patient has fasted from all food and drink except for water for at least 7 hours (e.g., at least 10 hours, e.g., about 10 hours) prior to administration of the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof and continues to fast for at least 30 minutes after administration; and the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof is administered once per day at a dosage of about 100 mg to about 800 mg.

[00149] In some embodiments, the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof is mavorixafor or a pharmaceutically acceptable salt thereof. It should be understood that, in any of the methods described herein, the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof may be a CXCR4 inhibitor other than mavorixafor or a pharmaceutically acceptable salt thereof. CXCR4 inhibitors include those described herein.

[00150] In some embodiments of a method of correcting an imbalance of an immune cell population in a subject, the patient is receiving G-CSF, GM-CSF, or a variant of either. In some embodiments, the patient is receiving a first dose of G-CSF, GM-CSF, or a variant of either, at a frequency disclosed herein. For instance, in some embodiments, the patient is patient is receiving a first dose once daily. In some embodiments, the patient receives a subsequent dose (e.g., first, second, third, or greater).

[00151] In some embodiments, the subject has a chronic immune cell imbalance. In some embodiments, the subject has an acute immune cell imbalance. In some embodiments, the immune cell imbalance is associated with a congenital primary immunodeficiency disease (PID). In some embodiments, the immune cell imbalance is associated with a disease state. In some embodiments, the disease state is cancer. In some embodiments, the cancer is renal cell carcinoma, clear cell renal cell carcinoma, papillary renal cancer, melanoma, pancreatic cancer, ovarian cancer, non-small cell lung cancer, Waldenstrom's macroglobulinemia (WM). In some embodiments, the cancer is a leukemia or lymphoma. In some embodiments, the PID is WHIM syndrome, chronic neutropenia or severe chronic neutropenia (SCN).

[00152] The cells of the immune system can be categorized as lymphocytes (T-cells, B-cells and NK cells), neutrophils, and monocytes/macrophages. These are all types of white blood cells. The major proteins of the immune system are predominantly signaling proteins (often called cytokines), antibodies, and complement proteins.

[00153] In some embodiments, a method provided by the present invention corrects an imbalance in B-cells in the subject. B-cells (sometimes called B-lymphocytes) are specialized cells of the immune system whose major function is to produce antibodies (also called immunoglobulins or gamma-globulins). B-cells develop in the bone marrow from hematopoietic stem cells. As part of their maturation in the bone marrow, B-cells are trained or educated so that they do not produce antibodies to healthy tissues. When mature, B-cells can be found in the bone marrow, lymph nodes, spleen, some areas of the intestine, and the bloodstream.

[00154] In some embodiments, a method provided by the present invention corrects an imbalance in T-cells in the subject. T-cells (sometimes called T-lymphocytes and often named in lab reports as CD3 cells) directly attack cells infected with viruses, and they also act as regulators of the immune system. T-cells develop from hematopoietic stem cells in the bone marrow but complete their development in the thymus. The thymus is a specialized organ of the immune system in the chest. Within the thymus, immature lymphocytes develop into mature T-cells and T-cells with the potential to attack normal tissues are eliminated. The thymus is essential for this process, and T-cells cannot develop if the fetus does not have a thymus. Mature T-cells leave the thymus and populate other organs of the immune system, such as the spleen, lymph nodes, bone marrow and blood. Each T-cell reacts with a specific antigen, just as each antibody molecule reacts with a specific antigen.

[00155] T-cells have different abilities to recognize antigen and are varied in their function. There are "killer" or cytotoxic T-cells (often denoted in lab reports as CD8 T-cells), helper T-cells (often denoted in lab reports as CD4 T-cells), and regulatory T-cells. Each has a different role to play in the immune system. Killer, or cytotoxic, T-cells perform the actual destruction of infected cells. Killer T-cells protect the body from certain bacteria and viruses that have the ability to survive and even reproduce within the body's own cells. Killer T-cells also respond to foreign tissues in the body, such as a transplanted organ. The killer cell must migrate to the site of infection and directly bind to its target to ensure its destruction. Helper T-cells assist B-cells to produce antibodies and assist killer T-cells in their attack on foreign substances. Regulatory T-cells suppress or turn off other T-lymphocytes.

[00156] Natural killer (NK) cells are so named because they easily kill cells infected with viruses. They are said to be "natural killer" cells as they do not require the same thymic education that T-cells require. NK cells are derived from the bone marrow and are present in relatively low numbers in the bloodstream and in tissues. They are important in defending against viruses and possibly preventing cancer as well.

[00157] In some embodiments, a method provided by the present invention corrects an imbalance in neutrophils in the subject. Neutrophils or polymorphonuclear leukocytes (polys or PMN's) are the most numerous of all the types of white blood cells, making up about half or more of the total. They are also called granulocytes and appear on lab reports as part of a complete blood count (CBC with differential). They are found in the bloodstream and can migrate into sites of infection within a matter of minutes. These cells, like the other cells in the immune system, develop from hematopoietic stem cells in the bone marrow. Neutrophils increase in number in the bloodstream during infection and are in large part responsible for the elevated white blood cell count seen with some infections. They are capable of leaving the bloodstream and accumulating in tissues during the first few hours of an infection. Their major role is to ingest bacteria or fungi and kill them.

[00158] In some embodiments, a method provided by the present invention corrects an imbalance in monocytes (monocytopenia) in the subject. Monocytes are closely related to neutrophils and are found circulating in the bloodstream. They make up 5-10 percent of the white blood cells. They also line the walls of blood vessels in organs like the liver and spleen. Here they capture microorganisms in the blood as the microorganisms pass by. Monocytopenia is a reduction

in blood monocyte count (ANC) to <500/mcL (< 0.5×10^9/L). Risk of certain infections is increased. It is diagnosed by complete blood count with differential. Typical treatment includes hematopoietic stem cell transplantation.

[00159] Macrophages are essential for killing fungi and certain bacteria. Macrophages live longer than neutrophils and are especially important for slow growing or chronic infections. Macrophages can be influenced by T-cells and often collaborate with T-cells in killing microorganisms.

[00160] In some embodiments, the subject has an imbalance of an immune cell population selected from T-cells, B-cells, NK cells, neutrophils, and monocytes. In some embodiments, the subject has leukopenia, neutropenia, or monocytopenia. In some embodiments, the subject exhibits a low total white blood cell (WBC) count.

[00161] In another aspect, the present disclosure provides a method of reducing the dose or frequency of dose of G-CSF, GM-CSF, or a variant of either, required to treat neutropenia in a patient comprising determining an initial absolute neutrophil count (ANC) of the patient; and reducing the dose or frequency of dose of G-CSF, GM-CSF, or a variant of either, to a second dose of G-CSF, GM-CSF, or a variant of either, sufficient to lower the initial ANC of the patient, wherein the patient has fasted from all food and drink except for water for at least 7 hours (e.g., at least 10 hours, e.g., about 10 hours) prior to administration of the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof and continues to fast for at least 30 minutes after administration; and the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof is administered once per day at a dosage of about 100 mg to about 800 mg.

[00162] In some embodiments, the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof is mavorixafor or a pharmaceutically acceptable salt thereof. It should be understood that, in any of the methods described herein, the CXCR4 inhibitor or a pharmaceutically acceptable salt thereof may be a CXCR4 inhibitor other than mavorixafor or a pharmaceutically acceptable salt thereof. CXCR4 inhibitors include those described herein.

[00163] In some embodiments, the method further comprises determining the patient's ANC after the patient has been receiving the second dose for at least one week; and reducing the second dose or frequency of the second dose to a third dose, wherein the third dose or frequency of the third dose is reduced 50% relative to the second dose.

[00164] In some embodiments, the second dose is administered less frequently than daily. In

some embodiments, the second dose is administered every other day. In some embodiments, the second dose is administered once per week.

[00165] As discussed above, any of the methods described herein may improve certain side-effects or symptoms associated with treatment with CXCR4 inhibitors and/or G-CSF, GM-CSF, or a variant of either. In some embodiments, the methods described herein produce an improvement in the frequency, severity, duration of infections or time to next infection; the emergence and/or clearance of oral ulcers; the appearance and/or clearance of gingivitis; or any combination of the foregoing. In some embodiments, the methods described herein produce an improvement in the extent, duration, and/or emergence of G-CSF-induced bone pain, myalgia, splenomegaly, thrombocytopenia, interstitial pneumonitis, MDS, AML, fibrosis, periodontitis, fatigue, or any combination of the foregoing.

[00166] In some embodiments of any of the methods described herein, the patient has a CXCR4 mutation. In some embodiments, the patient has a WHIM, ELANE, HAX1, G6PC3, GSD1b, GATA2, WAS, or SBDS mutation.

[00167] In some embodiments of the methods described herein, a first or starting dosage of G-CSF, CM-CSF, or a variant of either, is increased or decreased to a second dose to achieve an ANC of at least 500 cells/μL and/or an absolute leukocyte count (ALC) of at least 1000/μL. In some embodiments, the first or starting dose of any of the methods described herein is increased or decreased to achieve an ANC of between about 1,000 cells/μL and 10,000 cells/μL. In some embodiments, the first or starting dose of any of the methods described herein is increased or decreased to achieve an ANC of between about 1,000 cells/μL and 10,000 cells/μL; between about 1,000 cells/μL and 9,000 cells/μL; between about 1000 cells/μL and 8,000 cells/μL; between about 1,000 cells/μL and 7,000 cells/μL; between about 1,000 cells/μL and 6,000 cells/μL; between about 1,000 cells/μL and 5,000 cells/μL; between about 1,000 cells/μL and 4,000 cells/μL; between about 1,000 cells/μL and 3,000 cells/μL; between about 1,000 cells/μL and 2,000 cells/μL; between about 2,000 cells/μL and 10,000 cells/μL; between about 2,000 cells/μL and 9,000 cells/μL; between about 2,000 cells/μL and 8,000 cells/μL; between about 2,000 cells/μL and 7,000 cells/μL; between about 2,000 cells/μL and 6,000 cells/μL; between about 2,000 cells/μL and 5,000 cells/μL; between about 2,000 cells/μL and 4,000 cells/μL; between about 2,000 cells/μL and 3,000 cells/μL; between about 3,000 cells/μL and 10,000 cells/μL; between about 3,000 cells/μL and 9,000 cells/μL; between about 3,000 cells/μL and 8,000 cells/μL;

between about 3,000 cells/μL and 7,000 cells/μL; between about 3,000 cells/μL and 6,000 cells/μL; between about 3,000 cells/μL and 5,000 cells/μL; between about 3,000 cells/μL and 4,000 cells/μL; between about 4,000 cells/μL and 10,000 cells/μL; between about 4,000 cells/μL and 9,000 cells/μL; between about 4,000 cells/μL and 8,000 cells/μL; between about 4,000 cells/μL and 7,000 cells/μL; between about 4,000 cells/μL and 6,000 cells/μL; between about 4,000 cells/μL and 5,000 cells/μL; between about 5,000 cells/μL and 10,000 cells/μL; between about 5,000 cells/μL and 9,000 cells/μL; between about 5,000 cells/μL and 8,000 cells/μL; between about 5,000 cells/μL and 7,000 cells/μL; between about 5,000 cells/μL and 6,000 cells/μL; between about 6,000 cells/μL and 10,000 cells/μL; between about 6,000 cells/μL and 9,000 cells/μL; between about 6,000 cells/μL and 8,000 cells/μL; between about 6,000 cells/μL and 7,000 cells/μL; between about 7,000 cells/μL and 10,000 cells/μL; between about 7,000 cells/μL and 9,000 cells/μL; between about 7,000 cells/μL and 8,000 cells/μL; between about 8,000 cells/μL and 10,000 cells/μL; between about 8,000 cells/μL and 9,000 cells/μL; or between about 9,000 cells/μL and 10,000 cells/μL. In some embodiments, the first or starting dose of any of the methods described herein is increased or decreased to achieve an ANC of about 1,000; 2,000; 3,000; 4,000; 5,000; 6,000; 7,000; 8,000; 9,000; or 10,000 cells/μL.

[00168] It should be understood that in some embodiments, any subsequent increases or decreases in dosages of the methods described herein (e.g., second, third, fourth, or greater) may achieve any of the aforementioned ANC levels.

[00169] In some embodiments, the methods described herein achieve an ANC of at least 500 cells/μL and/or an ALC of at least 1000/μL.

[00170] In some embodiments, when a patient is receiving the first or starting dosage of G-CSF, GM-CSF, or a variant of either, and the patient's ANC is less than about 500 cells/μL, less than about 1,000 cells/μL, or less than about 1,500 cells/μL, or higher, the second dose is 10%, 20%, 30%, 40%, 50%, or greater relative to the first dose. It should be understood that any subsequent dosage (e.g., in any subsequent treatment period) may be increased accordingly.

[00171] In some embodiments, when a patient is receiving the first or starting dosage of G-CSF, GM-CSF, or a variant of either, and the patient's ANC is greater than about 10,000 cells/μL, about 9,000 cells/μL, 8,000 cells/μL, 7,000 cells/μL, 6,000 cells/μL, 5,000 cells/μL, 4,000 cells/μL, or lower, the second dose is about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% lower relative to the first dose. It should be understood that

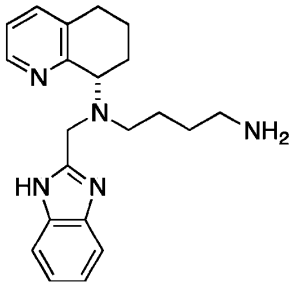
any subsequent dosage (e.g., in any subsequent treatment period) may be decreased accordingly.

[00172] In some embodiments, the frequency of dosage in a first or starting dose of G-CSF, GM-CSF, or variant of either, is reduced or increased, for example, reduced or increased in frequency by at least 25%, 50%, 75%, or 90%. It should be understood that any subsequent dosage (e.g., second, third, fourth, or greater), in any subsequent treatment period, may be increased or decreased accordingly. In some embodiments, the interval between dosage administration, is increased (e.g., once every three days, rather than once every two days).

CXCR4 Inhibitors

[00173] As described herein, a variety of CXCR4 inhibitors may be used in accordance with the present disclosure.

[00174] In some embodiments, the CXCR4 inhibitor is mavorixafor (X4P-001; AMD11070), or a pharmaceutically acceptable salt thereof. Mavorixafor is currently in clinical development in patients with cancer (renal cell carcinoma), Waldenström's Macroglobulinemia, and with warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome. The chemical formula is: $C_{21}H_{27}N_5$; and molecular weight is 349.48 amu. The chemical structure of mavorixafor is as follows according to Formula I:



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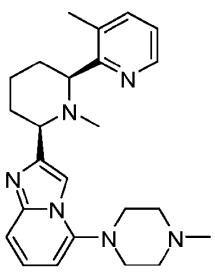
[00175] In some embodiments, the CXCR4 inhibitor is one of those described in the following documents, or a pharmaceutically acceptable salt thereof: WO2017223229, WO2017223239, WO2017223243, WO2019126106, WO2020/264292, WO2003/022785, WO2003/055876, WO2004/106493, WO2004/091518, WO2004/093817, WO2006/049764, WO2005/090308, WO2021/263203, WO2023059903, or WO2006/039250. Each of the foregoing documents is hereby incorporated by reference in its entirety.

