

METHODS FOR TREATING NEUTROPENIA

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Application No. 63/608,007, filed December 8, 2023; the contents of which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to methods for treating neutropenia, such as severe chronic idiopathic neutropenia, including certain genetically defined congenital forms of neutropenia, using a compound that inhibits CXC Receptor type 4 (CXCR4) in combination with a standard of care agent such as G-CSF, whereby the standard of care agent may be adjusted over the course of treatment.

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/ μ L. Severe neutropenia (ANC <500 cells/ μ L) 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 *HAXI*, *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 transplantation and/or treatment with cord blood stem cells. More recently, co-administration of CXCR4 inhibitors and G-CSF have been shown to be useful for treating neutropenias.

[0007] While the standard treatment for severe neutropenia includes administration of G-CSF, there is evidence that the specific levels of G-CSF are important in certain safety and tolerability outcomes. For instance, certain levels of G-CSF may induce bone pain, myalgia, splenomegaly, thrombocytopenia, interstitial pneumonitis, Myeloid Dysplastic Syndrome (MDS), Acute Myeloid Leukemia, fibrosis, periodontitis, and fatigue. Patient and physician surveys support the idea that there is an unmet need for therapies for neutropenia aside from the sole FDA-approved therapy, G-CSF, due to convenience/compliance issues as well as serious side effects.

[0008] Thus, for treatments that involve co-administration of G-CSF with one or more

additional therapeutics (e.g., CXCR4 inhibitors), there remains a need for more effective treatments of neutropenia and associated diseases while increasing safety and tolerability. The present invention addresses this need and provides other related advantages.

SUMMARY OF THE INVENTION

[0009] In one aspect, the present disclosure provides a method for treating neutropenia in a patient 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.

[0010] In another aspect, the present disclosure provides a method for treating neutropenia in a patient comprising administering to the patient an effective amount of a CXCR4 inhibitor for a first treatment period; and after the first treatment period, administering to the patient a starting dosage of G-CSF, GM-CSF, or a variant of either, for a second treatment period.

[0011] 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 at least about one month.

[0012] In another aspect, 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.

[0013] 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.

BRIEF DESCRIPTION OF THE FIGURES

[0014] FIG. 1 depicts a graphical representation of the protocol for Clinical Trial NCT04154488.

[0015] FIG. 2 depicts the disposition of 18 eligible patients participating in Clinical Trial NCT04154488.

[0016] FIG. 3 depicts mean ANC levels in a 24 year-old female with chronic idiopathic neutropenia over 6 months of treatment with mavorixafor and varying amounts of G-CSF. ULN = Upper Limit of Normal. LLN = Lower Limit of Normal.

[0017] FIG. 4 depicts mean ANC levels in a 20 year-old female with chronic idiopathic neutropenia over 6 months of treatment with mavorixafor and varying amounts of G-CSF.

[0018] FIG. 5 depicts mean ANC levels in a 39 year-old male with cyclic neutropenia over 6 months of treatment with mavorixafor and G-CSF.

[0019] FIG. 6 depicts a graphical representation of patient assessment in a G-CSF dose-reduction study.

[0020] FIG. 7 depicts the mean G-CSF dose reduction and mean patient ANC levels in a G-CSF dose-reduction study.

[0021] FIG. 8 depicts mean G-CSF dose reduction and mean patient ANC levels in patients with Congenital Neutropenia.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

[0022] It has now been found that the dose or dose frequency of G-CSF, or a variant thereof, when used in combination with CXCR4 inhibitors such as mavorixafor (X4P-001), may be adjusted in the methods of 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.

[0023] 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 . “Mild neutropenia” is generally described

as a patient having an ANC between 1000 and 1500 cells/uL. “Moderate neutropenia” is generally understood to refer to patients having an ANC between 500 and 1500 cells/uL. As used herein, “severe neutropenia” means that the patient has an ANC that is at or below 500 cells/uL. 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 uL, thus remaining ‘neutropenic’. For example, a patient with severe neutropenia [ANC < 500 cells/uL] may be treated using the methods of the present invention, until the patient’s ANC is raised to 1000 cell/uL. 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.

[0024] 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.

[0025] It should be understood that G-CSF, as used herein, may also refer to variants of G-CSF, such as pegylated G-CSF (peg-filgrastim), or to treatment with GM-CSF.

[0026] As used herein, the “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.

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

[0027] 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/ μ L. 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/ μ L 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).

[0028] 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.

[0029] In some embodiments, the patient is male. In some embodiments, the patient is female.

[0030] In some embodiments, the patient is less than 50 years old. In some embodiments, the patient is at least 50 years old.

[0031] 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.

[0032] 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.

[0033] In some embodiments, mavorixafor and G-CSF act with cooperativity, either additively or synergistically.

[0034] 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.

[0035] 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.

[0036] 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.

[0037] 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,

[0038] 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.

[0039] 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.

[0040] 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.

[0041] 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

[0042] 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).

[0043] 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/ μ L (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

[0044] 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/ μ L (Maciejewski-Duval et al. (2016) J Leukoc Bio. 99:1065-76) and often low lymphocyte levels from 112 to 1987 cells/ μ L (Vinh et al. (2010) Blood. 115:1519-29) or 490 to 2900 $\times 10^6$ /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).

[0045] 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.

[0046] 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).

[0047] CXCR3 inhibitors (e.g., mavoxixafor) may prove a useful bridge to transplant because of the potential to improve both the neutropenia and the lymphopenia in these patients.

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

[0048] 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/ μ L, 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).

[0049] 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).

[0050] 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.

[0051] 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 be 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.

[0052] 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.

[0053] In certain embodiments, the present invention comprises use of a starting dosage of filgrastim 0.1 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.

[0054] 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 loratidine; opioids; and dose reduction of G-CSFs are considered as second line therapy (Lambertini et al. (2014) Crit. Rev. Oncol. Hematol. 89:112-128).

[0055] 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.

[0056] 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).

