A Phase III, Double-blind, Randomized, Crossover Study of Plerixafor Versus G-CSF in the Treatment of Patients with WHIM Syndrome

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LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse Event/Adverse Experience
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
AR	Adverse Reaction
ARDS	Acute Respiratory Distress Syndrome
b.i.d.	Twice per day (bis in die)
CFR	Code of Federal Regulations
CBC	Complete Blood Count (with differential)
CC	Clinical Center
CrCl	Creatinine Clearance (calculated)
CRF	Case Report Form
CRIS	Clinical Research Information System (for NIH Clinical Center)
CSO	Clinical Safety Office
CXCL12	CXC chemokine ligand 12, aka SDF-1
CXCR4	CXC chemokine receptor 4
DEXA	Dual-energy X-ray Absorptiometry
DCR	Division of Clinical Research
DSMB	Data and Safety Monitoring Board
EBV	Epstein-Barr Virus
ECHO	Echocardiogram
EOT	End of Treatment
EKG	Electrocardiogram
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
GCP	Good Clinical Practices
G-CSF	Granulocyte Colony-Stimulating Factor
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
GRK	G Protein-Coupled Receptor Kinase
GU	Genitourinary
GYN	Gynecology
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HSC	Hematopoietic Stem Cell
ICH	International Conference on Harmonization
IgA, IgE, IgG, IgM	Immunoglobulins A, E, G, M
IIT	Investigator Initiated Trial
IND	Investigational New Drug
IRB	Institutional Review Board
ISS	Infection Severity Score
IVIg	Intravenous Immunoglobulin

LHD	Laboratory of Host Defenses
LMI	Laboratory of Molecular Immunology
LMF	Local Medical Facility
MDS	Myelodysplastic Syndrome
MED	Minimum Effective Dose
MM	Multiple Myeloma
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIH-HRPP	National Institutes of Health – Human Research Protection Program
NIH-CC	National Institutes of Health Clinical Center
OCRPRO	Office of Clinical Research Policy and Regulatory Operations
OHRP	Office for Human Research Protection
PFT	Pulmonary Function Test
PI	Principal Investigator
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QOL	Quality of Life
RCHSPP	Regulatory Compliance and Human Subjects Protection Program
SAE	Serious Adverse Event
SAR	Suspected Adverse Reaction
SCN	Severe Congenital Neutropenia
SRCP	Safety Review and Communication Plan
SDF-1	Stromal Cell-Derived factor-1, aka CXCL12
SQ	Subcutaneous (Injection)
SUSAR	Serious and Unexpected Suspected Adverse Reaction
TISS	Total Infection Severity Score
TPN	Total Parenteral Nutrition
WBC	White Blood Cell Count
WHIMS	Warts, Hypogammaglobulinemia, Infections, and Myelokathexis Syndrome
UP	Unanticipated Problem
UPnonAE	Unanticipated Problem that is not an Adverse Event

PROTOCOL SUMMARY

Full Title:	A Phase III, Double-blind, Randomized, Crossover Study of Plerixafor Versus G-CSF in the Treatment of Patients with WHIM Syndrome
Short Title:	Plerixafor vs. G-CSF in WHIMS
Clinical Phase:	III
IND Sponsor:	OCRPRO/DCR/NIAID
Conducted by:	Laboratory of Molecular Immunology/NIAID
Principal Investigator:	David H. McDermott, MD
Sample Size:	N=20
Accrual Ceiling:	n = 30
Study Population:	Subjects (≥10 and ≤75 years of age) with WHIMS
Accrual Period:	36 months
	Study Design: This is a double-blinded, randomized, crossover study comparing the efficacy of the chemokine receptor CXCR4 antagonist plerixafor to G-CSF in subjects with a clinical diagnosis of WHIMS and mutations in the C-terminus of chemokine receptor CXCR4. Eligible subjects who give informed consent are randomized to 1 year of treatment with either plerixafor or G-CSF, followed by a crossover to the second drug for 1 year. Each treatment arm is preceded by a 2-day washout period followed by an 8-week equilibration period during which study drug dosing is initiated and adjusted to establish an ANC of approximately 500-1500 cells/μL. A subject's ANC is monitored every 2 months during the one-year treatment periods and study drug dosage adjusted for ANC ≤500 cells/μL or ≥7500 cells/μL. Participants maintain a study Memory Aid in which they record daily treatments and any new symptoms. After completing both treatments, subjects are offered G-CSF and enter a post-treatment observation period during which they continue to submit the study Memory Aid. The study completion visit occurs 5-6 months after the last day of the second year of treatment.
Study Duration:	6 years
Study Agent/Intervention:	plerixafor (Mozobil™)
Comparator:	G-CSF (Neupogen™, filgrastim)
Primary Objective:	Compare the severity of infection during treatment with each drug