[00176] In some embodiments, the CXCR4 inhibitor is selected from mavorixafor,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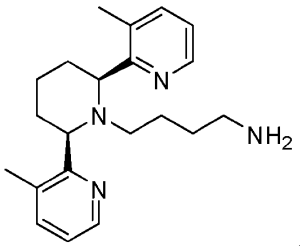
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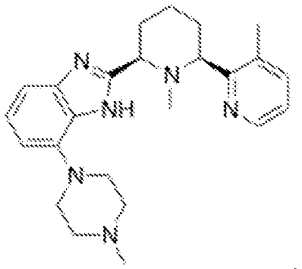
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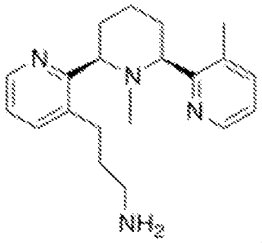
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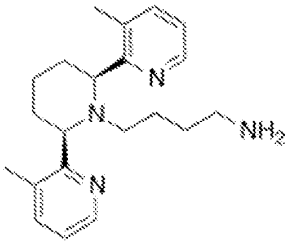
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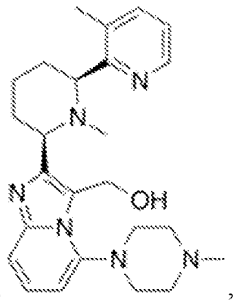
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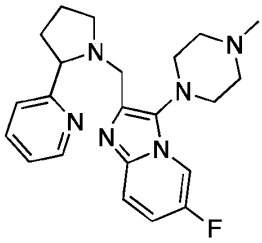
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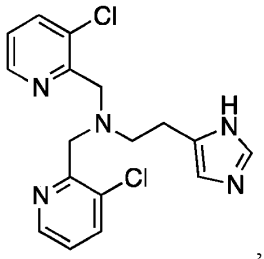
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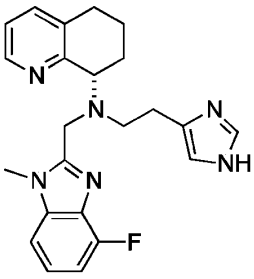
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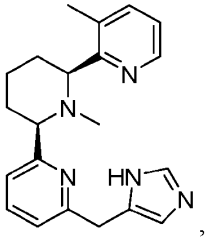
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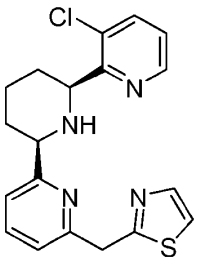
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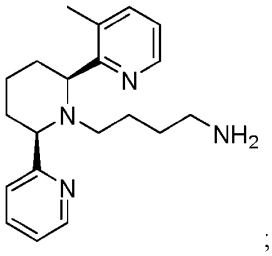
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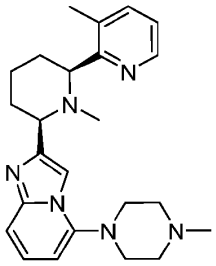
or a pharmaceutically acceptable salt or composition thereof.

[00177] In some embodiments, the CXCR4 inhibitor is plerixafor or a pharmaceutically acceptable salt thereof.

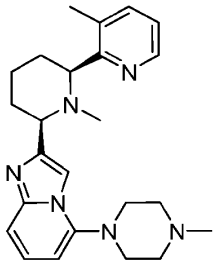
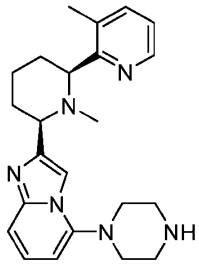
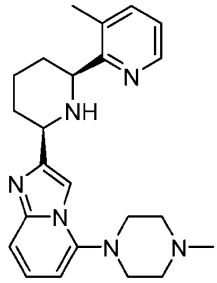
[00178] In some embodiments, the CXCR4 inhibitor is mavorixafor or a pharmaceutically acceptable salt or composition thereof.

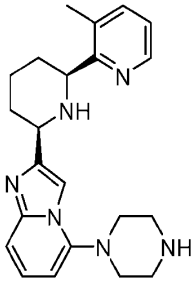
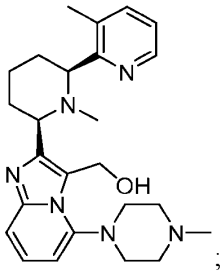
[00179] In some embodiments, the CXCR4 inhibitor is:



or a pharmaceutically acceptable salt thereof.

[00180] In some embodiments, the CXCR4 inhibitor is selected from the following:

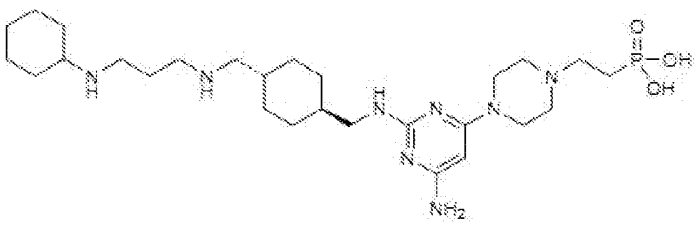
 ,  ,  ,

 , and  ;

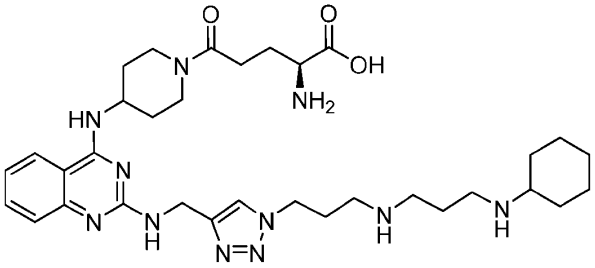
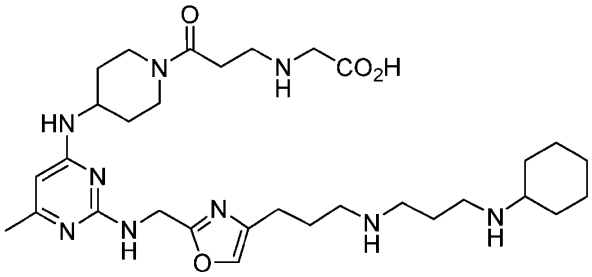
or a pharmaceutically acceptable salt thereof.

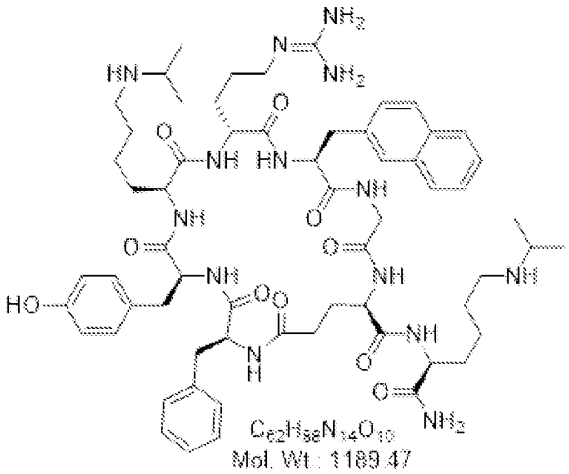
[00181] In some embodiments, the CXCR4 inhibitor is one of those described in Table 1, below. Each document listed in Table 1 is hereby incorporated by reference in its entirety.

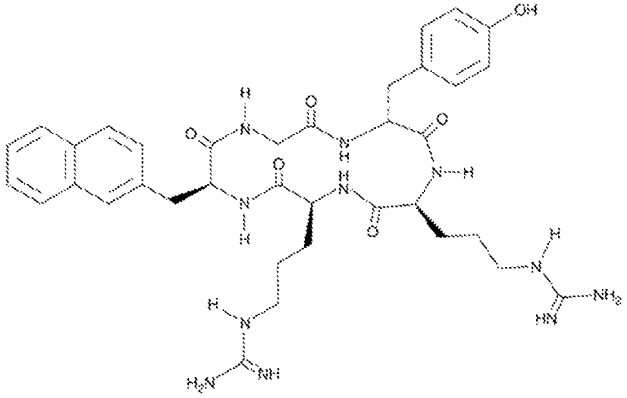
Table 1: Exemplary CXCR4 Inhibitors

Molecule/Company	Status and Relevant Information
Burixafor: TG-0054: Taigen Biotechnology, Inc. (2-{4-[6-amino-2-({[(1r,4r)-4-({[3-(cyclohexylamino)propyl] amino}methyl)cyclohexyl]methyl}amino)pyrimidin-4-yl]piperazin-1-yl}ethyl) phosphonic acid	 6/8/2014 - ScinoPharm Taiwan, Ltd. (twse:1789) specializing in the development and manufacture of active pharmaceutical ingredients, and TaiGen Biotechnology (4157.TW; F*TaiGen) jointly announced today the signing of a manufacturing contract for the clinical supply of the API of Burixafor. **NCT00822341:** Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of TG-0054 With Single IV Doses Escalation in Healthy Volunteers
Bioline RX: BTK140 BL-8040 Peptide [14-mer]	Clinical trials HSC mobilization; Multiple Myeloma; T-ALL; Metastatic Pancreatic; Acute Myeloid Leukemia; Metastatic Pancreatic; Metastatic Gastric; Metastatic NSCLC. **Beider et al. (2014) Mol Cancer Ther; 13(5); 1155–69.** **NCT02763384 BL-8040 and Nelarabine** for Relapsed or Refractory T-Acute Lymphoblastic Leukemia/ Lymphoblastic Lymphoma: the addition of BL-8040 to nelarabine as a salvage therapy for patients with relapsed/refractory T-ALL/LBL will result in a higher CR rate than nelarabine alone without an increase in toxicity **NCT01010880:** Safety Study of a Chemokine Receptor (CXCR4) Antagonist in ***Multiple Myeloma*** Patients

Molecule/Company	Status and Relevant Information
Bristol Myers: Ulocuplumab; BMS-936564 MDX-1338	Ulocuplumab is a fully human IgG4 kappa anti-CXCR4 monoclonal, being developed by Bristol-Myers Squibb as a potential oncology therapeutic. Peptide sequences and structural details for this antibody are available from its IMGT/mAb-DB record. BLAST sequence analysis of the heavy and light chain peptide sequences of ulocuplumab, reveal identical matches with sequences claimed in patent US8450464. This identifies clone F7GL as the likely candidate for ulocuplumab. **Kashyap et al. (2015) Oncotarget 7:2809-2822** **NCT01359657** BMS-936564 Alone and in Combination With Lenalidomide (Revlimid)/ Dexamethasone or Bortezomib (Velcade)/Dexamethasone in Relapsed/Refractory Multiple Myeloma **NCT01120457:** First in Human Study to Determine the Safety, Tolerability and Preliminary Efficacy of BMS-936564 in Subjects With Acute Myelogenous Leukemia and Selected B-cell Cancers
Proximagen Ltd: PRX177561	**Gravina et al. (2017) Journal of Hematology and Oncology 10:** Brain-penetrating CXCR4 antagonist
Pfizer: PF-06747143	Zhang et al. (2017) Scientific Reports; **Targeting primary acute myeloid leukemia with a new CXCR4 antagonist IgG1 antibody (PF-06747143) Phase I trial**
Polyphore: POL6326 (balixafortide)	**5NCT01905475:** CXCR4 Antagonism for Cell Mobilisation and Healing in *Acute Myocardial Infarction* (CATCH-AMI) (CATCH-AMI) **NCT01841476** Safety and Efficacy of POL6326 for Mobilization of Hematopoietic Stem Cells in Healthy Volunteers

Molecule/Company	Status and Relevant Information
CX549 (2S)-2-amino-5-[4-[[2-[[1-[3-[3-(cyclohexylamino)propylamino]propyl]triazol-4-yl]methylamino]quinazolin-4-yl]amino]piperidin-1-yl]-5-oxopentanoic acid	 **CX549** CX549 is a C-X-C chemokine receptor type 4 (CXCR4) antagonist [2], CXCR4 being the receptor for the chemokine CXCL12. CX549 is claimed as compound 63 in patent WO2016048861
BPRCX807	 **BPRCX807** **Song et al. (2021) PNAS 118:e2015433118**

Molecule/Company	Status and Relevant Information
LY2510924 Ei Lilly Cyclic Peptide	**Cyclo[Phe-Tyr-Lys(iPr)-D-Arg-2-Nal-Gly-D-Glu]-Lys(iPr)-NH2**  **Peng et al (2015) Molecular Cellular Therapeutics; 14:480-490** **NCT02737072**: A Study of LY2510924 in Combination With Anti-PD-L1 Antibody, Durvalumab (MEDI4736) in Participants With Solid Tumors
TC14012 peptidomimetic	Arg-Arg-Nal-Cys-Tyr-Cit-Lys-D-Cit-Pro-Tyr-Arg-Cit-Cys-Arg-NH2 **[RRACYXKXPYRXCR]** Disulphide bond between cysteine residues at positions 4 and 14; amidation of C-terminal arginine residue; residue 3 is 3-napthylalanine (Nal); residues 6 and 8 are citruliline (Cit) and D-citruliline (D-Cit) (N^5-aminocarbonylornithine) respectively
USL-311 Originally developed by Ligand; licensed to Usher-Smith **And to Proximagen**	 **WO2018162924A1** **NCT02765165:** Phase 1/2 Study of ***USL311 Alone and in Combination With Lomustine*** in Subjects With Advanced Solid

Molecule/Company	Status and Relevant Information
	Tumors and ***Relapsed/Recurrent Glioblastoma Multiforme (GBM);*** USL311 as Single Agent and in Combination With ***Lomustine (CCNU)*** in Subjects With Advanced Solid Tumors
Adimab -Antibodies	**US20100227774A1** Claim 1 claims an antibody that binds to loop 6 of human CXCR4.
FC131	
CTCE-9908 **Chemokine Therapeutics Corporation**	a peptide antagonist (amino acid sequence: KGVSLSYR-X-RYSLSVGK Faber et al. (2007) J. Biomedicine and Biotechnology 2007:Art. ID 26065
GMI 1359 **Glycomimetics Heterobifunctional Compounds**	WO 2016-089872 DISCLOSURE OF COMPOUNDS 9 and 16 CXCR4i - E-Selectin antagonist **Zhang et al.** Steele, et al. CANCER RESEARCH (2015): 75(Supp) Abstract 425 Abstract 425: A small molecule glycomimetic antagonist of E-selectin and CXCR4 (GMI-1359) prevents pancreatic tumor metastasis and improves chemotherapy
REVIEWS	Tamamura et al. (2008)Perspectives in Medicinal Chemistry 2:1-9 Debnath et al. (2013) Theranostics 3:47-75 Li et al. (2018) Eur. J. Med Chem. 149:30-44

Dosage and Formulation

[00182] In some embodiments, the dosage of CXCR4 inhibitor is a well-tolerated dose that achieves a satisfactory therapeutic result, without causing any severe or treatment-limiting toxicities.

[00183] As used herein, the term "well-tolerated" in reference to a dose of CXCR4 inhibitor (e.g., mavorixafor) means a dose that can be given to a patient without the patient experiencing any treatment-limiting toxicities. As used herein, "treatment-limiting toxicities" (TLTs) means that the patient experiences one or more of the toxicities in **Table 2**:

Table 2: Treatment-Limiting Toxicities

Toxicity	Treatment-Limiting Toxicity Criteria
Hematology	Grade 4 neutropenia lasting more than 7 consecutive days Grade 3 or 4 neutropenia with fever (temperature of > 38.5°C) Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding Grade 4 anemia Grade 4 lymphopenia
Non-Hematology Events	Any ≥ Grade 3 clinical events or laboratory events, except for the events described below, which are TLTs only if they meet the criteria below.
Gastrointestinal	Grade 3 or 4 nausea, vomiting, or diarrhea lasting ≥ 48 hours despite optimal medical management
Hepatobiliary	≥ Grade 2 total bilirubin elevation with ≥ Grade 2 ALT/AST elevation ≥ Grade 3 ALT/AST elevation lasting ≥ 5 days or Grade 4 ALT/AST elevation
Pneumonitis	Grade 2 pneumonitis lasting > 7 days despite optimal treatment
Hypertension	Grade 3 hypertension lasting > 7 days despite optimal treatment
Infection	Grade 3 infection or fever in the absence of neutropenia lasting > 5 days
Electrolytes	Grade 3 electrolyte abnormalities lasting > 7 days
Rash and/or photosensitivity	≥ Grade 3 rash or photosensitivity lasting > 7 days despite optimal treatment
Fatigue	Grade 3 electrolyte abnormalities lasting > 7 days

Immune-related toxicities (except pneumonitis)	Grade 3 immune related toxicities lasting > 7 days despite optimal treatment
Others	Any other ≥ Grade 2 toxicity that, in the opinion of a treating physician is considered to be a clinically unacceptable risk

Grading: As defined by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events, version 4.03).