[0057] 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 mavoxixafor, and G-CSF, or a variant thereof, or with a CXCR4 inhibitor, such as mavoxixafor, 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 mavoxixafor, 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/ μ L) to prevent infections and other manifestations of neutropenia (e.g., oral ulcers).

[0058] 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).

[0059] 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.

[0060] 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. In some embodiments, the first treatment period and the second treatment period do not overlap.

[0061] 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.

[0062] 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.

[0063] 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.

[0064] 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.

[0065] 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.

[0066] 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.

[0067] 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.

[0068] 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.

[0069] 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.

[0070] 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.

[0071] 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.

[0072] 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.

[0073] 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.

[0074] It should be understood that the dosing frequency can also be increased by any of the amounts described above.

[0075] 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.

[0076] It may also be beneficial to begin administering G-CSF after a patient is already being treated with a CXCR4 inhibitor.

[0077] 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.

[0078] 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.

[0079] 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.

[0080] 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.

[0081] 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 about 3 months. 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 about 4 months, about 5 months, about 6 months, about 7 months, about 8 months, about 9 months, about 10 months, about 11 months, or about 12 months.

[0082] 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 about 3 months and continuing with dose reduction through a subsequent period of about 3 months.

[0083] In some embodiments, the amount and/or dosing frequency is reduced by about 50% after the patient has received the CXCR4 inhibitor for about 3 months. In some embodiments, the amount and/or dosing frequency is reduced by about 70% after the patient has received the CXCR4 inhibitor for about 6 months.

[0084] In some embodiments, the amount and/or dosing frequency is reduced by about 50% after the patient has received the CXCR4 inhibitor for about 3 months and further reduced in subsequent months. In some embodiments, the amount and/or dosing frequency is reduced by about 50% after the patient has received the CXCR4 inhibitor for about 3 months and further reduced by an additional about 20% over the 3 subsequent months.

[0085] In some embodiments, the amount and/or dosing frequency is reduced by about 25-50% after the patient has received the CXCR4 inhibitor for about 3 months and further reduced in subsequent months. In some embodiments, the amount and/or dosing frequency is reduced by about 25-50% after the patient has received the CXCR4 inhibitor for about 3 months and further reduced by an additional about 10-40% over the 3 subsequent months.

[0086] In some embodiments, the amount and/or dosing frequency is reduced by about 25-50% after the patient has received the CXCR4 inhibitor for about 3 months and further reduced over a further 3-24 months until dosing of G-CSF, GM-CSF, or a variant of either, is completely discontinued.

[0087] 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. 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.

[0088] 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 receiving a first dose once daily. In some embodiments, the patient receives a subsequent dose (e.g., first, second, third, or greater).

[0089] 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).

[0090] 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.

[0091] 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.

[0092] 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.

[0093] 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.

[0094] 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.

[0095] 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.

[0096] 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 $<500/\text{mcL}$ ($< 0.5 \times 10^9/\text{L}$). Risk of certain infections is increased. It is diagnosed by complete blood count with differential. Typical treatment includes hematopoietic stem cell transplantation.

[0097] 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.

[0098] 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.

[0099] 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.

[00100] 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.

[00101] 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.

[00102] 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.

[00103] 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.

[00104] 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.

[00105] 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.

[00106] In some embodiments, the methods described herein increase absolute neutrophil count (ANC) to a level greater than or equal to 500/ μ L and/or increase absolute lymphocyte count (ALC) to a level greater than or equal to 1000/ μ L.

[00107] In some embodiments, said patient originally exhibits ANC less than 600/ μ L and/or ALC less than 1000/ μ L before treatment. In some embodiments, said patient originally exhibits ANC less than 500/ μ L and/or ALC less than 650/ μ L before.

[00108] In some embodiments, a method described herein results in an increase or decrease in ANC levels to at least about 500/ μ L, at least about 600/ μ L, at least about 700/ μ L, at least about 800/ μ L, at least about 900/ μ L, at least about 1000/ μ L, at least about 1,100/ μ L, at least about 1,200/ μ L, at least about 1,300/ μ L, at least about 1,400/ μ L, at least about 1,500/ μ L, or to about that of a human with a normally-functioning immune system, on at least 85% of assessments.

[00109] In some embodiments, a method described herein results in an increase or decrease in ALC to at least about 1000/ μ L, about 1,200/ μ L, or about 1,500/ μ L, or to about that of a human with a normally-functioning immune system, on at least 85% of assessments.

[00110] 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.

[00111] 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.

[00112] 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/ μ L and/or an absolute leukocyte count (ALC) of at least 1000/ μ L. 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/ μ L and 10,000 cells/ μ L. 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/ μ L and 10,000 cells/ μ L; between about 1,000 cells/ μ L and 9,000 cells/ μ L; between about 1000 cells/ μ L and 8,000 cells/ μ L; between about 1,000 cells/ μ L and 7,000 cells/ μ L; between about 1,000 cells/ μ L and 6,000 cells/ μ L; between about 1,000 cells/ μ L and 5,000 cells/ μ L; between about 1,000 cells/ μ L and 4,000 cells/ μ L; between about 1,000 cells/ μ L and 3,000 cells/ μ L; between about 1,000 cells/ μ L and 2,000 cells/ μ L; between about 2,000 cells/ μ L and 10,000 cells/ μ L; between about 2,000 cells/ μ L and 9,000 cells/ μ L; between about 2,000 cells/ μ L and 8,000 cells/ μ L; between about 2,000 cells/ μ L and 7,000 cells/ μ L; between about 2,000 cells/ μ L and 6,000 cells/ μ L; between about 2,000 cells/ μ L and 5,000 cells/ μ L; between about 2,000 cells/ μ L and 4,000 cells/ μ L; between about 2,000 cells/ μ L and 3,000 cells/ μ L; between about 3,000 cells/ μ L and 10,000 cells/ μ L; between about 3,000 cells/ μ L and 9,000 cells/ μ L; between about 3,000 cells/ μ L and 8,000 cells/ μ L; between about 3,000 cells/ μ L and 7,000 cells/ μ L; between about 3,000 cells/ μ L and 6,000 cells/ μ L; between about 3,000 cells/ μ L and 5,000 cells/ μ L; between about 3,000 cells/ μ L and 4,000 cells/ μ L; between about 4,000 cells/ μ L and 10,000 cells/ μ L; between about 4,000 cells/ μ L and 9,000 cells/ μ L; between about 4,000 cells/ μ L and 8,000 cells/ μ L; between about 4,000 cells/ μ L and 7,000 cells/ μ L; between about 4,000 cells/ μ L and 6,000 cells/ μ L; between about 4,000 cells/ μ L and 5,000 cells/ μ L; between about 5,000 cells/ μ L and 10,000 cells/ μ L; between about 5,000 cells/ μ L and 9,000 cells/ μ L; between about 5,000 cells/ μ L and 8,000 cells/ μ L;