Secondary Objectives:

1) Compare component measures of infections.
2) Measure the control of warts with plerixafor versus G-CSF.
3) Demonstrate the safety of plerixafor and G-CSF as long-term therapy.
4) Compare the symptoms of chronic infections.
5) Compare quality of life (QOL).
6) Compare drug tolerability and assess subject drug preference.
7) Compare the increase of leukocyte levels from baseline.

Exploratory Objective: Measure type, location, and cause of infections.

Primary Endpoint: The primary endpoint is infection severity, which is measured as a composite of multiple weighted parameters according to rules defined in Appendix D.

Secondary Endpoints:

1) Component measures of infections: incidence and duration of infections, fever, antibiotic treatment, and hospitalization.
2) Control of warts as defined by at least a 50% reduction in numbers, areas or size of existing warts, or in new warts occurring during treatment.
3) Blood count and immunological parameters.
4) Clinical measures of chronic infection.
5) Treatment side effects.
6) Quality of life scores.
7) Treatment preference.

Exploratory Endpoint: Identify causative organisms and locations of infections in WHIMS patients.

PRÉCIS

Warts, hypogammaglobulinemia, infections, and myelokathexis syndrome (WHIMS) is a rare combined primary immunodeficiency disorder caused by gain-of-function mutations in the gene for the chemokine receptor CXCR4. Normally, CXCR4 is expressed on most leukocyte subsets and functions in part to promote hematopoietic stem cell (HSC) and neutrophil homing to and retention in bone marrow. WHIM mutations alter the CXCR4 carboxyl terminus, which enhances and prolongs receptor signaling.(1) As a result, egress of normally produced and functional neutrophils from the bone marrow to the blood is impaired causing neutropenia, a bone marrow pathologic finding referred to as myelokathexis. A similar mechanism may also affect other leukocyte subsets since WHIM patients usually are panleukopenic. Consequently, WHIM patients are predisposed to frequent acute bacterial infections, especially in the sinopulmonary tract, that may cause chronic morbidity, respiratory insufficiency and in some cases premature death. WHIM patients also have marked difficulty clearing infections with Human Papillomavirus (HPV), resulting in persistent cutaneous and anogenital warts that in several reported cases have evolved into cancer. Several deaths have also occurred due to cancer associated with Epstein - Barr virus (EBV) infection. Therapies currently used for WHIMS are non-specific and expensive, and include Granulocyte Colony-Stimulating Factor (G-CSF) (the drug currently approved by the Food and Drug Administration (FDA) to treat severe congenital neutropenia), intravenous immunoglobulin (IVIg), and prophylactic antibiotics. None of these measures has been formally evaluated for efficacy in WHIM syndrome (WHIMS); however, in our clinical experience based on the treatment of 24 WHIM patients seen at the National Institutes of Health (NIH) since 2006, recurrent bacterial infections continue to occur, despite the fact that the absolute neutrophil count (ANC) can be readily maintained above 500 cells/microliter by G-CSF and IgG levels can be restored to the normal range by IVIg. Thus, there continues to be a major unmet medical need for effective therapy in WHIMS despite the availability and application of best therapy for neutropenia and hypogammaglobulinemia in these patients. Plerixafor (Mozobil™) is a specific small molecule antagonist of CXCR4, licensed by the FDA for HSC mobilization for transplantation in cancer, and is therefore a logical candidate for molecularly targeted treatment of WHIMS.(2) The goal of treatment would be to reduce CXCR4 signaling to normal, not to zero, thus, absent any off-target effects, targeted chronic treatment with this agent may be safe. In this regard, 2 recent short term Phase I dose-escalation studies of plerixafor, one from our group, in a total of 9 patients demonstrated that the drug could safely mobilize not only neutrophils, but also all other leukocyte subsets that are decreased in the blood of WHIM patients.(3, 4) A follow-up Phase I study, conducted by our group, in 3 patients given plerixafor 0.02-0.04 mg/kg/d for 6 months demonstrated that these hematopoietic effects were durable.(5) Moreover, the frequency of infection was reduced on plerixafor as compared to retrospective data mined for the three years before starting therapy and prospective data collected for one year after ending therapy, even though 2 of the patients were taking G-CSF during the comparison time periods. No new warts occurred during treatment and several existing warts improved or resolved. Although these results are encouraging, the small number of patients studied, limited duration of drug treatment, and retrospective mining of control data leave open to question whether plerixafor is truly efficacious for clinical outcomes in WHIMS. The randomized, double-blinded, crossover trial described here is designed to answer this question by establishing the long-term safety and clinical efficacy (primary endpoint: infection severity; multiple secondary endpoints including wart control) of plerixafor as compared to G-CSF in the treatment of WHIMS patients 10-75 years of age. G-CSF as a comparator is required because of its approved use in patients with severe congenital neutropenia (SCN).