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; TLT = treatment-limiting toxicity.

[00184] In some embodiments, a CXCR4 inhibitor (e.g., mavorixafor), or a pharmaceutically acceptable salt thereof, can be administered orally (PO) once daily (QD). In some embodiments, the CXCR4 inhibitor is administered orally (PO) once daily (QD). In some embodiments, the CXCR4 inhibitor is administered orally (PO) twice daily (BD).

[00185] In some embodiments, the CXCR4 inhibitor described herein is mavorixafor, or a pharmaceutically acceptable salt thereof.

[00186] In certain embodiments, the mavorixafor, pharmaceutically acceptable salt thereof, or composition comprising mavorixafor or a pharmaceutically acceptable salt thereof is administered orally (PO) once daily (QD) or twice daily (BID), in an amount from about 25 mg to about 800 mg daily. In certain embodiments, the dosage composition may be provided twice a day in divided dosage, approximately 12 hours apart. In other embodiments, the dosage composition may be provided once daily. The terminal half-life of mavorixafor has been generally determined to be between about 12 to about 24 hours, or approximately 14.5 hrs. In certain embodiments, the dosage of mavorixafor useful in the invention is from about 25 mg to about 1200 mg daily. In other embodiments, the dosage of mavorixafor useful in the invention may range from about 25 mg to about 1000 mg daily, from about 50 mg to about 800 mg daily, from about 50 mg to about 600 mg daily, from about 50 mg to about 500 mg daily, from about 50 mg to about 400 mg daily, from about 100 mg to about 800 mg daily, from about 100 mg to about 600 mg daily, from about 100 mg to about 500 mg daily, from about 100 mg to about 400 mg daily; from about 200 mg to

about 800 mg daily, from about 200 mg to about 600 mg daily, from about 300 mg to about 600 mg daily, from about 200 mg to about 500 mg daily from about 200 mg to about 400 mg daily.

[00187] In other embodiments, the dosage of mavorixafor or a pharmaceutically acceptable salt thereof is administered in a dosage range from about 100 mg to about 800 mg daily, from about 200 mg to about 600 mg daily, from about 300 mg to about 500 mg daily, or from about 350 mg to about 450 mg daily; or in a daily dosage of about 100 mg/day; 125 mg/day; 150 mg/day; 175 mg/day; 200 mg/day; 225 mg/day; 250 mg/day; 275 mg/day; 300 mg/day; 325 mg/day; 350 mg/day; 400 mg/day; 425 mg/day; 450 mg/day; 475 mg/day; 500 mg/day; 525 mg/day; 550 mg/day; 575 mg/day; 600 mg/day; 625 mg/day; 650 mg/day; 675 mg/day; 700 mg/day; 725 mg/day; 750 mg/day; 775 mg/day or 800 mg/day. In unusual cases, the dosage of mavorixafor or a pharmaceutically acceptable salt thereof may be administered in an amount in excess of 800 mg/day, while taking care to minimize or avoid any adverse effects of such administration.

[00188] In some embodiments of the methods described herein, the dosage (e.g., starting dose, first dose, second dose, third dose, fourth dose, etc.) of G-CSF, GM-CSF, or a variant of either, is in a range of about 0.2 mcg/kg to 6.0 mcg/kg. In some embodiments, the dosage is in a range of about 0.2 mcg/kg to 0.5 mcg/kg, 0.2 mcg/kg to 0.8 mcg/kg, 0.2 mcg/kg to 1.0 mcg/kg, 0.2 mcg/kg to 1.2 mcg/kg, 0.5 mcg/kg to 0.8 mcg/kg, 0.5 mcg/kg to 1.0 mcg/kg, 0.5 mcg/kg to 1.5 mcg/kg, 1.0 mcg/kg to 1.5 mcg/kg, 1.0 mcg/kg to 1.8 mcg/kg, , 1.0 mcg/kg to 2.0 mcg/kg, 1.5 mcg/kg to 2.0 mcg/kg, 1.5 mcg/kg to 2.5 mcg/kg, 2.0 mcg/kg to 2.5 mcg/kg, 2.0 mcg/kg to 3.0 mcg/kg, 2.5 mcg/kg to 3.0 mcg/kg, 2.5 mcg/kg to 3.5 mcg/kg, 3.0 mcg/kg to 3.5 mcg/kg, 3.0 mcg/kg to 4.0 mcg/kg, 3.5 mcg/kg to 4.0 mcg/kg, 3.5 mcg/kg to 4.5 mcg/kg, 4.0 mcg/kg to 4.5 mcg/kg, 4.0 mcg/kg to 5.0 mcg/kg, 4.5 mcg/kg to 5.0 mcg/kg, 4.5 mcg/kg to 5.5 mcg/kg, 5.0 mcg/kg to 5.5 mcg/kg, 5.0 mcg/kg to 6.0 mcg/kg, once or twice daily, every other day, every third day, weekly, every 2 weeks, monthly, or as otherwise prescribed by a treating physician. Administration may be by injection, either intravenous (iv), subcutaneous (sc) or intramuscular (im), or as otherwise prescribed by a treating physician.

[00189] In certain embodiments, a method disclosed herein may comprise administering a composition comprising mavorixafor, or a pharmaceutically acceptable salt thereof, one or more diluents, a disintegrant, a lubricant, a flow aid, and a wetting agent. In some embodiments, a disclosed method comprises administering a composition comprising 25 mg to 1200 mg mavorixafor, or a pharmaceutically acceptable salt thereof, microcrystalline cellulose, dibasic

calcium phosphate dihydrate, croscarmellose sodium, sodium stearyl fumarate, colloidal silicon dioxide, and sodium lauryl sulfate. In some embodiments, a disclosed method comprises administering a unit dosage form wherein said unit dosage form comprises a composition comprising 25 mg to 200 mg mavorixafor, or a pharmaceutically acceptable salt thereof, microcrystalline cellulose, dibasic calcium phosphate dihydrate, croscarmellose sodium, sodium stearyl fumarate, colloidal silicon dioxide, and sodium lauryl sulfate. In certain embodiments, a disclosed method comprises administering a unit dosage form comprising a composition comprising mavorixafor, or a pharmaceutically acceptable salt thereof, present in an amount of about 25 mg, about 40 mg, about 50 mg, about 80 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, or about 1200 mg. In some embodiments, a provided composition (or unit dosage form) is administered to the patient once per day, twice per day, three times per day, or four times per day. In some embodiments, a provided composition (or unit dosage form) is administered to the patient once per day or twice per day.

[00190] In some embodiments, a disclosed method comprises administering a unit dosage form comprising a composition comprising:

(a) mavorixafor, or a pharmaceutically acceptable salt thereof, as about 10-30% by weight of the composition;

(b) microcrystalline cellulose as about 60-80% by weight of the composition;

(c) croscarmellose sodium as about 5-10% by weight of the composition;

(d) sodium stearyl fumarate as about 0.5-2% by weight of the composition; and

(e) colloidal silicon dioxide as about 0.1-1.0 % by weight of the composition.

[00191] In some embodiments, a disclosed method comprises administering a unit dosage form comprising a composition comprising:

(a) mavorixafor, or a pharmaceutically acceptable salt thereof, as about 15% by weight of the composition;

(b) microcrystalline cellulose as about 78% by weight of the composition;

(c) croscarmellose sodium as about 6% by weight of the composition;

(d) sodium stearyl fumarate as about 1% by weight of the composition; and

(e) colloidal silicon dioxide as about 0.2% by weight of the composition.

[00192] In some embodiments, a disclosed method comprises administering a unit dosage form comprising a composition comprising:

(a) mavorixafor, or a pharmaceutically acceptable salt thereof, as about 10-20% by weight of the composition;

(b) microcrystalline cellulose as about 25-40% by weight of the composition;

(c) dibasic calcium phosphate dihydrate as about 35-55% by weight of the composition;

(d) croscarmellose sodium as about 4-15% by weight of the composition;

(e) sodium stearyl fumarate as about 0.3-2% by weight of the composition;

(f) colloidal silicon dioxide as about 0.1-1.5% by weight of the composition; and

(g) sodium lauryl sulfate as about 0.1-1.5% by weight of the composition.

[00193] In some embodiments, a disclosed method comprises administering a unit dosage form comprising a composition comprising:

(a) mavorixafor, or a pharmaceutically acceptable salt thereof, as about 13% by weight of the composition;

(b) microcrystalline cellulose as about 32% by weight of the composition;

(c) dibasic calcium phosphate dihydrate as about 44% by weight of the composition;

(d) croscarmellose sodium as about 8% by weight of the composition;

(e) sodium stearyl fumarate as about 1.4% by weight of the composition;

(f) colloidal silicon dioxide as about 0.4% by weight of the composition; and

(g) sodium lauryl sulfate as about 0.7% by weight of the composition.

[00194] In some embodiments, a disclosed method comprises administering a unit dosage form comprising a composition comprising:

(a) mavorixafor, or a pharmaceutically acceptable salt thereof, as about 35-75% by weight of the composition;

(b) microcrystalline cellulose as about 5-28% by weight of the composition;

(c) dibasic calcium phosphate dihydrate as about 7-30% by weight of the composition;

(d) croscarmellose sodium as about 2-10% by weight of the composition;

(e) sodium stearyl fumarate as about 0.3-2.5% by weight of the composition;

(f) colloidal silicon dioxide as about 0.05-1.2% by weight of the composition; and

(g) sodium lauryl sulfate as about 0.2-1.2% by weight of the composition.

[00195] Inasmuch as it may be desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for co-administration of the compositions. Thus the kit of the invention includes two or more separate pharmaceutical compositions, at least one of which contains a compound of the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

[00196] The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically includes directions for administration and may be provided with a memory aid.

[00197] The examples below explain the invention in more detail. The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. The present invention, however, is not limited in scope by the exemplified embodiments, which are intended as illustrations of single aspects of the invention only, and methods which are functionally equivalent are within the scope of the invention. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

[00198] The contents of each document cited in the specification are herein incorporated by reference in their entireties.

EXEMPLIFICATION

Example 1: A Phase 1b/2, Open-Label, Multicenter Study of Mavorixafor in Patients with Congenital Neutropenia and Chronic Neutropenia Disorders

[00199] A 2-part, open-label, multicenter study of mavorixafor (X4P-001) is conducted in participants diagnosed with chronic neutropenia.

Table 1: Study Objectives and Endpoints

Objectives	Endpoints
Part 1	
Primary	
To evaluate the safety and tolerability of a single dose of mavorixafor.	Safety and tolerability of mavorixafor in participants, as assessed by TEAEs, clinical laboratory evaluations, vital signs, electrocardiogram (ECG) assessments, and physical examinations.
To evaluate the effect of a single dose of mavorixafor on ANC.	Change and fold change from Baseline in ANC over 8 hours on D1 following a single dose of mavorixafor.
Secondary	
To characterize the PK profile of a single dose of mavorixafor.	Serum concentrations of mavorixafor in relation to ANC and area under the curve (AUC) for ANC (AUC_{ANC}) over 8 hours.
Exploratory	
To evaluate the effect of a single dose of mavorixafor on ALC, total WBC, and absolute monocyte count (AMC).	Change and fold change from Baseline in ALC, AMC, and WBC and AUC for ANC, ALC, AMC, and WBC (AUC_{ANC}, AUC_{ALC}, AUC_{AMC}, AUC_{WBC}) over 8 hours
To evaluate the effect of a single dose of mavorixafor on lymphocyte subsets.	Immunophenotyping of lymphocyte subsets as assessed by fluorescence activated cell sorting.
Part 2	
Primary	
To evaluate the safety and tolerability of 6-month chronic dosing of mavorixafor.	Safety and tolerability of mavorixafor in participants, as assessed by TEAEs, clinical laboratory evaluations, vital signs, ECG assessments, and physical examinations.

Objectives	Endpoints
To evaluate the effect of 6-month chronic dosing of mavorixafor on ANC.	Change and fold change from Baseline in ANC at D1, month 1 (M1), M3, and M6 visits.
Secondary	
To characterize the multidose PK profile of mavorixafor during 6 months of chronic dosing.	Serum concentrations of mavorixafor following 6 months of dosing.
To evaluate the effect of 6-month chronic dosing of mavorixafor on ALC, total WBC, and AMC.	Change and fold change from Baseline in ALC, AMC, and WBC and AUC_{ANC}, AUC_{ALC}, AUC_{AMC}, AUC_{WBC}) during 6 months of dosing.
Exploratory	
To evaluate the effect of 6-month chronic dosing of mavorixafor on lymphocyte subsets.	Phenotyping/gene expression profiling as assessed by Epiontis identification (EpiID) or quantitative polymerase chain reaction (qPCR).
To evaluate the incidence and duration of infection-related events during 6 months of chronic mavorixafor dosing, including febrile episodes, oral ulcers, hospitalizations, and antibiotic use.	Incidence and duration of infection-related events, including infection-related health care utilization assessed by an administered questionnaire.
To evaluate success of G-CSF dose adjustment in participants treated concurrently with mavorixafor (QD for 6 months) and G-CSF.	G-CSF dose adjustment as measured by reduction in total monthly dose.
To evaluate the change in G-CSF levels in participants following acute and 1 month of chronic mavorixafor dosing.	Change in G-CSF levels after acute (1 day), 1 month and 6 months of chronic mavorixafor dosing as well as at the 30D post EOT visit

Objectives	Endpoints
To evaluate the change in cytokine levels in participants following acute and 1 month of chronic mavorixafor dosing.	Change in cytokine levels after acute (1 day), 1 month and 6 months of chronic mavorixafor dosing as well as at the 30D post EOT visit
To evaluate the change in osteocalcin levels in participants following acute and 1 month of chronic mavorixafor dosing.	Change in osteocalcin levels after acute (1 day), 1 month and 6 months of chronic mavorixafor dosing as well as at the 30D post EOT visit
To evaluate the C-X-C chemokine receptor type 4 (CXCR-4) pathway in participants treated with chronic mavorixafor.	Changes in biomarkers of the CXCR-4 pathway via peripheral blood mononuclear cells (PBMCs) and serum/plasma collection including but not limited to CXCR-4 internalization, circulating levels of cytokines, G-CSF, and abnormalities of neutrophil morphology on peripheral blood smears.
To evaluate the incidence and severity of bone pain.	Incidence and severity of bone pain during 6 months of dosing as assessed by an administered questionnaire.
To evaluate the response to treatment with mavorixafor as measured by the participant.	Patient-reported outcomes (PROs) related to impact of chronic neutropenia via Patient-Reported Outcomes Measurement Information System Fatigue Short Form (PROMIS SF), Pediatric Quality of Life Inventory™ (PedsQL™) in pediatric and adult populations, and Patient Global Impression of Change (PGI-C).
To evaluate the response to treatment with mavorixafor as measured by the Investigator.	Clinician-reported outcome (ClinRO) related to impact of chronic neutropenia via Clinical Global Impression of Change (CGI-C).

Objectives	Endpoints
To evaluate potential molecular markers from physiological pathways that may be affected by mavorixafor (optional).	Blood samples for exploratory analysis, including but not limited to, PBMCs, CD34+ cells, whole blood samples for immunophenotyping of neutrophils, whole blood for phagocytosis assay, and bone-specific alkaline phosphatase isoform.