between about 5,000 cells/ μ L and 7,000 cells/ μ L; between about 5,000 cells/ μ L and 6,000 cells/ μ L; between about 6,000 cells/ μ L and 10,000 cells/ μ L; between about 6,000 cells/ μ L and 9,000 cells/ μ L; between about 6,000 cells/ μ L and 8,000 cells/ μ L; between about 6,000 cells/ μ L and 7,000 cells/ μ L; between about 7,000 cells/ μ L and 10,000 cells/ μ L; between about 7,000 cells/ μ L and 9,000 cells/ μ L; between about 7,000 cells/ μ L and 8,000 cells/ μ L; between about 8,000 cells/ μ L and 10,000 cells/ μ L; between about 8,000 cells/ μ L and 9,000 cells/ μ L; or between about 9,000 cells/ μ L and 10,000 cells/ μ L. 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/ μ L.

[00113] 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.

[00114] In some embodiments, the methods described herein achieve an ANC of at least 500 cells/ μ L and/or an ALC of at least 1000/ μ L.

[00115] 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/ μ L, less than about 1,000 cells/ μ L, or less than about 1,500 cells/ μ L, 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.

[00116] 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/ μ L, about 9,000 cells/ μ L, 8,000 cells/ μ L, 7,000 cells/ μ L, 6,000 cells/ μ L, 5,000 cells/ μ L, 4,000 cells/ μ L, 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.

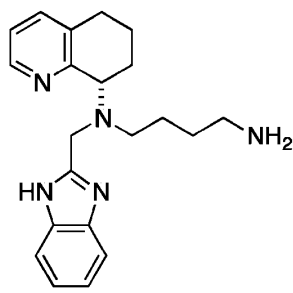
[00117] In some embodiments, the frequency of dosage in a first or starting dose of G-CSF, GM-CSF, or variant of either, is reduced or increased, for example, reduced or increased in frequency by at least 25%, 50%, 75%, or 90%. It should be understood that any subsequent dosage (e.g., second, third, 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

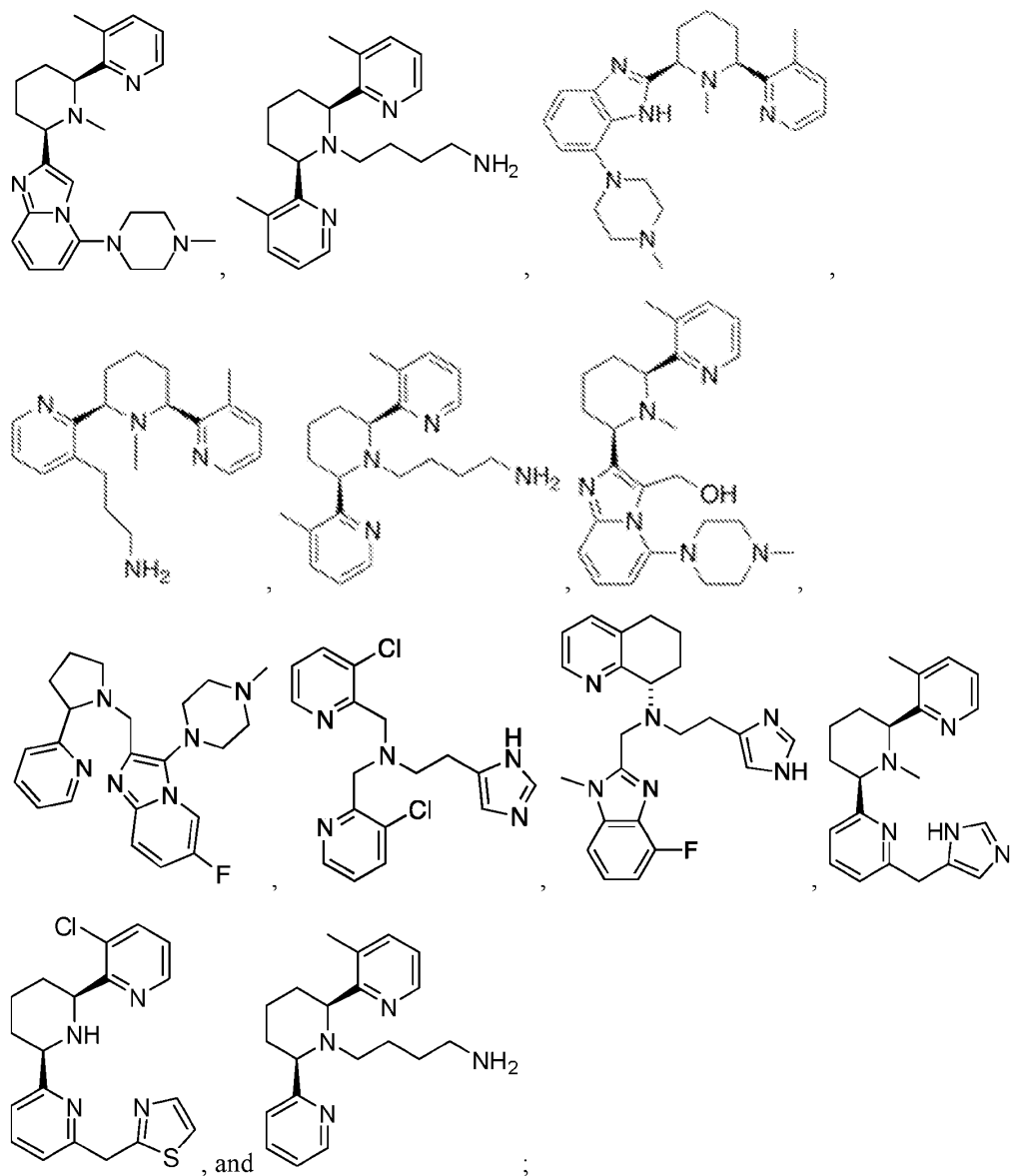
[00118] As described herein, a variety of CXCR4 inhibitors may be used in accordance with the present disclosure.