Brief outline of study—we intend to randomize 20 patients and treat them in a double-blinded manner for 1 year with G-CSF and 1 year with plerixafor using a crossover design to allow direct comparison of infection severity during treatment with both agents, at doses determined by the patient's individual neutrophil response. A schedule of events has been provided in Appendix A. Data will be analyzed as

specified in the Statistics section (Section 14) after randomization. Tolerability and patient drug preference will also be assessed.

STUDY SCHEMA

w = week(s)
d = day(s)

1 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Background Information

1.1.1 CXCR4

CXCR4 is a member of the chemokine receptor family, which consists of 18 related 7 transmembrane-domain, G protein-coupled chemoattractant receptors that regulate leukocyte trafficking.(6, 7) According to studies in gene knockout mice, CXCR4 is essential for life and plays a fundamental role in the hematopoietic, cardiovascular, reproductive, and nervous systems during embryonic development.(8) In the hematopoietic system, CXCR4 is important for hematopoietic stem cell and neutrophil trafficking between blood and bone marrow. In particular, reduced CXCR4 signaling promotes egress of these cells from marrow whereas increased CXCR4 signaling promotes homing to and retention of these cells in bone marrow.(9) CXCR4 is also an important HIV co-receptor (with CD4) used by the virus for target cell infection, but only for a minority of HIV strains, which are found in patients mainly during the late stages of disease.(10)

1.1.2 WHIMS

Warts, hypogammaglobulinemia, infections, and myelokathexis syndrome (WHIMS) is a rare congenital immunodeficiency disorder caused by various mutations that increase CXCR4 signaling.(11, 12). All cases that have been genetically characterized to date involve truncation and missense mutations in the intracellular tail of the receptor that are inherited in an autosomal dominant manner.(1, 13) This domain normally mediates negative regulation of the receptor through G protein-coupled receptor kinase (GRK)-mediated phosphorylation and beta-arrestin-mediated internalization, providing a potential mechanism for the increased signaling that is observed.(14) Consistent with this, truncated WHIMS receptors have been reported to undergo reduced ligand-dependent receptor down-regulation.(15, 16) One WHIMS patient has been identified who lacks CXCR4 mutations, however this individual has decreased expression of GRK3, which normally mediates CXCR4 desensitization.(17) Another family has recently been identified with 2 affected members with a recessive mutation in CXCR2. Thus, WHIMS can be thought of as a disease caused by excessive CXCR4 function or insufficient CXCR2 function, which validates the fundamental role of these receptors in homeostatic leukocyte trafficking in humans. A mouse model in which a human WHIMS CXCR4 mutation (S338X) was knocked into one mouse CXCR4 locus phenocopies panleukopenia and revealed abnormal immune organ architecture.(18, 19) It is possible that mutations in other immunoregulatory genes may also cause a similar syndrome.