[00200] Study design Overview: A 2-part, open-label, multicenter study of mavorixafor in participants diagnosed with CN disorder defined as follows: In Part 1 and Part 2, participants not on G-CSF: CIN is defined as participants presenting with an ANC of ≤ 1,000 cells/μL, diagnosed at least 6 months prior to the Screening visit, and not attributable to drugs or specific genetic, infectious, inflammatory, systemic autoimmune disorder, or malignant cause as determined in the clinical evaluation performed as part of routine clinical care. Participants diagnosed with autoimmune neutropenia on the basis of anti-neutrophil antibodies are considered as having CIN and can be enrolled in the trial; *Note*: For analysis purposes, participants with diagnosed autoimmune neutropenia will be grouped with idiopathic neutropenia. Congenital Neutropenia conditions, defined as any congenital neutropenia, regardless of genetic variant, in participants presenting with an ANC of ≤ 1,000 cells/μL; Cyclic Neutropenia conditions will be eligible to enroll if at the time of enrollment participants are neutropenic defined as ANC of ≤ 1,000 cells/μL. In Part 1 and Part 2, participants on G-CSF, independent of the type of neutropenia, must not have a lower limit ANC at the Screening visit and should not have an upper ANC limit ≥ 10,000 cells/μL. Eligible participants must be ≥ 12 years of age and weigh ≥ 15 kg.

Part 1:

[00201] Participants have two 8-hour study visits during the study: the day before mavorixafor administration (Baseline [Day (D)-1]) and at the administration of mavorixafor (D1). Documentation of mavorixafor administration including date, time, and dose of mavorixafor will be recorded.

[00202] Starting at Screening, participants may not modify their G-CSF regimen unless it is due to infection or other medically justified reason. Any G-CSF treatment including any change after Screening must be stabilized for ≥ 14 days prior to Baseline (D-1) assessments. Any G-CSF

administration should occur at the same time of day as mavorixafor administration. Any change in G-CSF treatment will be documented in the concomitant medication page in the electronic database.

[00203] Screening Assessments: Participants are advised of the value of genetic screening in the discussion of the trial design and objectives. After signing the informed consent form (ICF), participants undergo a blood test (or buccal sample) to complete genetic screening for genetic variants in genes known to cause chronic neutropenia using targeted NGS, unless the participant has a prior historical record of genetic status documented and provided to the study site or refuses genetic testing.

[00204] Participants are screened for eligibility at a Screening visit occurring ≤ 28 days prior to D1. Screening (D-28 to D-1) Assessments include: Physical examination; Medical/surgical history including infections within the past year; Height and weight; Vital signs (heart rate [HR], blood pressure [BP], and temperature); ECG at time 0; NGS genotyping, if applicable; Blood assessment (hematology, serum chemistry, and serology measures); Serum pregnancy test for women of childbearing potential (WOCBP) (Note: Follicle-stimulating hormone (FSH) test is performed at Screening to confirm postmenopausal status in female participants who have been amenorrheic for at least 12 consecutive months); Concomitant medication; AE monitoring.

[00205] Baseline assessments include: Inclusion/exclusion criteria (G-CSF stability); Symptom-directed physical examination; Vital signs (HR, BP, and temperature); Blood sampling to monitor ALC, AMC, ANC, and WBC levels at the following times: 0, 60 minutes (± 5 minutes), and 2, 3, 4, 6, and 8 hours (± 15 minutes each). These Baseline values will be averaged and will be thereafter referred to as "Baseline" (i.e., Baseline ALC); Blood sampling to monitor the immunophenotyping profile of lymphocyte subsets as assessed by fluorescence-activated cell sorting (FACS) at time 0, 4, and 8 hours; Blood safety assessments (hematology, serum chemistry) and urine pregnancy test for WOCBP; Concomitant medication; AE monitoring.

[00206] The administration of mavorixafor occurs on D1. All eligible participants are treated with mavorixafor orally (PO) QD in the morning for 1 day. The mavorixafor dose is 400 mg QD for adults. For adolescents (12 to < 18 years of age) weighing > 50 kg, the mavorixafor dose is 400 mg QD. Adolescents weighing ≤ 50 kg will receive mavorixafor 200 mg QD.

[00207] Post-treatment Assessments: Participants are monitored for safety throughout the study. Investigators may perform additional blood draws to monitor participant safety. All

participants receive a post treatment Safety Follow-up Phone Call (remote) at 7D post-D1 (+ 2D).

Part 2:

[00208] In Part 2, participants receive QD PO dosing of mavorixafor for 6 months. In Part 2, participants who are taking chronic G-CSF as background therapy are allowed to continue on their individualized G-CSF dosing for a minimum of 8 weeks. After 8 weeks, Investigators are encouraged to consider reducing the dose and/or frequency of G-CSF as long as the participant's ANC remains > 500 cells/μL. For participants who prematurely discontinue from the study, an EOT visit is conducted followed by an EOS/Safety follow-up visit 30 days (± 14 days) post–last dose of study treatment.

[00209] Screening Assessments: In some instances, eligible Part 1 participants directly roll over to the Baseline (D-3 to D-1) visit in Part 2 following the Day 7 (+ 2D) Safety Follow-up phone call in Part 1. If eligible participants do not complete the Baseline visit of Part 2 $\leq$ 6 weeks following the Safety Follow-up phone call, participants are re-screened to confirm eligibility. After signing the ICF, participants are screened for eligibility (i.e., meeting the full inclusion and exclusion criteria) unless an extension is granted by the Medical Monitor.

[00210] In some instances, participants do not need to enter Part 1 and start with the Part 2 Screening visit.

[00211] Screening ($\leq$ 6 weeks prior to D1) Assessments include: Infection Assessments (Note: Infection assessments should take place prior to any other procedures); CN treatment history, Medical/surgical history including infections within the past year; NGS genotyping, if applicable; Physical examination (complete); Height and weight; Vital signs (HR, BP, and temperature); ECG at time 0 and 2 hours (± 15 minutes); Blood assessment (hematology, serum chemistry, and serology measures); Serum pregnancy test for WOCBP (Note: FSH test is performed at Screening to confirm postmenopausal status in female participants who have been amenorrheic for at least 12 consecutive months); Concomitant medication monitoring; AE monitoring; Urinalysis.

[00212] Baseline (D-3 to D-1) assessments include: Symptom-directed physical examination; Vital signs (HR, BP, and temperature); Infection Assessments; PRO and bone pain and G-CSF burden administered questionnaires (Note: PRO and administered questionnaires are to be completed after infection assessments but before any other procedures. The PGI-C is not to be assessed at Baseline); Blood sampling to monitor ALC, AMC, ANC, and WBC levels at the following times: 0, 60 minutes (± 5 minutes), and 2, 3, 4, 6, and 8 hours (± 15 minutes each). These

Baseline values are averaged and are thereafter referred to as "Baseline" (i.e., Baseline ALC); Phenotyping/gene expression profiling as assessed by EpiID or qPCR at time 0, 4, and 8 hours (± 15 minutes each); Ophthalmologic (all study participants) (can occur anytime between the Screening visit and D-1); Fasted endocrine evaluation of hypothalamic-pituitary-gonadal axis (H-P-G) for testicular safety assessment (male participants) (Note: It is recommended that male participants (12 to ≤ 50 years old) be fasted for 12 hours prior to hormonal testing); G-CSF, cytokine, and osteocalcin levels (to establish Baseline values); Optional blood samples for exploratory analysis; Blood safety assessments (hematology, serum chemistry) and urine pregnancy test for WOCBP; Concomitant medication and AE monitoring; Urinalysis.

[00213] The administration of mavorixafor occurs daily for 6 months starting on D1. The mavorixafor dose is 400 mg QD for adults. For adolescents (12 to < 18 years of age) weighing > 50 kg, the mavorixafor dose is 400 mg QD. Adolescents weighing ≤ 50 kg receive mavorixafor 200 mg QD. Dose reductions are allowed only for tolerability or safety reasons but only with written approval by the Medical Monitor and the Sponsor.

[00214] Treatment assessments include: Infection assessments throughout the treatment period (Note: Infection assessments should take place prior to any other procedures); PRO, ClinRO, and bone pain and G-CSF burden questionnaires administered at M1, M3, and M6 (Note: PRO, ClinRO, and the bone pain and G-CSF burden questionnaire should take place after infection assessments but prior to any other scheduled assessments); Symptom-directed physical examination on D1, M1, M3, and M6; Body weight at time 0 on D1, M1, M2, M3, M4, M5, M6; Vital signs (HR, BP, and temperature) on D1, M1, M2, M3, M4, M5, M6; ECG is performed at time 0- and 2-hours post-dose (± 15 minutes) on D1, M1, and M6 (Note: When performed on the same day, ECG must be done before blood draws); Consider G-CSF dose adjustment at M2, M3, M4, M5, and M6; Blood sampling to monitor ALC, AMC, ANC, and WBC levels and PK sampling is performed on D1, M1, M3, and M6 at the following times: 0 (pre-dose and up to 15 minutes prior), 60 minutes (± 5 minutes), and 2, 3, 4, 6, and 8 hours (± 15 minutes each) post-dose (Note: 8-hour blood sampling collection should be performed at the same time(s) as for prior visits to avoid any diurnal variation); Peak and trough PK sampling and ALC, AMC, ANC, and WBC sampling occurs at M2, M4, and M5 (Note: Trough is defined as pre-dose (time 0) and peak is defined as occurring 2 to 4 hours post-dose); Phenotyping/gene expression profiling as assessed by EpiID or qPCR at time 0 (pre- dose), 4 and 8 hours (± 15 minutes each) post-dose at D1, M1,

and M6; Optional blood samples for exploratory analysis at M1, M3, and M6; G-CSF, cytokine, and osteocalcin levels on D1, M1, M6, and 30D post EOT visits; Ophthalmologic (all study participants) assessment at M6. The M6 EOT ophthalmology assessment window extends through the end of the safety follow up visit window; Fasted endocrine evaluation of H-P-G axis for testicular safety assessment at M6 (male participants) (Note: It is recommended that male participants (12 to ≤ 50 years old) be fasted for 12 hours prior to hormonal testing); Blood safety assessments (hematology, serum chemistry) and urine pregnancy test for WOCBP (Note: In the event of an infection during the study, participants may receive any SOC including antibiotics and/or procedures (i.e., abscess drainage)); Mavorixafor compliance check; Concomitant medication and AE monitoring at every visit; Urinalysis at every visit.

[00215] Participants will be monitored for safety throughout the study. Investigators may perform additional blood draws to monitor participant safety. All participants have an EOT Follow-up visit scheduled for 30D post-EOT (± 14D).

[00216] Post-treatment assessments include: Infection assessment; (Note: Infection assessment should take place prior to any other procedures); PRO, ClinRO, and bone pain and G-CSF burden questionnaires administered (Note: PRO, ClinRO, and administered questionnaires should take place after infection assessments prior to other scheduled assessments); Symptom directed physical examination; Body weight; Vital signs (HR, BP, and temperature); ECG at time 0 and 2 hours (± 15 minutes); One-time ALC/AMC/ANC/WBC draw (optional); G-CSF, cytokine, and osteocalcin levels on D1, M1, M6, and 30D post EOT visits; Blood safety assessments (hematology, serum chemistry, and serology) and urine pregnancy test for WOCBP (Note: In the event of an infection during the study, participants may receive any SOC including antibiotics and/or procedures (i.e., abscess drainage)); Concomitant medication and AE monitoring; urinalysis.

[00217] An unscheduled visit may occur in Part 1, or Part 2, for any medically justified reason. These visits may be in-person or via telephone. If performed remotely, any clinically mandated laboratory tests are performed using a local laboratory and entered as unscheduled test results (identified as infection related). These tests may include, at the Investigator's discretion, complete blood count (including but not limited to ANC), cultures, C-reactive protein, imaging studies, and any other relevant evaluations.

[00218] Requests for home health visits are reviewed and approved by on a case-by-case basis.

Home health visits are an option applicable for all study visits, including Screening and Baseline. All efforts are made to ensure home health visits are conducted to the same standard as in-person visits. In the event any assessment is not collected at the home health visit, it will be documented as a protocol deviation and the Investigator or designee will follow-up via phone call or at the next scheduled visit to ensure participant safety was not impacted by the missed assessment.

[00219] Up to approximately 50 participants are enrolled in total. Of the 50 participants enrolled: No more than approximately 40 participants are planned for enrollment diagnosed with CIN; No more than approximately 3 participants are planned for enrollment diagnosed with cyclic neutropenia; No more than approximately 7 participants are planned for enrollment diagnosed with congenital neutropenia. All efforts are made to enroll at least 20 participants not on G-CSF across all disease condition subtypes.

Table 2: Monitoring and Management Procedures for Potential Risks for Mavorixafor

Potential Risk	**Clinical Monitoring and Risk Management Procedures**
Participant monitoring and management are conducted throughout the trial.	• In **Part 1**, mavorixafor is administered by study personnel; the participants will be observed post-dose. • In **Part 2**, mavorixafor is administered in the clinic and at home. • In **Part 1** and **Part 2**, ongoing monitoring is conducted for AEs. • In **Part 1** and **Part 2**, ongoing monitoring of all concomitant medications (prescription, over-the-counter, herbal, and vitamins) is conducted to avoid potential drug-drug interactions. • In **Part 1** and **Part 2**, safety laboratory tests is conducted throughout the study • In **Part 1** and **Part 2,** regularly scheduled clinical evaluations, including vital signs and symptom-directed physical examinations, are conducted In **Part 1** and **Part 2,** 12-lead ECGs are performed throughout the study
Mavorixafor is primarily metabolized by CYP3A4. Monitoring and management of concomitant medications is conducted.	Concomitant use of strong inhibitors of CYP3A4 should be done with caution, with approval of the Medical Monitor. • Grapefruit, grapefruit juice, and Seville orange containing products are prohibited.

Potential Risk	Clinical Monitoring and Risk Management Procedures
Mavorixafor is a strong inhibitor of CYP2D6.	• Unless otherwise indicated by MM following review, drugs which are primarily metabolized by or are sensitive substrates of CYP2D6 for a period starting 14 days or 5 half-lives, whichever is longer, prior to administration of mavorixafor and during the study.
Emergency use of prohibited medication.	• If use of a prohibited medication cannot be avoided, the Investigator can prescribe the prohibited medication and hold the study treatment. • The Investigator or designee should report the emergency use of the prohibited medication to the Medical Monitor within 24 hours.
All AEs should be reported to the Sponsor.	• The Sponsor conducts a routine review of all reported AEs to determine safety risks and management. • Any risks that will potentially impact participant safety are shared with the Investigator.
LFT abnormalities were observed in rats with a salt of mavorixafor.	• Safety laboratory tests including monitoring of liver function occur during the study.
Eye anomalies were observed in 1 animal model using a different salt form than that being studied in this protocol.	• Ophthalmology examination and monitoring occur during the study.
Embryo-fetal toxicity was observed in the animal model of an approved CXCR-4 antagonist, Mozobil (plerixafor).	• WOCBP who are heterosexually active must agree to use an effective method of contraception, during the study and through 4 weeks after the last dose of study medication, or abstain from sexual intercourse for this time. • Male participants are advised to use an effective method of contraception, to prevent passage of study intervention through the ejaculate during the study and through 4 weeks after the last dose of study medication.
It has not been examined whether mavorixafor is excreted in human milk.	• Breastfeeding participants are excluded from study participation.
Testicular toxicity was observed at the highest dose tested in the chronic dog toxicology study.	• Monitoring for testicular development via testicular safety monitoring (male study participants 12 to ≤ 50 years of age only) is done every 6 months

[00220] Participant Inclusion Criteria: All participants (Part 1 and Part 2) must: Sign the ICF and be willing and able to comply with the protocol; Be ≥ 12 years of age at the time of signing

the ICF; Weigh ≥ 15 kg; Agree to use a highly effective form of contraception if sexually active; Participants may be eligible for the study whether they are on or off G-CSF treatment (Note: Participants who are on G-CSF must be on a stable dose for ≥ 14 days prior to the Baseline visit); (Note: Participants who are on G-CSF will not have an ANC lower limit at the Screening visit but should not have an ANC ≥ 10,000 cells/μL); (Note: Participants who are not on G-CSF must be off for ≥ 14 days prior to the Baseline visit and have an ANC ≤ 1,000 cells/□L at the Screening visit); Have been diagnosed with chronic neutropenia ≥ 6 months prior to the Screening visit that is not attributable to medications, active or recent (≤ 3 months) infections, or malignant cause (Note: Participants with Shwachman-Diamond syndrome, Cohen syndrome, and warts, hypogammaglobulinemia, infections and myelokathexis (WHIM) syndrome are eligible. Other types of chronic neutropenic disorders may also be eligible for enrollment upon discussion and approval with Sponsor and Study Medical Monitor); Participants with congenital neutropenia must have results of the genetic testing before enrolling in the study unless they had refused genetic testing; Part 2: Participants enrolled in the study before implementation of Protocol Version 8.0 must have completed Part 1 and exhibited a positive response to treatment (i.e., had a ≥ 2-fold increase in Baseline ANC or reached an ANC of ≥ 1,500 cells/μL on D1 post-dose); Part 2: Participant has a history of symptomatic chronic neutropenia confirmed by the Investigator.