[00119] 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:



[00120] 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.

[00121] In some embodiments, the CXCR4 inhibitor is selected from mavorixafor,

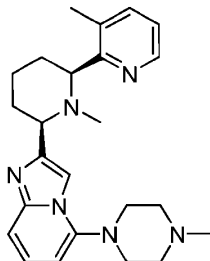


or a pharmaceutically acceptable salt or composition thereof.

[00122] In some embodiments, the CXCR4 inhibitor is plerixafor or a pharmaceutically acceptable salt thereof.

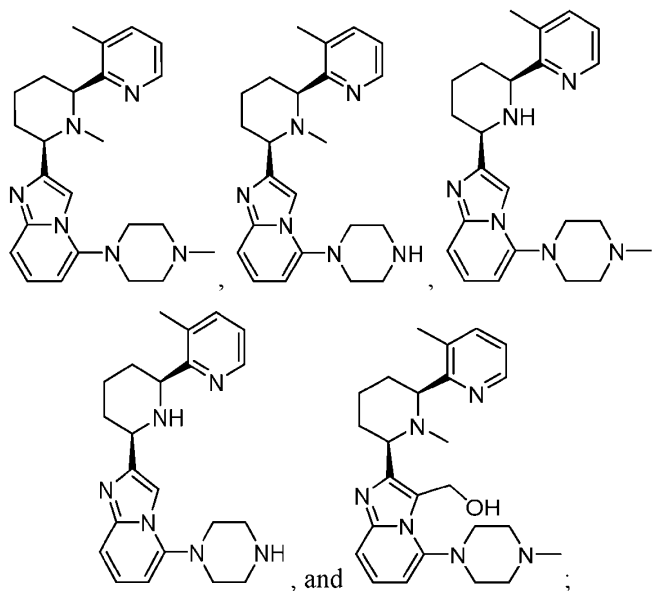
[00123] In some embodiments, the CXCR4 inhibitor is mavorixafor or a pharmaceutically acceptable salt or composition thereof.

[00124] In some embodiments, the CXCR4 inhibitor is:



or a pharmaceutically acceptable salt thereof.

[00125] In some embodiments, the CXCR4 inhibitor is selected from the following:

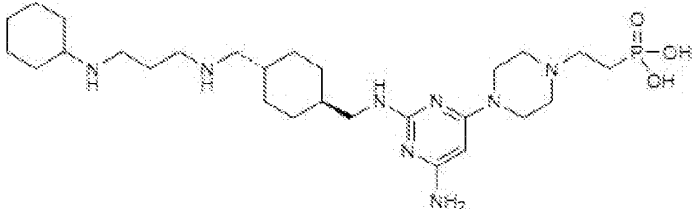


or a pharmaceutically acceptable salt thereof.

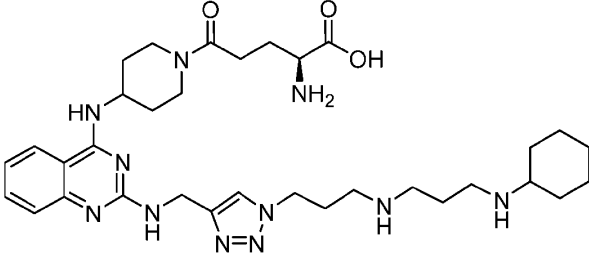
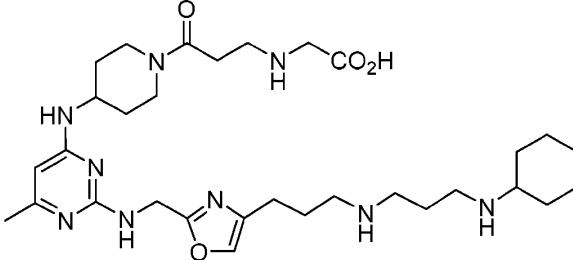
[00126] In some embodiments, the CXCR4 inhibitor is one of those described in Table 1, below.

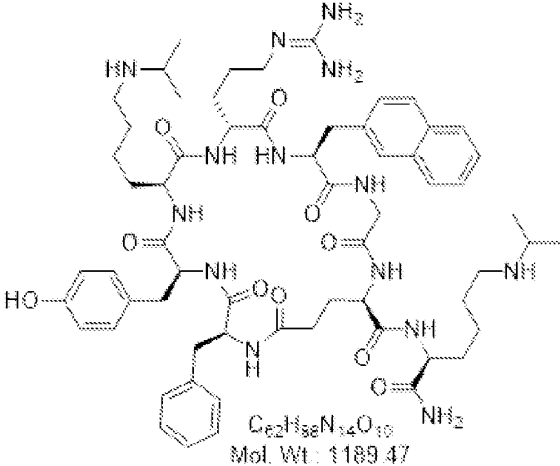
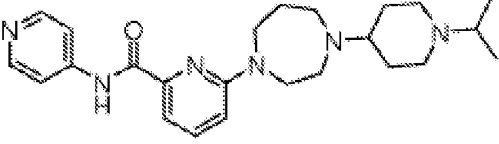
Each document listed in Table 1 is hereby incorporated by reference in its entirety.