[00221] Participants with any of the following are excluded from participation in the study: Known systemic hypersensitivity to the mavorixafor drug substance or its inactive ingredients; Is pregnant, breastfeeding, or plans to become pregnant over the next 8 months; Known history of a positive serology or viral load for HIV or a known history of acquired immune deficiency syndrome; Known active SARS-CoV-2 virus (COVID-19) infection or a positive test within the local accepted clinical and governmental guidelines for a communicable window (Note: Participants with prior COVID-19 exposure are permitted to enroll if they have a negative test and conform with local guidelines); (At the Screening visit, has laboratory test results meeting one or more of the following criteria: Positive hepatitis C virus (HCV) antibodies with confirmation by HCV-ribonucleic acid polymerase chain reaction reflex testing; Positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb) Note: If a participant tests negative for HBsAg but positive for HBcAb, the participant would be considered eligible if the participant tests positive for the antibody to HBsAg reflex testing)); (At the Screening visit, has laboratory test results meeting ≥ 1 of the following criteria: Hemoglobin < 9.0 g/dL; Platelets < 30,000/μL;

Estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 m2, as estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; Serum aspartate transaminase > 2.5 × upper limit of normal (ULN); Serum alanine transaminase > 2.5 × ULN; Total bilirubin > 1.5 × ULN (unless due to Gilbert's syndrome, in which case total bilirubin ≥ 3.0 × ULN and direct bilirubin > 1.5 × ULN)); (≤ 14 days before D1, received any of the following treatments: Systemic glucocorticoids (> 5 mg prednisone equivalent per day); Medication prohibited based on CYP2D6 potential for interaction); Has an infection requiring use of systemic antibiotics ≤ 4 weeks before the Baseline visit; Has a medical or personal condition that may potentially compromise the safety of the participant, or may preclude the participant's successful completion of the clinical study or that in the opinion of the Investigator or the Sponsor could interfere with the objectives of the study (Examples include poorly controlled chronic conditions such as, hypertension, diabetes, coronary disease, congestive heart failure, asthma, chronic obstructive pulmonary disease, cardiac arrhythmia); Has had major surgery ≤ 4 weeks before the Baseline visit; Inability to ingest mavorixafor capsules; Has an active malignancy or history (≤ 5 years prior to enrollment) in the study of solid, metastatic, or hematologic malignancy (Exception: basal cell carcinoma in situ of the skin that has been adequately treated); Diagnosed or has suspected congenital long QT syndrome. Any history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes); any history of arrhythmia will be discussed with the Sponsor's Medical Monitor before participant's entry into the study; prolonged corrected QT interval using Fridericia's (QTcF) formula at the Screening visit ECG (> 450 ms)

[00222] In the interest of their safety and to facilitate assessment of both safety and treatment effect, the participants in this study are requested to agree to the following restrictions during the study: Not start any new prescription medications, except as prescribed or approved by the Investigator or if required in an emergency; Not take any over-the-counter medications, except as instructed or approved by the Investigator; Do not consume grapefruit , grapefruit juice and Seville orange containing products, which are variable inhibitors of CYP3A4 and are prohibited. Seville oranges (or bigarade) are a particularly tart orange often used for making marmalade. During this study, participants should not consume or use marmalades, oils, powders, or preserves that have orange or orange flavor in them and only eat fresh oranges that the participant knows are not Seville oranges; (Fasting: Each participant receives doses of mavorixafor or placebo in the morning. Participants are instructed to fast overnight (≥ 10 hours) from all food and drink (except

for water) and for 30 minutes post-dose; Study treatment (mavorixafor or placebo capsules) should be swallowed whole and should not be chewed or broken down. It is recommended that male participants (12 to ≤ 50 years old) be fasted for 12 hours prior to hormonal testing that occurs at Baseline (pre-dose) and M6 (Note: Participants for whom the scheduling requirements and eating restrictions represent significant difficulties should be discussed with the Medical Monitor to develop the most effective regimen possible)).

[00223] Precautionary Medications, Treatments, and Procedures for Women of Childbearing Potential and Male Participants: A WOCBP is defined as any female participant who has had menarche who is not postmenopausal or has not had a documented hysterectomy, bilateral tubal ligation, or bilateral oophorectomy.

[00224] A postmenopausal state is defined as no menses for at least 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient and the participant is required to use a highly effective method of contraception.

[00225] All sexually active women, regardless of childbearing potential, must use a highly effective method of contraception from Screening, during participation in the study, and through at least 4 weeks after the last dose of mavorixafor. Acceptable methods include: Systemic hormonal contraceptives when used with an additional barrier method (e.g., male condom): (Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (either oral, intravaginal, or transdermal); Progesterone-only hormonal contraception associated with inhibition of ovulation (either oral, injectable, or implantable)); Intrauterine device; Intrauterine hormone-releasing system; Bilateral tubal occlusion; Vasectomized partner who has received a medical assessment of surgical success (when the partner is the sole partner); Sexual abstinence (refraining from heterosexual intercourse during the entire period of risk associated with the study treatment). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant; Double barrier methods of contraception are acceptable, such as condoms with spermicide.

[00226] All WOCBP undergo serum pregnancy test at Screening and a urine pregnancy test every visit thereafter; a negative result is required to dispense mavorixafor. WOCBP must notify

the site if a menstrual cycle is missed. Participants who become pregnant are discontinued from the study.

[00227] All female participants who were not yet fertile when enrolled in the study should report the moment of menarche to the Investigator or designee, and at each visit, the Investigator or designee inquires whether menarche has occurred in all female participants enrolled in the study who do not have menarche at Screening.

[00228] Fertile males are required to use a male condom (with spermicide) with a sexual partner who is a WOCBP starting at Screening, during participation in the study, and through 4 weeks after the last dose of mavorixafor.

[00229] Reasons for Withdrawal or Termination: Part 1 study completion is defined as having completed 1 day of mavorixafor and an additional Safety Follow-up period 7D (+ 2D) post-dose. Part 2 study completion is defined as having completed 6-month QD dosing of mavorixafor and completion of the 30-day post EOT Safety Follow up visit. To provide consistent accounting of participant disposition, the Investigator or designee completes the appropriate electronic case report form (eCRF) and select the primary reason for withdrawal from the following standard categories: AE, includes any AE (clinical or laboratory, serious or nonserious, regardless of relation to mavorixafor) that represents the reason mavorixafor was discontinued, including the medical judgment of the Investigator based on the best interests of the participant; Participant withdrawal of consent; Lost to follow-up – the participant stopped coming for visits; Study termination by the Sponsor, for any reason; Other reasons per the Investigator that define a need to discontinue participant engagement in the study (e.g., low compliance, chemotherapy, etc).

[00230] Dose Adjustment: If a participant receiving study treatment has an AE that is Common Terminology Criteria for Adverse Events (CTCAE) Grade $\geq$ 2 and suspected to be related to mavorixafor, study drug may be managed as follows: Mavorixafor may be held (dose interrupted) until the AE improves to Grade $\leq$ 1; In the case of a safety concern, it is acceptable for Investigators or designee to interrupt mavorixafor and inform the Medical Monitor. A Data Monitoring Committee (DMC) may be consulted on an ad hoc basis for AEs and treatment alterations to determine necessary action to study treatment.

[00231] Certain medications that are substrates of CYP2D6 are prohibited. In the event that a strong CYP3A4 inhibitor is required, the Investigator contacts the Medical Monitor. If Investigator and Medical Monitor conclude that one of these drugs must be used, the 400 mg QD dose of

mavorixafor is reduced. Participants return to the 400 mg QD dose if the strong inhibitor medication has been stopped. For adolescent participants aged 12 to < 18 weighing ≤ 50 kg at Screening, the dose of mavorixafor may be reduced from 200 mg to 100 mg if co-administration with a potent inhibitor of CYP3A4 is necessary but may be maintained at 200 mg QD with appropriate medical monitoring. In the event of other situations in which a dose reduction may be considered appropriate, the Investigator consults the Medical Monitor. In the event of an emergency in which a prohibited medication cannot be avoided after the first dose of study treatment; the Investigator can prescribe the prohibited medication and hold the study treatment. The Investigator reports the emergency use of the prohibited medication to the Medical Monitor within 24 hours. Finally, in the case of documented safety concerns, it is acceptable for Investigators to reduce the dose of mavorixafor and inform the Medical Monitor.

[00232] Efficacy Assessments: ALC, AMC, ANC, and WBC are measured for the calculation of AUCs.

[00233] In Part 1, dense ALC, AMC, ANC, and WBC sampling occurs at the following time points: Time 0, 60 minutes (± 5 minutes), and 2, 3, 4, 6, and 8 hours (each ± 15 minutes) on D-1 (Baseline); Time 0 (pre-dose and up to 15 minutes prior), 60 minutes (± 5 minutes), and 2, 3, 4, 6, and 8 hours (each ± 15 minutes) post-dose on D1. Absolute lymphocyte count, AMC, ANC, and WBC are determined by standard methods. Whole blood samples are sent to a central laboratory selected by the Sponsor (Note: In the event central laboratory analysis is not feasible, whole blood samples may be analyzed at a local laboratory).

[00234] Blood sampling to monitor the immunophenotyping profile of lymphocyte subsets as assessed by FACS occurs at Baseline (D-1) at time 0 (pre-dose), 4, and 8 hours (± 15 minutes each) post-dose and on D1 at time 0 (pre-dose) and 4 hours and 8 hours (post-dose). The FACS analysis consists of the following panel of markers: CD3/CD4 (T helper cells), CD3/CD8 (cytotoxic T cells), CD4/CD8 ratio, CD19 (B cells), and CD16/CD56 (NK cells). Other markers may be measured.

[00235] In Part 2, dense ALC, AMC, ANC, and WBC sampling occurs at the following time points: Time 0, 60 minutes (± 5 minutes), and 2, 3, 4, 6, and 8 hours (each ± 15 minutes) on D-3 to D-1 (Baseline); Time 0 (pre-dose and up to 15 minutes prior), 60 minutes (± 5 minutes), and 2, 3, 4, 6, and 8 hours (each ± 15 minutes) post-dose on D1, M1, M3, and M6.

[00236] Blood sampling to monitor the phenotyping/gene expression profile of lymphocyte

subsets is assessed by EpiID/qPCR. Measurement will occur at Baseline (D-3 to D-1) at time 0 and 4 hours (± 15 minutes) and 8 hours (± 15 minutes) later and on D1, M1, and M6 at time 0 (pre-dose and up to 15 minutes prior) and 4 hours and 8 hours (each ± 15 minutes) post-dose.

[00237] In Part 2, peak and trough ALC, AMC, ANC, and WBC sampling occurs at M2, M4, and M5 (Note: Trough is defined as pre-dose (time 0) and peak is defined as occurring 2 to 4 hours post-dose).

[00238] Optional blood samples for exploratory analysis, including but not limited to, PBMCs, CD34+ cells, whole blood samples for immunophenotyping of neutrophils, whole blood for phagocytosis assay, and bone-specific alkaline phosphatase isoform, are assessed at Baseline (D-3 to D-1) at time 0 and 4 hours (± 15 minutes) and 8 hours (± 15 minutes) later and on D1, M1, M3, and M6 at time 0 (pre-dose and up to 15 minutes prior) and 4 hours and 8 hours (each ± 15 minutes) post-dose.

Example 2: A Phase 3, randomized, double-blind, placebo-controlled, multicenter study of mavorixafor in participants with congenital and acquired primary autoimmune and idiopathic chronic neutropenic disorders who are experiencing recurrent and/or serious infections

[00239] A 2-part, open-label, multicenter study of mavorixafor (X4P-001) is conducted in participants diagnosed with chronic neutropenia.

Table 3: Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of mavorixafor regarding infection rate and ANC in participants with chronic neutropenia who are not receiving chronic G-CSF treatment and in the overall population regardless of background therapy	Co-primary endpoints: 1. Infection rate based on infections adjudicated by a blinded independent AC during the 12-month treatment period 2. Proportion of ANC responders. An ANC responder is a participant meeting the definition of a positive ANC response for at least 3 out of 6 visits (Weeks 4, 8, 13, 26, 39, and 52) during the 52-week treatment period, with at least one positive ANC response at Week 39 or Week 52, where a positive ANC response is defined as: • Increase of ANC > 500 cells/μL from baseline To control the overall type I error for testing the subgroup without G-CSF and in the full population (regardless of baseline G-CSF use), a hierarchical testing approach will be adopted. First, both will be tested in participants who are not

Objectives	Endpoints
	receiving chronic G-CSF treatment and then both will be tested in the overall population.
Key Secondary Endpoints	
Each secondary endpoint will be tested first in participants who are not receiving chronic G-CSF treatment and then in the overall population. These endpoints will be tested in an order as follows:	
To evaluate severity of infections (during 12 months)	Infection severity based on severity of infections adjudicated by a blinded independent AC during the 12-month treatment period
To evaluate duration of infections (during 12 months)	Infection duration based on duration of infections adjudicated by a blinded independent AC during the 12-month treatment period in those participants who developed infections
To evaluate incidence of antibiotic use (during 12 months)	Antibiotic use due to infection, characterized by the frequency of antibiotic use during the 12-month treatment period
To evaluate QoL via PROs (change from baseline to 12 months) – PROMIS SF fatigue	Change from baseline to Week 52 in PROMIS SF Fatigue Questionnaire total score
To evaluate incidence of oral ulcers (during 12 months)	Oral ulcers, as assessed by presence or absence of ulcers during the 12-month treatment period
Supportive Endpoints	
To evaluate duration of positive ANC response	Duration of positive ANC response (time from first positive ANC response to loss of positive ANC response without subsequent resumption of response)
To evaluate duration of positive ANC response in participants with chronic neutropenia who are not receiving chronic G-CSF treatment	In participants not receiving chronic G-CSF, duration of positive ANC response (time from first positive ANC response to loss of positive ANC response without subsequent resumption of response)
To evaluate levels of circulating neutrophils through the first 12 weeks on treatment	Proportion of participants with a positive ANC response in at least 2 of 3 possible visits during the first 12 weeks on treatment (Week 4, 8, and 13 visits): • Increase of mean ANC > 500 cells/μL from baseline
To evaluate changes in hematologic parameters (other than ANC) over 52 weeks	Absolute and fold change from baseline for total absolute lymphocyte count, absolute monocyte count, ANC, and white blood cell count at each visit during the 12-month treatment period
Exploratory Endpoints	
To evaluate duration of antibiotic use (during 12 months)	Antibiotic use due to infection, characterized by the duration of antibiotic use during the 12-month treatment period

Objectives	Endpoints
To evaluate QoL via PROs (change from baseline to 12 months)	Change from baseline to each visit through Week 52 in total scores for the following PROs: • Pediatric Quality-of-Life Inventory™ questionnaire • PROMIS SF Pain and Physical Function questionnaires • PGI-C • PGI-S
To characterize oral ulcers (during 12 months)	Change from baseline in ulcer bothersomeness on a rating scale during 12 months
To assess the exposures of mavorixafor in participants with chronic neutropenia	Plasma concentrations of mavorixafor in participants with chronic neutropenia at predefined timepoints
To assess PK, safety, and efficacy	Relationship between mavorixafor PK characteristics and safety and efficacy
To assess somatic mutations associated with clonal hematopoiesis	Baseline and Month 12 or end of treatment (for those on study through at least week 26) genetic testing of bone marrow from participants with congenital neutropenia for somatic variants associated with transformation
Safety and Tolerability	
To evaluate the safety and tolerability of 12-month chronic dosing of mavorixafor in participants with chronic neutropenia	Assessed by treatment-emergent adverse events graded using Common Terminology Criteria for Adverse Events version 5, clinical laboratory evaluations, vital signs, and electrocardiogram assessments

[00240] Overall design summary: To be eligible for the study, participants must have a diagnosis of congenital or acquired primary autoimmune and idiopathic CN disorder. Participants must be ≥ 12 years of age, have an ANC of < 1000 cells/μL during screening (single ANC value from hematology), confirmed by mean ANC < 1000 cells/μL at and baseline, and meet all the eligibility criteria. Participants are eligible for study inclusion regardless of current background therapy regimen (where background therapy is defined as the participant's current treatment regimen, and options include, but are not limited to, G-CSF, immunoglobulin replacement therapy, prophylactic antibiotics, or "watchful waiting"). All participants must be suffering sequelae of CN, specifically at least 2 recurrent and/or serious infections in the last 12 months that required use of antibiotics (intravenous/oral) and/or a visit to a healthcare facility (including but not limited to emergency room visit, urgent care facility, primary care physician's office, or in-patient hospitalization); therefore, patients receiving background therapy are inadequately controlled and experiencing recurrent and/or serious infections despite use of their current treatment regimens.

[00241] Participants are randomly assigned in a 1:1 ratio to the following 2 arms, stratified by type of CN (congenital or acquired primary autoimmune and idiopathic) and whether G-CSF is used at baseline: Arm 1 includes participants receiving mavorixafor + background therapy. Arm 2 includes participants receiving placebo + background therapy.

[00242] G-CSF administration (dose and schedule) is maintained throughout the study with the exception of dosing changes permitted for safety reasons. After signing the informed consent form (ICF)/assent, participants will provide a buccal sample to complete genetic screening for genetic variants in genes in a comprehensive immune and cytopenia panel to characterize participant type of CN. Those who have confirmed prior genetic testing indicating the presence of a known pathogenic variant associated with CN that confirms classification as congenital are not required to provide this sample. A bone marrow aspirate or biopsy is collected during the screening visit for all participants without prior documentation of bone marrow aspirate or biopsy in the previous 9 months. A stored sample from within 9 months can be tested locally for eligibility review. Participants are screened for eligibility at the screening visit.

[00243] Participants receive mavorixafor or placebo. Adults ($\geq$ 18 years of age) receive mavorixafor 400 mg or placebo once daily (QD). Adolescents ($\geq$ 12 to < 18 years of age) weighing > 50 kg receive mavorixafor 400 mg or placebo QD. Adolescents ($\geq$ 12 to < 18 years of age) weighing $\leq$ 50 kg receive mavorixafor 200 mg or placebo QD.

[00244] The first dose of study treatment is administered on Day 1. Prior to administering study drug, an electrocardiogram (ECG) will be performed, followed by a blood draw at t = 0. After the ECG and the blood draw, the dose of the study drug will be given (within 15 minutes). At 2 hours post dose ($\pm$ 30 minutes), an ECG will be performed, followed by the t = 2 hours ($\pm$ 15 minutes) blood draw.

[00245] Participants are contacted by telephone, approximately 24 to 72 hours prior to each scheduled study visit to check whether the participant feels that they may have an ongoing infection, and to remind the participant not to take their study treatment at home on the day of the visit, as the study treatment is administered during the visit. In the event of symptoms consistent with infection, all attempts are made to conduct the scheduled visit to collect safety information and perform study treatment accountability/dispensation. Once the infection has been resolved, an additional unscheduled visit is performed to collect the efficacy data.

[00246] Treatment Period: Participants receive blinded study treatment daily starting from Day

1 through the Week 52/Day 365 visit. Participants completing the Week 52/Day 365 visit are offered the option to participate in a separate long-term extension study. Participants who choose to join the long term follow-up study are provided with open-label mavorixafor until it is commercially available or Sponsor terminates the study.

[00247] If a participant discontinues early for any reason other than withdrawal of consent/assent, an early termination (ET) follow-up is completed. If deemed necessary by the Investigator, an in-person ET visit is performed followed by an end of study (EOS)/safety follow up visit. EOS visit are performed 30 days (± 14 days) post Week 52/Day 365 visit or ET visit

[00248] Objectives and Endpoints: The objectives and endpoints for this study are summarized in Table 4.

Table 4: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of mavorixafor regarding infection rate and ANC in participants with chronic neutropenia who are not receiving chronic G-CSF treatment and in the overall population regardless of background therapy	Co-primary endpoints: 1. Infection rate based on infections adjudicated by a blinded independent AC during the 12-month treatment period 2. Proportion of ANC responders. An ANC responder is a participant meeting the definition of a positive ANC response for at least 3 out of 6 visits (Weeks 4, 8, 13, 26, 39, and 52) during the 52-week treatment period, with at least one positive ANC response at Week 39 or Week 52, where a positive ANC response is defined as: • Increase of ANC > 500 cells/μL from baseline To control the overall type I error for testing the subgroup without G-CSF and in the full population (regardless of baseline G-CSF use), a hierarchical testing approach will be adopted. First, both will be tested in participants who are not receiving chronic G-CSF treatment and then both will be tested in the overall population.
Key Secondary Endpoints	
Each secondary endpoint is tested first in participants who are not receiving chronic G-CSF treatment and then in the overall population. These endpoints are tested in an order as follows:	
To evaluate severity of infections (during 12 months)	Infection severity based on severity of infections adjudicated by blinded, independent AC during the 12-month treatment period
To evaluate duration of infections (during 12 months)	Infection duration based on duration of infections adjudicated by blinded, independent AC during the 12-month treatment period in those patients who developed infections
To evaluate incidence of antibiotic use (during 12 months)	Antibiotic use due to infection, characterized by the frequency of antibiotic use during the 12-month treatment period
To evaluate QoL via PROs (change from baseline to 12 months) – PROMIS SF fatigue	Change from baseline to Week 52 in PROMIS SF Fatigue Questionnaire total score
To evaluate incidence of oral ulcers (during 12 months)	Oral ulcers, as assessed by presence or absence of ulcers during the 12-month treatment period
Supportive Endpoints	
To evaluate duration of positive ANC response	Duration of positive ANC response (time from first positive ANC response to loss of positive ANC response without subsequent resumption of response)
To evaluate duration of positive ANC response in participants with chronic neutropenia who are not receiving chronic G-CSF treatment	In patient not receiving chronic G-CSF, duration of positive ANC response (time from first positive ANC response to loss of positive ANC response without subsequent resumption of response)

To evaluate levels of circulating neutrophils through the first 12 weeks on treatment	Proportion of participants with a positive ANC response in at least 2 of 3 possible visits during the first 12 weeks on treatment (Week 4, 8, and 13 visits): • Increase of ANC > 500 cells/μL from baseline
To evaluate changes in hematologic parameters (other than ANC) [during 12 months]	Absolute and fold change from baseline for total absolute lymphocyte count, absolute monocyte count, ANC, and white blood cell count at each visit during the 12-month treatment period
Exploratory Endpoints	
To evaluate duration of antibiotic use (during 12 months)	Antibiotic use due to infection, characterized by the duration of antibiotic use during the 12-month treatment period
To evaluate QoL via PROs (change from baseline to 12 months)	Change from baseline to each visit through Week 52 in total scores for the following PROs: • Pediatric Quality-of-Life Inventory™ questionnaire • PROMIS SF Pain and Physical Function questionnaires • PGI-C • PGI-S
To characterize oral ulcers (during 12 months)	Change from baseline in ulcer bothersomeness on a rating scale during 12 months
To assess the exposures of mavorixafor in participants with chronic neutropenia	Plasma concentrations of mavorixafor in participants with chronic neutropenia at predefined timepoints
To assess PK, safety, and efficacy	Relationship between mavorixafor PK characteristics and safety and efficacy
To assess somatic mutations associated with clonal hematopoiesis	Baseline and Month 12 or end of treatment (for those on study through at least week 26) genetic testing of bone marrow from participants with congenital neutropenia for somatic variants associated with transformation
Safety and Tolerability	
To evaluate the safety and tolerability of 12-month chronic dosing of mavorixafor in participants with chronic neutropenia	Assessed by treatment-emergent adverse events graded using Common Terminology Criteria for Adverse Events version 5, clinical laboratory evaluations, vital signs, and electrocardiogram assessments

[00249] Eligibility: To be eligible for the Phase 3, randomized, double-blind, placebo-controlled study, participants must have a diagnosis of congenital or acquired primary autoimmune and idiopathic CN disorder. Participants must be ≥ 12 years of age, have an ANC of < 1000 cells/μL during screening (single ANC value from hematology), confirmed by mean ANC of < 1000 cells/μL at baseline, and meet all the eligibility criteria.

[00250] All participants must be suffering sequelae of CN, specifically at least 2 recurrent

and/or serious infections in the last 12 months that required use of antibiotics and/or a visit to a healthcare facility (see Section 5.1); therefore, patients receiving background therapy are inadequately controlled and experiencing recurrent and/or serious infections despite use of their current treatment regimens.

[00251] Treatment Arms: Participants are randomly assigned in a 1:1 ratio to the following 2 arms, stratified by type of CN (congenital or acquired primary autoimmune and idiopathic) and whether G-CSF is used at screening: Arm 1 includes participants receiving mavorixafor + background therapy. Arm 2 includes participants receiving placebo + background therapy. (Note: Background therapy is defined as the participant's current treatment regimen. Options include, but are not limited to, G-CSF, immunoglobulin replacement therapy, prophylactic antibiotics, or "watchful waiting". Up to 40% of participants enrolled receive chronic G-CSF background therapy). Enrollment of participants with congenital neutropenic disorders associated with bone marrow failure may be capped at approximately 15 participants. If genetic testing does not indicate the presence of a known pathogenic variant associated with CN that confirms classification as congenital, the type of CN will be determined by the Investigator's clinical judgement.

[00252] G-CSF administration (dose and schedule) is maintained throughout the study, with the exception of dosing changes permitted for safety reasons. Participants are advised of the value of genetic screening in the discussion of the study design and objectives. After signing the informed consent form (ICF)/assent, participants will provide a buccal sample to complete genetic screening for genetic variants in genes in a comprehensive immune and cytopenia panel to characterize participant type of CN. Those who have confirmed prior genetic testing indicating the presence of a known pathogenic variant associated with CN that confirms classification as congenital are not required to provide this sample. A bone marrow aspirate or biopsy is collected as part of the screening visit for patients without prior documentation of bone marrow aspirate or biopsy in the previous 9 months. A stored sample from within 9 months can be tested locally for eligibility review.

[00253] In the event of a systemic infection, between the screening and baseline visits that may, in the opinion of the Investigator, have an effect on ANC, the baseline visit is postponed or repeated, as deemed appropriate by the Investigator, to confirm trough ANC < 1000 cells/μL. Screening and baseline visit procedures may be repeated locally (screening visit only) or centrally (screening or baseline visit) as deemed appropriate by the Investigator due to infection, G-CSF

dose timing, circadian rhythm, or other concomitant medication effects. Repeat measures should be justified with reason to believe the measure would change and should be limited to 3 times for any single type of event. In the event an infection lasts longer than the screening period (70 days), then participant is expected to reconfirm the eligibility criteria (including the laboratory tests). Systemic infections must be resolved prior to the first administration of study treatment. If an infection occurs at any time between screening and prior to the receipt of first dose of study drug, this event is recorded as a non-treatment related AE.

[00254] Participants receive mavorixafor or placebo. Participants weighing > 50 kg receive mavorixafor 400 mg or placebo QD. Participants weighing ≤ 50 kg receive mavorixafor 300 mg or placebo QD.

[00255] Participants are instructed to fast overnight from all food and drink (except for water) and for 30 minutes post dose.

[00256] The first dose of study treatment is administered on the morning of Day 1, followed by an ECG at 2 hours post dose (± 30 minutes), and a blood draw between 2-4 hours (± 30 minutes) post dose.

[00257] To avoid multiple needle sticks, an indwelling catheter may be used for blood sampling for PK, ALC, absolute monocyte count (AMC), ANC, and WBC. During the study, information about potential infections is collected via multiple sources including Patient-Reported Outcomes (PROs) questionnaire and information collected by the Investigator and study team. Potential infection events are evaluated by a blinded, independent Adjudication Committee (AC) as outlined in the AC charter. The AC evaluates all potential infection data and determine whether an event is consistent with infection, the characteristics of the infection, the severity of the infection, and whether the participant may continue to participate in the study. The AC takes final arbiter decision on events of infections for the purpose of the efficacy analyses.

[00258] Participants are contacted by telephone, approximately 24 to 72 hours prior to each scheduled study visit to check whether the participant feels that they may have an ongoing infection, and to remind the participant not to take their study treatment at home on the day of the visit, as the study treatment will be administered during the visit and to confirm with participant that G-CSF dose is being appropriately held prior to the visit. In the event of symptoms consistent with infection, all attempts are made to conduct the scheduled visit to collect safety information and perform study treatment accountability/dispensation. Once the infection has been resolved, an

additional unscheduled visit should is performed to collect efficacy data.

[00259] Participants receive blinded study treatment daily starting from Day 1 through the Week 52/Day 365 visit. Participants completing the Week 52/Day 365 visit are offered the option to participate in a separate long-term extension study. Participants who choose to join the long-term extension study are provided with open label mavorixafor until it is commercially available, or the Sponsor terminates the study. For participants who prematurely discontinue from the study, an early termination (ET) visit is conducted (unless participant withdrew consent) followed by an end of study (EOS)/safety follow-up visit.

[00260] Inclusion Criteria: Participants are eligible to be included in the study only if all of the following criteria apply: Participants must be at least 12 years of age, at the time of signing the informed consent/assent, as per the local regulations and guidelines

[00261] Types of patients: Diagnosis of congenital or acquired primary autoimmune and idiopathic chronic neutropenic disorder $\geq$ 6 months prior to the screening visit that is NOT attributable to medications, active or recent infections or malignancy; Congenital Neutropenia, including but not limited to these classifications: Isolated with a permanent (non-cyclic) presentation, e.g., ELANE, CSF3R, CXCR2, WAS; Associated with extra-hematological manifestations, e.g., Barth syndrome, Cohen syndrome, G6PC3, Kostmann disease; Associated with metabolic disorders, e.g., glycogen storage disease 1b (GSD1b); Shwachman-Diamond syndrome; Acquired Primary Neutropenia: Chronic idiopathic neutropenia, Primary autoimmune neutropenia.

[00262] Other CN disorders that may be eligible for enrollment can be clarified and approved upon discussion with Study Medical Monitor and Sponsor:

- Have an ANC < 1000 cells/μL during screening (single ANC value from hematology) and confirmed trough mean ANC (mean value of multiple ANC measurements over 6 hours) at baseline visit, with no clinical evidence of infection. (Note: In the event of a systemic infection between the screening and baseline visits that may, in the opinion of the Investigator, have an effect on ANC, the baseline visit may be postponed or repeated, as deemed appropriate by the Investigator, to confirm trough ANC < 1000 cells/μL. Repeat measures should be justified with reason to believe the measure would change and should be limited to 3 times for any single type of event;
- Prior history of recurrent and/or serious infections during the 12 months preceding the

screening visit (i.e., suffering sequelae of CN), as defined by having at least 2 infections in the last 12 months that meet the following criteria: Infection requiring the use of antibiotics (intravenous [IV]/oral), OR infection requiring a visit to healthcare facility (including but not limited to emergency room visit, urgent care facility, primary care physician's office, or in-patient hospitalization); AND for all potential participants: infections considered by the Investigator to be likely related to the potential participant's CN disorder.