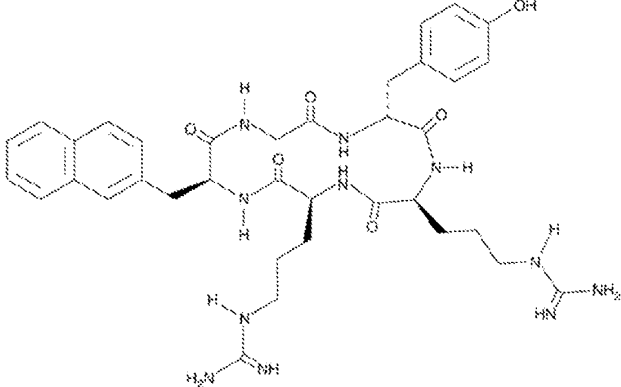
Table 1: Exemplary CXCR4 Inhibitors

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 <i>Multiple Myeloma</i> 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 <i>Acute Myocardial Infarction</i> (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-(cyclohexylamino)propyl]triazol-4-yl]methanol]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-naphthylalanine (Nal); residues 6 and 8 are citrulline (Cit) and D-citrulline (D-Cit) (N⁵-aminocarbonylornithine) respectively
USL-311 Originally developed by Ligand; licensed to Usher-Smith And to Proximagen	 WO2018162924A1 NCT02765165: Phase 1/2 Study of <i>USL311 Alone and in</i>

Molecule/Company	Status and Relevant Information
	<i>Combination With Lomustine</i> in Subjects With Advanced Solid Tumors and <i>Relapsed/Recurrent Glioblastoma Multiforme (GBM)</i>; USL311 as Single Agent and in Combination With <i>Lomustine (CCNU)</i> 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

[00127] 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.

[00128] As used herein, the term “well-tolerated” in reference to a dose of CXCR4 inhibitor (e.g., mavoxixafor) 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 $\geq$ 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 $\geq$ 48 hours despite optimal medical management
Hepatobiliary	$\geq$ Grade 2 total bilirubin elevation with $\geq$ Grade 2 ALT/AST elevation $\geq$ Grade 3 ALT/AST elevation lasting $\geq$ 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.

[00129] 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).

[00130] In some embodiments, the CXCR4 inhibitor described herein is mavorixafor, or a pharmaceutically acceptable salt thereof. As of May 2019, approximately 193 healthy volunteers and patients had been treated with mavorixafor in clinical studies (n= 70 healthy volunteers, n= 16 HIV, n= 99 oncology, n=8 WHIM syndrome). Overall, mavorixafor has been generally well tolerated, with no mavorixafor-related serious AEs (SAEs) causing a fatal outcome in any of the patients.

[00131] 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.

[00132] 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.

[00133] 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.

[00134] 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.

[00135] 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.

[00136] 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.

[00137] 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.

[00138] 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.

[00139] 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.

[00140] 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.

[00141] 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.

[00142] 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.

[00143] The contents of each document cited in the specification are herein incorporated by reference in their entireties.

EXEMPLIFICATION

Example 1: Preliminary Response Data and G-CSF Dose Reduction in Phase 2 Open-Label Study in Patients with Chronic Neutropenic Disorders

[00144] A Phase 2, open-label Study is conducted in patients with chronic neutropenic disorders.

[00145] Individuals (aged ≥ 12 years) with diagnosis of congenital neutropenia, CyN, or CIN ≥ 6 months prior and ANC $< 1000/\mu\text{L}$ (or no lower limit but $< 10,000/\mu\text{L}$ if on G-CSF) at screening visits were enrolled in the phase 2 trial. Eligible adult participants received once-daily 400 mg of mavorixafor while adolescents received weight-based dosing (> 50 kg, 400mg; ≤ 50 kg, 200 mg) for 6 months with or without G-CSF. Participants already on G-CSF continued their individualized G-CSF dosing for ≥ 8 weeks, followed by potential dose and/or frequency reduction based on monthly ANC assessments. Hematologic parameters, including ANC, were assessed over 8 hours on day 1 and at months 1 and 3, with continued assessment at month 6. At months 2 and 4 (assessment to continue at month 5), hematologic parameters were assessed within 2 to 4 hours of dosing to reduce trial burden. FIG. 1 depicts a graphical representation of the protocol for Clinical Trial NCT04154488. FIG. 2 depicts the disposition of 18 eligible patients participating in the trial.

[00146] Preliminary data from the first 3 participants on G-CSF receiving chronic once-daily oral mavorixafor for at least 2 months showed increases in mean ANC compared with baseline (BL) at all time points assessed in all participants. ANCs reached normal ranges for all participants. Increases in ANC supported physicians' decisions to reduce G-CSF dosing.

[00147] Two participants (P1 and P2) with CIN achieved increases in ANC that enabled initiation of G-CSF tapering at month 2. For P1, G-CSF dose was tapered to 50% at month 2, and further G-CSF tapering occurred at month 3. ANC remained within normal ranges during this period. At month 4, G-CSF dosing was fully withdrawn, and the participant continued daily mavorixafor monotherapy (see FIG. 3). For P2, ANC increased $\sim 3\times$ baseline by month 2 (see FIG. 4). G-CSF dose was tapered to 50% after month 2. ANC remained within normal ranges during this period. At month 3, G-CSF dosing was fully withdrawn, and the participant continued daily mavorixafor monotherapy with an ANC ~ 1000 cells/ μL .

[00148] A third participant (P3) with CyN receiving mavorixafor daily with concurrent G-CSF showed increases in ANC over BL for 4 months (see FIG. 5).