[00263] Note: Although oral ulcers (i.e., canker sores, aphthous ulcers) are sequelae of CN, they are not considered as de novo infections for the purpose of eligibility. If the finding of the oral ulcer(s) and/or oral mucositis are either thought to be exacerbated by or as a result of an infection, e.g., fungal etiology, then they can be considered an infection. Recurrent herpes simplex virus (HSV) or human papillomavirus (HPV) oral or genital lesions are NOT classified for the purpose of this study as infections. If such lesions have signs of secondary bacterial or fungal etiology, they can be considered infections. Gingivitis is NOT to be considered an infection. Periodontitis can be considered an infection.

[00264] Participants who are on G-CSF or other active background therapy must have been receiving these therapies for $\geq$ 12 months, be on a stable dose and dosing schedule for $\geq$ 4 weeks prior to screening visit and remain on this dose and dosing schedule throughout the study (Note: for patients receiving chronic G-CSF treatment, dosing modifications may be considered for safety reasons [e.g., if ANC > 10,000 cells/μL for $\geq$ 4 weeks]).

[00265] Participants must be willing to keep their G-CSF or other background therapy doses/regimens stable (other than for safety reasons) for the duration of the study. Drugs which are (a) primarily metabolized by or are sensitive substrates of CYP2D6 are prohibited for a period starting 14 days or 5 half-lives, whichever is longer, prior to administration of study drug and during the study and (b) which are strong CYP3A4 inducers are prohibited for a period starting 7 days or 5 half-lives, whichever is longer, prior to the administration of study drug and during the study. If the Investigator and Medical Monitor conclude that a strong inhibitor of CYP3A4 must be used, the dose of mavorixafor will be modified. Grapefruit and Seville orange-containing products, which are variable inhibitors of CYP3A4, are prohibited from the day the first dose of study drug is given and during the study. Bone marrow biopsy or aspirate during screening (or prior documentation of bone marrow biopsy or aspirate within past 9 months) does not demonstrate evidence of hematological malignancy. Contraceptive use by men and women must be consistent

with local regulations regarding the methods of contraception for those participating in clinical studies.

[00266] Exclusion Criteria: Participants are excluded from the study if any of the following apply (1-21):

[00267] 1. A diagnosis of secondary neutropenia including those due to: Hypersplenism; Infection; Malignancy; Autoimmune disease, e.g., systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, graft-versus-host disease, thyroid disease; Nutritional deficiency, e.g., vitamin B12, folic acid, copper, caloric malnutrition; Drug-induced cause, e.g., chemotherapy, clozapine, antiretrovirals, antibiotics, monoclonal antibodies.

[00268] 2. A diagnosis of any of the following: Aplastic anemia; WHIM syndrome; Certain Congenital Neutropenias, including but not limited to these classifications are excluded: (Isolated with a cyclic presentation, e.g., ELANE; Associated with immune dysregulation, e.g., autoimmune lymphoproliferative syndrome, Familial hemophagocytic lymphohistiocytosis, Chédiak-Higashi syndrome; Associated with bone marrow failure, e.g., Fanconi Anemia, Diamond-Blackfan anemia, Telomere biology disorders; Neutropenia associated with a Duffy-null phenotype (formerly known as benign ethnic neutropenia)).

[00269] 3. A known history of positive serology or viral load for HIV or a known history of acquired immunodeficiency syndrome.

[00270] 4. Known active COVID 19 infection or a positive test within the local accepted clinical and governmental guidelines for a communicable window. (Note: Participants with prior COVID 19 exposure are permitted to enroll if they have a negative test and conform with local guidelines)

[00271] 5. Major surgery $\leq$ 6 weeks before the baseline visit requiring general anesthesia or which, in the opinion of the Investigator, may compromise the safety of the participant.

[00272] 6. A medical or personal condition that may potentially compromise the safety of the participant, may preclude the participant's successful completion of the clinical study, or could, in the opinion of the Investigator or the Sponsor, interfere with the objectives of the study.

[00273] 7. An active malignancy or history ($\leq$ 5 years prior to enrollment in the study) of solid, or hematologic malignancy. Exception: Basal cell carcinoma in situ of the skin that has been adequately treated.

[00274] 8. Patients who are awaiting HSCT due to somatic variants in genes associated with high risk for clonal proliferation.

[00275] 9. Diagnosed or suspected congenital long QT syndrome or any history of clinically significant (CS) ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes). Any history of arrhythmia is discussed with the Sponsor's Medical Monitor before the participant's entry into the study.

[00276] 10. Receiving or requiring any medication/therapy that is prohibited

[00277] 11. Received more than 1 dose of mavorixafor in the past.

[00278] 12. Received a CXCR4 antagonist (other than mavorixafor) in the past 6 months.

[00279] 13. Patients taking pegylated-G-CSF unless they have a diagnosis of congenital neutropenia confirmed at screening.

[00280] 14. Positive hepatitis C virus (HCV) antibodies with confirmation by HCV ribonucleic acid polymerase chain reaction reflex testing.

[00281] 15. Positive hepatitis B surface antigen (HbsAg) or hepatitis B core antibody (HbcAb). If the participant tests HbsAg negative, HbcAb positive, and hepatitis B surface antibody positive upon reflex testing, the participant would be considered eligible.

[00282] 16. Laboratory test results meeting ≥ 1 of the following criteria at the screening visit: Hemoglobin < 9.0 g/dL; Platelets $< 30{,}000/\mu L$; Estimated glomerular filtration rate ≤ 60 mL/min/1.73 m2, as estimated by the Chronic Kidney Disease Epidemiology Collaboration equation (age ≥ 18 years) or Schwartz equation (age 12-17 years); Serum aspartate transaminase $> 2.5 \times$ upper limit of normal (ULN); Serum alanine transaminase $> 2.5 \times$ ULN; Total bilirubin $> 1.5 \times$ ULN (unless due to Gilbert's syndrome, in which case total bilirubin $\geq 3.0 \times$ ULN and direct bilirubin $> 1.5 \times$ ULN)

[00283] 17. Prolonged corrected QT interval > 450 ms using Fridericia's formula at the screening visit.

[00284] 18. Participant is currently taking or has taken an investigational drug < 30 days prior to the screening visit, or 5 half-lives, whichever is longer.

[00285] 19. Participant is pregnant or breastfeeding.

[00286] 20. Unable and/or unwilling to swallow capsules.

[00287] 21. Known systemic hypersensitivity to the mavorixafor drug substance, its inactive ingredients, or the placebo.

[00288] Primary Endpoint Analysis: The following primary efficacy endpoints are determined in the ITT subgroup of participants without G-CSF and in the ITT set:

[00289] 1. Infection rate based on infections adjudicated by a blinded independent AC during the 12-month treatment period

[00290] 2. Proportion of participants meeting the definition of a positive ANC response for at least 2 out of 3 visits (Weeks 4, 8, and 13) during the first 3 months, defined as: ANC $\geq$ 1500 cells/μL, with the exception of participants with baseline ANC < 500 cells/μL; $\geq$ 2-fold increase in ANC from baseline, for participants with baseline ANC < 500 cells/μL

[00291] Supportive Endpoints:

[00292] Duration of positive ANC response for ANC responders only, defined as time from first positive ANC response to loss of positive ANC response without subsequent resumption of response, where the loss of ANC response is defined as the event of meeting one of the following criteria for at least 2 consecutive visits: The ANC level falls to <1,500 cells/μL for participants with baseline ANC ≥500 cells/μL; The ANC level falls to <500 cells/μL for participants with baseline ANC <500 cells/μL.

[00293] In participants not receiving chronic G-CSF, duration of positive ANC response for ANC responders only.

[00294] Proportion of participants with an overall positive ANC response during the 12-month treatment period.

[00295] Absolute and fold change from baseline for total ALC, absolute monocyte count, ANC, and white blood cell count at each visit during the 12-month treatment period.

Example 3: Food Effect of Mavorixafor in Healthy Volunteers

[00296] A randomized, phase I, open-label, single-center, single dose, 6-period, 6-sequence crossover study assessed the pharmacokinetics, safety, and tolerability of mavorixafor in healthy participants under fasted and fed state.

[00297] Mavorixafor was given in a randomized sequence under 6 different conditions: Condition A: MAV dose after an overnight fast of at least 10 hours; Condition B: Overnight fast of at least 10 hours, HIGH-fat meal (eaten in 30') + MAV immediately after meal; Condition C: Overnight fast of at least 10 hours, LOW-fat meal (eaten in 30') + MAV immediately after meal; Condition D: Overnight fast of at least 10 hours, MAV dosing + LOW-fat meal 30 minutes after MAV (eaten in 30'); Condition E: Afternoon fast of at least 4 hours, HIGH-fat meal (eaten in 30') + MAV in the evening (2h after meal completion); Condition F: Afternoon fast of at least 4 hours,

MAV dosing. No food or drink was allowed after MAV dosing except for condition D.

[00298] **FIG. 1** shows the effect of fed and fasted states on the mavorixafor C_{max}. Compared to a fasted state (10 h), subjects in fed (high fat) and fed (low fat) arms experienced a -66% and -55% reduction, respectively, in C_{max}. Similarly, relative to subjects who fasted (low fat after dosing), subjects who had an afternoon fast (4 h) dosing 2h after high fat food, or an afternoon fast (4 h), experienced a -59% and -43% reduction, respectively, in C_{max}. For the same conditions, AUC was also measured (**FIG. 2**). The fed (high fat) and fed (low fat) arms had a -55% and -51% reduction, respectively, in AUC compared to the fasted arm (10 h). The fasted arm with low fat (30 minutes after dosing) showed a -18% relative drop in AUC, while the afternoon fast (4 h) dosing 2 h after high fat food, and afternoon fast (4 h), arms showed -37% and -24% drops in AUC, respectively.

[00299] These observations may be explained as follows: Mavorixafor is freely soluble in the pH range 1.0 to 5.5 (> 70 mg/mL), slightly soluble at pH 6.8 (22 mg/mL) and slightly soluble at pH 7.5 (3.3 mg/mL). An elevated pH after food intake may have reduced the solubility of mavorixafor and hence absorption and exposure. Thus, mavorixafor is soluble at all pH values tested between 1.0 and 5.5, which covers the range of gastric pH expected to be encountered with administration according to the methods of the present invention. Hence, differences in PK and/or PD would not reasonably have been anticipated with changes in pH due to differing fasting regimens.

[00300] The condition "Overnight fast of at least 10 hours, MAV dosing + LOW-fat meal 30 minutes after MAV (eaten in 30')" showed a greater absorption (higher Cmax) but lower total exposure (AUC) compared to fasted state.

[00301] Summary statistics of plasma mavorixafor parameters by treatment conditions are presented in **Table 5**, below.

Table 5: Summary Statistics of Mavorixafor Plasma Pharmacokinetic Parameter by Treatment Condition (Pharmacokinetic Analysis Set)

Parameter (unit)	Statistics	Treatment Condition A (N = 20)	Treatment Condition B (N = 22)	Treatment Condition C (N = 21)	Treatment Condition D (N = 20)	Treatment Condition E (N = 22)	Treatment Condition F (N = 22)
C_{max} (ng/mL)	n	20	22	21	20	22	22
	Arithmetic Mean (CV%)	2369 (31.1)	882.8 (67.7)	1237 (68.6)	3013 (47.6)	998.5 (37.6)	1341 (34.6)
	Geometric Mean (geoCV%)	2251 (34.7)	753.2 (62.2)	1022 (68.2)	2511 (90.6)	936.3 (38.0)	1257 (39.7)
	Median	2295	799.5	957.0	2890	891.5	1390
	Minimum; Maximum	1140; 3390	197.0; 3200	405.0; 3750	165.0; 6120	465.0; 1790	648.0; 2170
T_{max} (h)	n	20	22	21	20	22	22
	Median	1.54	3.99	3.00	1.03	4.03	2.92
	Minimum; Maximum	0.50; 4.01	1.00; 6.05	0.99; 6.01	0.96; 6.00	1.52; 8.02	0.50; 6.01
t_{lag} (h)	n	20	22	21	20	22	22
	Median	0	0	0	0	0	0
	Minimum; Maximum	0; 0	0; 0	0; 0.51	0; 0	0; 0.50	0; 0.50
$AUC_{0\text{-last}}$ (h*ng/mL)	n	20	22	21	20	22	22
	Arithmetic Mean (CV%)	9887 (36.2)	4546 (45.9)	5171 (65.7)	7900 (34.2)	6219 (42.3)	7863 (46.4)
	Geometric Mean (geoCV%)	9156 (45.9)	4125 (50.3)	4403 (61.0)	7306 (48.2)	5769 (40.5)	7090 (50.1)
	Median	9667	4304	4465	7707	5803	7213
	Minimum; Maximum	2442; 17910	1073; 11800	1485; 15320	1594; 12240	2935; 13170	3005; 16100
$AUC_{0\text{-inf}}$ (h*ng/mL)	n	20	20	21	19	20	22
	Arithmetic Mean (CV%)	10560 (35.6)	4982 (46.5)	5585 (64.8)	8429 (35.0)	6560 (44.8)	8402 (46.5)
	Geometric Mean (geoCV%)	9793 (45.3)	4502 (51.9)	4769 (60.4)	7772 (49.1)	6048 (42.0)	7561 (50.8)
	Median	10610	4923	4787	8189	6036	7712
	Minimum; Maximum	2743; 18580	1193; 12740	1647; 16000	1750; 12910	3028; 14220	3152; 16880

%AUC$_{ex}$ (%)	n	20	20	21	19	20	22
	Arithmetic Mean (CV%)	6.453 (50.3)	8.202 (39.0)	7.633 (39.3)	6.172 (36.5)	6.336 (27.7)	6.173 (48.6)
	Geometric Mean (geoCV%)	5.815 (48.0)	7.635 (40.5)	7.140 (38.2)	5.772 (40.5)	6.117 (27.9)	5.718 (38.6)
	Median	5.721	7.983	7.337	5.356	6.476	5.177
	Minimum; Maximum	2.952; 13.97	4.181; 15.37	3.861; 15.23	2.015; 11.00	3.078; 11.62	3.175; 17.78
λ_z (1/h)	n	20	21	21	19	20	22
	Arithmetic Mean (CV%)	0.01733 (22.2)	0.01704 (17.9)	0.01700 (20.5)	0.01725 (18.6)	0.01921 (13.6)	0.01976 (19.6)
	Geometric Mean (geoCV%)	0.01688 (24.7)	0.01677 (19.0)	0.01664 (21.5)	0.01697 (18.5)	0.01903 (14.9)	0.01934 (22.5)
	Median	0.01809	0.01691	0.01727	0.01755	0.01955	0.01934
	Minimum; Maximum	0.009539; 0.02366	0.01011; 0.02387	0.009732; 0.02397	0.01223; 0.02410	0.01220; 0.02296	0.009183; 0.02755
$t^{1}/_{2}$ (h)	n	20	21	21	19	20	22
	Arithmetic Mean (CV%)	42.31 (26.7)	42.08 (20.4)	42.59 (22.7)	41.49 (18.2)	36.84 (16.4)	36.81 (27.1)
	Geometric Mean (geoCV%)	41.07 (24.7)	41.34 (19.0)	41.64 (21.5)	40.84 (18.5)	36.43 (14.9)	35.84 (22.5)
	Median	38.33	41.00	40.14	39.49	35.47	35.84
	Minimum; Maximum	29.30; 72.66	29.03; 68.59	28.92; 71.22	28.76; 56.66	30.19; 56.83	25.16; 75.48
CL/F (L/h)	n	20	20	21	19	20	22
	Arithmetic Mean (CV%)	45.44 (59.7)	101.5 (66.6)	96.28 (53.7)	58.90 (74.2)	71.14 (38.1)	59.12 (50.3)
	Geometric Mean (geoCV%)	40.84 (45.3)	88.86 (51.9)	83.87 (60.4)	51.47 (49.1)	66.14 (42.0)	52.91 (50.8)
	Median	37.69	81.25	83.57	48.84	66.28	51.98
	Minimum; Maximum	21.53; 145.8	31.41; 335.2	25.00; 242.9	30.98; 228.6	28.12; 132.1	23.70; 126.9
Vz/F (L)	n	20	20	21	19	20	22
	Arithmetic Mean (CV%)	2839 (81.6)	5995 (67.1)	5997 (63.7)	3530 (78.6)	3796 (46.1)	3069 (48.7)
	Geometric Mean (geoCV%)	2420 (54.7)	5168 (56.9)	5039 (68.4)	3032 (53.1)	3476 (44.6)	2736 (53.3)
	Median	2463	5132	5201	2875	3700	2950

	Minimum; Maximum	1092; 12150	1921; 19490	1169; 18630	1523; 14340	1570; 9333	1085; 6596

A = Mavorixafor dose after an overnight fast of at least 10 hours; B = Mavorixafor dose following HIGH-fat meal after an overnight fast of at least 10 hours; C = Mavorixafor dose following LOW-fat meal after an overnight fast of at least 10 hours; D = Mavorixafor dose after an overnight fast of at least 10 hours followed by LOW-fat meal; E = HIGH-fat meal after an afternoon fast of at least 4 hours followed by evening Mavorixafor dose 2 hours later; F = Mavorixafor dose after an afternoon fast of at least 4 hours.

Abbreviations: $AUC_{0\text{-}inf}$ = AUC from predose (time 0) extrapolated to infinite time; $AUC_{0\text{-}last}$ = AUC from predose (time 0) to the time of the last quantifiable concentration; $\%AUC_{ex}$ = Percentage of $AUC_{0\text{-}inf}$ that is due to extrapolation beyond tlast; CL/F = Total apparent body clearance; Cmax = Maximum observed plasma concentration; CV = coefficient of variation; geoCV = geometric coefficient of variation; n = Number of participants with non-missing values; N = Number of participants in pharmacokinetic analysis set in respective treatment condition; tlag = Time of first observation above the limit of quantification; Tmax = Time at which the maximum concentration occurs; t1/2 = Terminal elimination half-life; V_z/F = Apparent volume of distribution during terminal phase; λZ = Terminal elimination rate constant.

[00302] Pharmacokinetic Conclusions

[00303] GMR: geometric mean ratio; CI: confidence interval.

[00304] Administration of mavorixafor after an overnight fast of at least 10 hours resulted in a geometric mean (geoCV%) C_{max} of 2251 ng/mL (34.7%), geometric mean (geoCV%) $AUC_{0\text{-}inf}$ of 9793 h*ng/mL (45.3%), and geometric mean (geoCV%) $AUC_{0\text{-}last}$ of 9156 h*ng/mL (45.9%).

[00305] Administration of mavorixafor after an overnight fast of at least 10 hours followed by a HIGH-fat meal (eaten in 30 minutes) and a mavorixafor 400 mg dose (Condition B) decreases bioavailability of mavorixafor compared to fasting conditions (Condition A):

- The GMR (90% CI) for C_{max} was 33.800 (27.05, 42.23).
- The GMR (90% CI) for $AUC_{0\text{-}inf}$ was 44.677 (38.99, 51.19).
- The GMR (90% CI) for $AUC_{0\text{-}last}$ was 45.194 (39.33, 51.93).

[00306] Administration of mavorixafor after an overnight fast of at least 10 hours followed by a LOW-fat meal (eaten in 30 minutes) and a mavorixafor 400 mg dose (Condition C) decreases bioavailability of mavorixafor compared to fasting conditions (Condition A):

- The GMR (90% CI) for C_{max} was 45.251 (36.07, 56.77).
- The GMR (90% CI) for $AUC_{0\text{-}inf}$ was 48.861 (42.71, 55.90).
- The GMR (90% CI) for $AUC_{0\text{-}last}$ was 48.074 (41.72, 55.40).

[00307] Administration of mavorixafor after an overnight fast of at least 10 hours followed by a LOW-fat meal 30 minutes after the mavorixafor dosing (Condition D) does not modify mavorixafor bioavailability compared to fasting conditions (Condition A):

- The GMR (90% CI) for C_{max} was 114.125 (90.67, 143.65). Marginally outside the equivalence limits of 70-143%.
- The GMR (90% CI) for $AUC_{0\text{-}inf}$ was 82.144 (71.54, 94.31).
- The GMR (90% CI) for $AUC_{0\text{-}last}$ was 83.277 (72.13, 96.15).

[00308] Administration of mavorixafor in the evening 2 hours after a HIGH-fat meal (eaten in 30 minutes) taken after an afternoon fast of at least 4 hours (Condition E) decreases bioavailability of mavorixafor compared to fasting conditions (Condition A):

- The GMR (90% CI) for C_{max} was 41.085 (32.83, 51.42).
- The GMR (90% CI) for $AUC_{0\text{-}inf}$ was 63.446 (55.35, 72.73).
- The GMR (90% CI) for $AUC_{0\text{-}last}$ was 61.430 (53.38, 70.69).

[00309] Administration of mavorixafor after an afternoon fast of at least 4 hours (Condition F) decreases bioavailability of mavorixafor compared to fasting conditions (Condition A):

- The GMR (90% CI) for C_{max} was 56.514 (45.19, 70.68).
- The GMR (90% CI) for $AUC_{0\text{-}inf}$ was 76.057 (66.61, 86.84).
- The GMR (90% CI) for $AUC_{0\text{-}last}$ was 76.507 (66.51, 88.00).

[00310] Administration of a single mavorixafor dose after a LOW or a HIGH-fat meal taken after an overnight fast of at least 10 hours (Condition C and Condition B, respectively) decreases mavorixafor exposure between approximately 20% and 40% compared to the mavorixafor administration in the afternoon after a 4-hour fast (Condition F). The administration of mavorixafor after an overnight fast followed by LOW-fat meal 30 minutes later (Condition D) increases C_{max} by approximately 100% compared to dosing in the afternoon after a 4-hour fast (Condition F). The administration of mavorixafor in the evening 2 hours after a HIGH-fat meal (eaten in 30 minutes) taken after an afternoon fast of at least 4 hours (Condition E) decreases Cmax by 27% compared to dosing in the afternoon after a 4-hour fast (Condition F).

[00311] Administration of mavorixafor after an overnight fast of 10 hours but followed by a meal 30 minutes later does not modify mavorixafor bioavailability compared to fasting conditions (overnight fast of 10 hours with no food intake until 4 hours post dosing). However, if a meal was given before mavorixafor administration it decreased mavorixafor bioavailability compared to fasting conditions.

CLAIMS

We claim:

1. A method for treating neutropenia in a patient, comprising orally administering to the patient mavorixafor or a pharmaceutically acceptable salt thereof, wherein:

(i) the patient has fasted from all food and drink except for water for at least 7 hours prior to administration of the mavorixafor or a pharmaceutically acceptable salt thereof and continues to fast for at least 30 minutes after administration; and

(ii) the mavorixafor or a pharmaceutically acceptable salt thereof is administered once per day at a dosage of about 100 mg to about 800 mg.

2. The method of claim 1, wherein the patient receives about 400 mg mavorixafor or a pharmaceutically acceptable salt thereof per day if the patient is at least 18 years old; or the patient receives about 400 mg mavorixafor or a pharmaceutically acceptable salt thereof per day if the patient is 12 to 17 years old and weighing at least 50 kg; or the patient receives about 200 mg mavorixafor or a pharmaceutically acceptable salt thereof per day if the patient is 12 to 17 years old and weighing under 50 kg.

3. The method of claim 1 or 2, wherein the patient has fasted for at least 10 hours prior to administration of the mavorixafor or a pharmaceutically acceptable salt thereof.

4. The method of claim 1 or 2, wherein the patient has fasted for at least 9 hours, at least 10 hours, at least 11 hours, at least 12 hours, at least 13 hours, at least 14 hours, at least 15 hours, or at least 16 hours prior to administration of the mavorixafor or a pharmaceutically acceptable salt thereof.

5. The method of claim 1 or 2, wherein the patient has fasted for 8-16 hours prior to administration of the mavorixafor or a pharmaceutically acceptable salt thereof.

6. The method of any one of claims 1-5, wherein the patient continues to fast for at least 45 minutes, at least 1 hour, at least 1.5 hours, or at least 2 hours after administration.

7. The method of any one of claims 1-5, wherein the patient continues to fast for 30 minutes to 4 hours after administration.

8. The method of any one of claims 1-7, wherein the patient has an absolute neutrophil count (ANC) less than 1500 cells/μL prior to beginning treatment with mavorixafor or a pharmaceutically acceptable salt thereof that has persisted for at least 3 months.

9. The method of any one of claims 1-7, wherein the patient has an absolute neutrophil count (ANC) less than 1000 cells/μL prior to beginning treatment with mavorixafor or a pharmaceutically acceptable salt thereof that has persisted for at least 3 months.

10. The method of any one of claims 1-7, wherein the patient has an absolute neutrophil count (ANC) less than 600 cells/μL prior to beginning treatment with mavorixafor or a pharmaceutically acceptable salt thereof that has persisted for at least 3 months.

11. The method of any one of claims 1-7, wherein the patient has an absolute neutrophil count (ANC) less than 500 cells/μL prior to beginning treatment with mavorixafor or a pharmaceutically acceptable salt thereof.

12. The method of any one of claims 1-7, wherein the patient has an absolute neutrophil count (ANC) less than 400 cells/μL prior to beginning treatment with mavorixafor or a pharmaceutically acceptable salt thereof.

13. The method of any one of claims 1-12, wherein the patient has a congenital neutropenia or an acquired primary autoimmune or chronic idiopathic neutropenia prior to beginning treatment with mavorixafor or a pharmaceutically acceptable salt thereof.

14. The method of claim 13, wherein the patient has a congenital neutropenia.

15. The method of claim 13, wherein the patient has a primary acquired neutropenia.

16. The method of claim 15, wherein the primary acquired neutropenia is primary autoimmune neutropenia.

17. The method of claim 15, wherein the primary acquired neutropenia is idiopathic.

18. The method of any one of claims 1-17, wherein the patient has had the neutropenia at least 6 months prior to beginning treatment with mavorixafor or a pharmaceutically acceptable salt thereof.

19. The method of claim 13, wherein the neutropenia is not attributable to medications, active or recent infections or a malignancy.

20. The method of claim 13, wherein the neutropenia is a severe congenital neutropenia (SCN) associated with an ELANE, CSF3R, CXCR2, or WAS mutation.

21. The method of claim 18, wherein the neutropenia is non-cyclic.

22. The method of any one of claims 1-13, wherein the neutropenia is associated with extra-hematological manifestation selected from Barth syndrome, Cohen syndrome, G6PC3, and Kostmann disease; or is associated with glycogen storage disease 1b (GSD1b); or the patient has Shwachman-Diamond syndrome.

23. The method of any one of claims 1-22, wherein prior to beginning treatment with mavorixafor or a pharmaceutically acceptable salt thereof the patient has an elevated risk of an infection selected from respiratory tract infections, otitis media, stomatitis, urinary tract infections, pyelonephritis, skin abscesses, cellulitis, and sepsis.

24. The method of any one of claims 1-22, wherein the patient has had at least 7 infections over the past year, or at least 2 infections requiring hospitalization in the past year.

25. The method of any one of claims 1-24, wherein the method produces an improvement in

the:

a. frequency, severity, duration of infections or time to next infection
b. emergence and/or clearance of oral ulcers;
c. appearance and/or clearance of gingivitis;

or any combination of the foregoing.

26. The method of any one of claims 1-25, wherein the method achieves an absolute neutrophil count (ANC) of at least 500 cells/μL and/or an absolute leukocyte count (ALC) of at least 1000 cells/μL.

27. The method of any one of claims 1-26, wherein the method achieves an absolute neutrophil count (ANC) of about 500 cells/μL to 3,000 cells/μL.

28. The method of any one of claims 1-25, wherein the method achieves an absolute neutrophil count (ANC) of about 500 cells/μL to 3,000 cells/μL and an absolute leukocyte count (ALC) of about 1,000 to 3,000 cells/μL.

29. The method of any one of claims 1-25, wherein the method achieves, on at least 60% of assessments, an absolute neutrophil count (ANC) of at least 1500 cells/μL or, if the patient has an ANC level prior to treatment of 500 or less cells/μL, an increase in ANC of at least 2-fold.

30. The method of any one of claims 1-29, wherein the method provides an increased maximum plasma concentration of mavorixafor (C_{max}) or Area Under the Curve (AUC) as compared to mavorixafor administered to the patient in an un-fasted state.

31. The method of any one of claims 1-30, wherein the method provides a maximum plasma concentration of mavorixafor (C_{max}) of at least 3700 μg/mL and/or an Area Under the Curve over 24 hours (AUC_{0-24}) of at least 16,000 μg/mL.

32. The method of any one of claims 1-30, wherein the method provides a maximum plasma concentration of mavorixafor (C_{max}) of at least 4000 μg/mL and/or an Area Under the Curve over

24 hours (AUC_{0-24}) of at least 17,000 μg/mL.

33. The method of any one of claims 1-30, wherein the method provides a maximum plasma concentration of mavorixafor (C_{max}) of at least 4200 μg/mL and/or an Area Under the Curve over 24 hours (AUC_{0-24}) of at least 18,000 μg/mL.

34. The method of any one of claims 1-30, wherein the method provides a maximum plasma concentration of mavorixafor (C_{max}) of about 3700 to about 7500 μg/mL and/or an Area Under the Curve over 24 hours (AUC_{0-24}) of about 16,000 to 25,000 μg/mL.

35. The method of any one of claims 1-30, wherein the method provides a mean maximum plasma concentration of mavorixafor (C_{max}) in a group of 2 or more patients of about 3700 to about 7500 μg/mL and/or a mean Area Under the Curve over 24 hours (AUC_{0-24}) of about 16,000 to 25,000 μg/mL.

36. The method of any one of claims 1-30, wherein the method provides a mean maximum plasma concentration of mavorixafor (C_{max}) in a group of 2 or more patients that is about 15% to 30% greater than that in a comparable group of 2 or more patients administered mavorixafor in a non-fasted state; and/or the method provides a mean Area Under the Curve over 24 hours (AUC_{0-24}) in a group of 2 or more patients that is about 15% to 30% greater than that in a comparable group of 2 or more patients administered mavorixafor in a non-fasted state.

37. The method of any one of claims 1-36, wherein the patient is receiving treatment with G-CSF, GM-CSF, or a variant of either.

38. The method of claim 37, wherein the patient is receiving a first dose of G-CSF, GM-CSF, or a variant of either, once daily.

39. The method of claim 38, wherein the first dose of G-CSF, GM-CSF, or a variant of either, is about 5 mcg/kg.

40. The method of any one of claims 1-39, wherein the patient has an endogenous G-CSF concentration of about 10^2 pg/mL or lower.

41. The method of any one of claims 1-39, wherein the patient has an endogenous G-CSF concentration of between about 10^2 pg/mL and 10^4 pg/mL.

42. The method of any one of claims 1-39, wherein the patient has an endogenous G-CSF concentration of about 10^5 pg/mL or greater.

43. The method of any one of claims 1-39, wherein the patient does not have a genetic abnormality associated with WHIM syndrome (a gain-of-function mutation in the *CXCR4* gene).