[00149] *Conclusions:* Our report shows that chronic treatment with oral, once-daily mavorixafor in combination with G-CSF resulted in durable increases in ANC compared with BL for ≥ 3 months in 3 study participants. Reduction of injectable G-CSF dosing was implemented in 2 study participants with CIN following robust ANC increase observed after the first 2 months of combination treatment. These preliminary data also support the safety of concomitant treatment with G-CSF and mavorixafor. Additional data from the ongoing phase 2 study will further elucidate the potential of daily, oral mavorixafor as a treatment for CN and to reduce the burden and associated AEs of injectable G-CSF.

Example 2: ANC Response in CN Phase 2 Participants with G-CSF Dose Adjustments

[00150] Additional data were collected for 12 eligible participants of the study described in Example 1. Clinicians were given the option to reduce the G-CSF dose following the Month 2 visit. Of the 12 eligible patients, 75% (9 of 12) had the injectable G-CSF therapy reduced by the supervising physician. 33% (3 of 9) of those participants were taken completely off G-CSF prior to their Month 6 visit. This is graphically depicted in FIG. 6.

[00151] FIG. 7 shows the Mean G-CSF reduction over the course of the study and the mean ANC levels of patients who had their G-CSF reduced during the study. Reduction of G-CSF has the potential to improve patients' quality of life and lower long-term risk of malignancy associated with chronic G-CSF use. 89% (8 of 9) of patients had their G-CSF adjusted at the earliest possible timepoint (following the Month 2 visit). Mean ANC was maintained at normal levels ($>1,500$ cells/ μ L) through Month 6 of the study.

[00152] For participants with Congenital Neutropenia ($n=3$), mean ANC was maintained well above the upper limit of normal range (ULN) at Month 6 with a greater than 50% G-CSF reduction. Two of the three participants had G-CSF reduced by the earliest possible timepoint (Month 3), and none were completely taken off G-CSF by Month 6. As shown in FIG. 8, the mean reduction in G-CSF dose by Month 3 was 39% for the two participants, and the mean reduction in G-CSF dose by Month 6 was 56% for all 3 participants. FIG. 8 also shows the mean ANC of the three participants from baseline to Month 6.

CLAIMS

We claim:

1. A method for treating neutropenia in a patient, comprising:
 - (a) 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
 - (b) 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.
2. The method of claim 1, wherein the neutropenia is congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.
3. The method of claims 1 or 2, wherein the patient has a CXCR4 mutation.
4. The method of any one of claims 1-3, wherein the patient has a WHIM, ELANE, HAX1, G6PC3, GSD1b, GATA2, WAS, or SBDS mutation.
5. The method of any one of claims 1-4, wherein 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 leucocytes and/or erythrocytes and/or thrombocytes), a panleukocytopenia (cytopenia of neutrophils and/or monocytes and/or lymphocytes including B-cells, T-cells and/or NK cells), or any combination of the foregoing.
6. The method of any one of claims 1-5, wherein the CXCR4 inhibitor is administered daily.
7. The method of any one of claims 1-6, wherein the CXCR4 inhibitor is mavorixafor, or a pharmaceutically acceptable salt thereof.
8. The method of claim 7, wherein the mavorixafor, or a pharmaceutically acceptable salt thereof, is administered at a dose of about 100 mg/day to about 800 mg/day.

9. The method of claims 7 or 8, wherein the mavorixafor, or a pharmaceutically acceptable salt thereof, is administered at a dose of about 400 mg/day.
10. The method of any one of claims 1-9, wherein the starting dosage of G-CSF is a daily amount of about 5 mcg/kg.
11. The method of any one of claims 1-10, wherein the second dosage of G-CSF, GM-CSF, or a variant of either, is reduced by about 25-75% relative to the starting dosage of G-CSF.
12. The method of any one of claims 1-11, wherein the second dosage of G-CSF, GM-CSF, or a variant of either, is reduced by about 25% relative to the starting dosage.
13. The method of any one of claims 1-11, wherein the second dosage of G-CSF, GM-CSF, or a variant of either, is reduced by about 50% relative to the starting dosage.
14. The method of any one of claims 1-11, wherein the second dosage of G-CSF, GM-CSF, or a variant of either, is reduced by about 75% relative to the starting dosage.
15. The method of any one of claims 1-10, wherein the second dosage of G-CSF, GM-CSF, or a variant of either, is increased by about 25-75% relative to the starting dosage of G-CSF.
16. The method of any one of claims 1-10 or 15, wherein the second dosage of G-CSF, GM-CSF, or a variant of either, is increased by about 25% relative to the starting dosage.
17. The method of any one of claims 1-10 or 15, wherein the second dosage of G-CSF, GM-CSF, or a variant of either, is increased by about 50% relative to the starting dosage.
18. The method of any one of claims 1-10 or 15, wherein the second dosage of G-CSF, GM-CSF, or a variant of either, is increased by about 75% relative to the starting dosage.

19. The method of any one of claims 1-18, wherein the first treatment period has a duration of about 1-12 months.
20. The method of any one of claims 1-19, wherein the first treatment period has a duration of about 1 month.
21. The method of any one of claims 1-20, wherein the second dosage of G-CSF, GM-CSF, or a variant of either, in the second treatment period is further reduced or increased as needed in a subsequent treatment period.
22. The method of claim 21, wherein the second dosage of G-CSF, GM-CSF, or a variant of either, is further reduced or increased by 25-75% to arrive at a third dosage for a third treatment period.
23. The method of any one of claims 1-22, wherein the starting dosage of G-CSF, GM-CSF, or a variant of either, is increased or decreased by about 1-50% a month during the second treatment period.
24. The method of claim 23, wherein the starting dosage is decreased by about 10% a month.
25. The method of claim 23, wherein the starting dosage is decreased by about 25% a month.
26. The method of claim 23, wherein the starting dosage is decreased by about 50% a month.
27. The method of any one of claims 1-26, wherein dosing with G-CSF, GM-CSF, or a variant of either, is stopped after the second treatment period.
28. The method of any one of claims 1-27, wherein the frequency of dosing G-CSF, GM-CSF, or a variant of either, is decreased from daily.

29. The method of claim 28, wherein the frequency of dosing is decreased to every other day.
30. The method of claim 28, wherein the frequency of dosing is decreased to once per week.
31. The method of and one of claims 1-30, wherein dosing with G-CSF, GM-CSF, or a variant of either, is stopped between about 1-6 months after beginning treatment.
32. The method of any one of claims 1-31, 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.
33. The method of any one of claims 1-32, wherein the method produces an improvement in:
- a. extent and/or duration and/or emergence of G-CSF-induced bone pain;
 - b. extent and/or duration and/or emergence of G-CSF-induced myalgia;
 - c. extent and/or duration and/or emergence of G-CSF-induced splenomegaly;
 - d. extent and/or duration and/or emergence of G-CSF-induced thrombocytopenia;
 - e. extent and/or duration and/or emergence of G-CSF-induced interstitial pneumonitis;
 - f. emergence of G-CSF-induced MDS (Myeloid Dysplastic Syndrome) and/or AML;
 - g. extent and/or duration and/or emergence of G-CSF-induced fibrosis;
 - h. extent and/or duration and/or emergence of G-CSF-induced periodontitis;
 - i. extent and/or duration and/or emergence of fatigue;
- or any combination of the foregoing.
34. A method for treating neutropenia in a patient in need thereof, comprising:
- (a) administering to the patient an effective amount of a CXCR4 inhibitor for a first treatment period; and

(b) after the first treatment period, administering to the patient a starting dosage of G-CSF, GM-CSF, or a variant of either, for a second treatment period;

wherein the first treatment period and the second treatment period do not overlap.

35. The method of claim 34, wherein the neutropenia is congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

36. The method of claims 34 or 35, wherein the patient has a CXCR4 mutation.

37. The method of any one of claims 34-36, wherein the patient has a WHIM, ELANE, HAX1, G6PC3, GSD1b, GATA2, WAS, or SBDS mutation.

38. The method of any one of claims 34-37, wherein the CXCR4 inhibitor is administered daily.

39. The method of any one of claims 34-38, wherein the CXCR4 inhibitor is mavorixafor, or a pharmaceutically acceptable salt thereof.

40. The method of claim 39, wherein the mavorixafor, or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 100 mg/day to about 800 mg/day.

41. The method of claims 39 or 40, wherein the mavorixafor, or a pharmaceutically acceptable salt thereof, is administered at a dose of about 400 mg/day.

42. The method of any one of claims 34-41, wherein the starting dosage of G-CSF, GM-CSF, or a variant of either, is a daily amount of about 5 mcg/kg.

43. The method of any one of claims 34-42, wherein the starting dosage of G-CSF, GM-CSF, or a variant of either, is reduced by about 25-75% to a second dosage during the second treatment period.

44. The method of any one of claims 34-43, wherein the starting dosage of G-CSF, GM-CSF, or a variant of either, is reduced by about 25% to a second dosage during the second treatment period.
45. The method of any one of claims 34-43, wherein the starting dosage of G-CSF, GM-CSF, or a variant of either, is reduced by about 50% to a second dosage during the second treatment period.
46. The method of any one of claims 34-43, wherein the starting dosage of G-CSF, GM-CSF, or a variant of either, is reduced by about 75% to a second dosage during the second treatment period.
47. The method of any one of claims 34-42, wherein the starting dosage of G-CSF, GM-CSF, or a variant of either, is increased by about 25-75% to a second dosage during the second treatment period.
48. The method of any one of claims 34-42 or 47, wherein the starting dosage of G-CSF, GM-CSF, or a variant of either, is increased by about 25% to a second dosage during the second treatment period.
49. The method of any one of claims 34-42 or 47, wherein the starting dosage of G-CSF, GM-CSF, or a variant of either, is increased by about 50% to a second dosage during the second treatment period.
50. The method of any one of claims 34-42 or 47, wherein the starting dosage of G-CSF, GM-CSF, or a variant of either, is increased by about 75% to a second dosage during the second treatment period.
51. The method of any one of claims 34-50, wherein the first treatment period has a duration

of about 1-12 months.

52. The method of any one of claims 34-51, wherein the first treatment period has a duration of about 1 month.

53. The method of any one of claims 34-42, wherein the dose of G-CSF, GM-CSF, or a variant of either, in the second treatment period is further reduced or increased as needed in a subsequent treatment period.

54. The method of claim 53, wherein the dose of G-CSF, GM-CSF, or a variant of either, is further reduced or increased by 25-75% to arrive at a third dosage for a third treatment period.

55. The method of any one of claims 34-44, wherein dosing with G-CSF, GM-CSF, or a variant of either, is stopped after the second treatment period.

56. The method of any one of claims 34-55, wherein the frequency of dosing G-CSF, GM-CSF, or a variant of either, is decreased from daily during the second or third treatment period.

57. The method of claim 56, wherein the frequency of dosing is decreased to every other day.

58. The method of claim 56, wherein the frequency of dosing is decreased to once per week.

59. The method of and one of claims 34-58, wherein dosing with G-CSF, GM-CSF, or a variant of either, is stopped between about 1-6 months after beginning treatment.

60. 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 at least about one month.

61. The method of claim 60, wherein the neutropenia is congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.
62. The method of claim 60 or 61, wherein the patient has a CXCR4 mutation.
63. The method of any one of claims 60-62, wherein the patient has a WHIM, ELANE, HAX1, G6PC3, GSD1b, GATA2, WAS, or SBDS mutation.
64. The method of any one of claims 60-63, wherein the CXCR4 inhibitor is administered daily.
65. The method of any one of claims 60-64, wherein the CXCR4 inhibitor is mavorixafor, or a pharmaceutically acceptable salt thereof.
66. The method of claim 65, wherein the mavorixafor, or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 100 mg/day to about 800 mg/day.
67. The method of claim 65 or 66, wherein the mavorixafor, or a pharmaceutically acceptable salt thereof, is administered at a dose of about 400 mg/day.
68. The method of any one of claims 60-67, wherein the patient is receiving G-CSF, GM-CSF, or a variant of either, in a daily amount of about 5 mcg/kg.
69. The method of any one of claims 60-68, wherein the patient has received the CXCR4 inhibitor, or pharmaceutically acceptable salt thereof, for about one to four months.
70. The method of any one of claims 60-69, wherein the patient has received the CXCR4 inhibitor, or pharmaceutically acceptable salt thereof, for about one month.

71. The method of any one of claims 60-69, wherein the patient has received the CXCR4 inhibitor, or pharmaceutically acceptable salt thereof, for about two months.
72. The method of any one of claims 60-69, wherein the patient has received the CXCR4 inhibitor, or pharmaceutically acceptable salt thereof, for about three months.
73. The method of any one of claims 60-72, wherein the dose of G-CSF, GM-CSF, or a variant of either, is reduced by about 25-75%.
74. The method of any one of claims 60-73, wherein the dose of G-CSF, GM-CSF, or a variant of either, is reduced by about 25%.
75. The method of any one of claims 60-73, wherein the dose of G-CSF, GM-CSF, or a variant of either, is reduced by about 50%.
76. The method of any one of claims 60-73, wherein the dose of G-CSF, GM-CSF, or a variant of either, is reduced by about 75%.
77. The method of any one of claims 60-76, wherein the frequency of dosing of G-CSF, GM-CSF, or a variant of either, is increased.
78. The method of any one of claims 60-77, wherein the frequency of dosing of G-CSF, GM-CSF, or a variant of either, is increased from once daily to twice daily.
79. The method of any one of claims 60-76, wherein the frequency of dosing of G-CSF, GM-CSF, or a variant of either, is decreased.
80. The method of any one of claims 60-76 or 79, wherein the frequency of dosing of G-CSF, GM-CSF, or a variant of either, is decreased to the frequency of between once every other day to once weekly.

81. The method of any one of claims 60-76 or 79-80, wherein the frequency of dosing of G-CSF, GM-CSF, or a variant of either, is decreased to once every other day.
82. The method of any one of claims 60-76 or 79-80, wherein the frequency of dosing of G-CSF, GM-CSF, or a variant of either, is decreased to once weekly.
83. The method of any one of claims 1-82, wherein the method achieves an absolute neutrophil count (ANC) of at least 500 cells/ μ L and/or an absolute leukocyte count (ALC) of at least 1000 cells/ μ L.
84. The method of any one of claims 1-82, wherein the method achieves an absolute neutrophil count (ANC) of about 500 cells/ μ L to 3,000 cells/ μ L.
85. The method of any one of claims 1-82, wherein the method achieves an absolute neutrophil count (ANC) of about 500 cells/ μ L to 3,000 cells/ μ L and an absolute leukocyte count (ALC) of about 1,000 to 3,000 cells/ μ L.
86. 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.
87. The method of claim 86, wherein the patient has a CXCR4 mutation.
88. The method of claim 86 or 87, wherein the patient has a WHIM, ELANE, HAX1, G6PC3, GSD1b, GATA2, WAS, or SBDS mutation.
89. The method of any one of claims 86-88, wherein the patient is receiving treatment with G-CSF, GM-CSF, or a variant of either.

90. The method of claim 89, wherein the patient is receiving a first dose of G-CSF, GM-CSF, or a variant of either, once daily.

91. The method of claim 90, wherein the first dose of G-CSF, GM-CSF, or a variant of either, is about 5 mcg/kg.

92. The method of claim 90 or 91, wherein the first dose is increased or decreased to a second dose to achieve an absolute neutrophil count (ANC) of at least 500 cells/ μ L and/or an absolute leukocyte count (ALC) of at least 1000 cells/ μ L.

93. The method of any one of claims 90-92, wherein the first dose is increased or decreased to achieve an absolute neutrophil count (ANC) of between about 1000 cells/ μ L and 10,000 cells/ μ L.

94. The method of any one of claims 90-93, wherein when the patient is receiving the first dose and the patient's ANC is less than about 1,500 cells/ μ L, the second dose is 50% greater relative to the first dose.

95. The method of any one of claims 90-93, wherein when the patient is receiving the first dose and the patient's ANC is greater than about 10,000 cells/ μ L, the second dose is 50% lower relative to the first dose.

96. 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:

- (a) determining an initial absolute neutrophil count (ANC) of the patient; and
- (b) 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.

97. The method of claim 96, wherein the patient is being administered a dose of a CXCR4

inhibitor, or a pharmaceutically acceptable salt thereof.

98. The method of claim 97, wherein the CXCR4 inhibitor is mavoxixafor, or a pharmaceutically acceptable salt thereof.

99. The method of any one of claims 96-98, wherein the patient's initial ANC is greater than or equal to about 10,000 cell/ μ L.

100. The method of any one of claims 96-99, wherein the second dose or frequency of the second dose is reduced 50% relative to the dose or the frequency of the dose.

101. The method of any one of claims 96-100, further comprising:

(c) determining the patient's ANC after the patient has been receiving the second dose for at least one week;

(d) 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.

102. The method of any one of claims 96-101, wherein the dose of G-CSF, GM-CSF, or a variant of either, is a daily dose.

103. The method of claim 102, wherein the second dose administered less frequently than daily.

104. The method of claim 103, wherein the second dose is administered every other day.

105. The method of claim 103, wherein the second dose is administered once per week.

106. The method of any one of claims 1-105, wherein the patient has an endogenous G-CSF concentration of about 10^2 pg/mL or lower.

107. The method of any one of claims 1-105, wherein the patient has an endogenous G-CSF concentration of between about 10^2 pg/mL and 10^4 pg/mL.

108. The method of any one of claims 1-105, wherein the patient has an endogenous G-CSF concentration of about 10^5 pg/mL or greater.