The acronym WHIMS highlights four clinical manifestations of the disease: warts, hypogammaglobulinemia, infections, and myelokathexis. Warts are refractory to medical treatment in WHIMS and can evolve into fatal skin and anogenital cancer. Hypogammaglobulinemia is moderate and variable. Nevertheless, WHIMS patients have been reported to have poor immunologic memory after vaccination, and the resulting low levels of immunoglobulins may predispose them to frequent sinopulmonary infections.(20) Perhaps the earliest and most highly penetrant clinical finding is neutropenia, usually severe, which appears to be caused by abnormal retention of mature neutrophils, a critical effector cell in innate immunity, in the bone marrow. Most patients also have panleukopenia. This picture, which is known as myelokathexis, the 'M' in WHIMS, further predisposes the patient to typical bacterial skin, soft tissue, and sinopulmonary infections. When the absolute neutrophil count (ANC) is reduced below ~500 cells/µL in patients receiving cytoreductive therapy for diseases such as cancer, the risk of infection with bacteria and fungi increases: however, the precise relationship between ANC and infection risk in WHIMS has not been defined. During infection in WHIMS patients, neutropenia often improves and may temporarily normalize, suggesting that the inhibition of marrow release of neutrophils can be overcome in the presence of infection. However, the end result of frequent infections in WHIMS patients can be serious, with loss of hearing, teeth, and lung function. Dental disease consists of HPV related oral cancers, severe caries, periodontitis, dental abscesses, and premature tooth loss. Older

patients can develop severe bronchiectasis resembling cystic fibrosis, and fatal respiratory failure. Case reports of fatal meningitis and Epstein-Barr virus-induced lymphoma in patients with WHIMS provide evidence that other immunological problems present in WHIMS patients are clinically significant.(21, 22) In addition, an increased prevalence of tetralogy of Fallot has been observed in WHIM patients.(23)

Current therapeutic recommendations in WHIMS are non-specific, expensive, associated with significant side effects, and based on limited direct clinical data. Daily or every other day injection of G-CSF is commonly given to increase the ANC, based on a placebo-controlled clinical trial that demonstrated G-CSF safety and efficacy in reducing the risk of infection in patients with severe congenital neutropenia (SCN) of various etiologies.(24) On the basis of this trial, SCN was approved as an indication for G-CSF therapy. However, only a few patients with WHIMS were included in the trial, so that the actual efficacy of G-CSF in modulating clinical endpoints specifically in WHIMS is not known. Monthly infusions of intravenous immunoglobulin (IVIg) or subcutaneous immunoglobulin are also given to those WHIMS patients who have severe hypogammaglobulinemia; however, its efficacy in this setting has not been studied.(1) Anecdotal evidence suggests that together these measures may not affect HPV infection in WHIMS patients, nor would they be expected to, and do not fully prevent infections (Figure 1).(25) Thus, there is a clear unmet medical need for new treatments in these patients. For these reasons and because of expense and side effect considerations (see below), it is clear that direct studies quantifying the clinical efficacy of G-CSF specifically in WHIMS as well as development of more specific treatment modalities in WHIMS are needed.

1.2 Description of Study Agent: Mozobil™ (plerixafor)

The Food and Drug Administration (FDA) approved plerixafor (Mozobil™) injection in 2008 for use in combination with G-CSF to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM).(26) Plerixafor was initially developed as an antiretroviral compound for the treatment of human immunodeficiency virus (HIV).(27) It was found to be a specific and reversible inhibitor of the chemokine receptor and HIV co-receptor CXCR4, and its plasma concentrations closely correlated with the ability to inhibit CXCR4 HIV viral entry into target cells. While initial studies showed that it was a safe and effective antiviral drug in animals and humans, CXCR4-using virus is not common in initial HIV infection and the drug is not orally bioavailable, limiting its usefulness for treating HIV. However in early human studies, it was noted to cause a dramatic and rapid increase in white blood cell count (WBC).

This was consistent with other studies in mice showing that CXCR4 is a strong bone marrow retention factor for leukocytes in general and neutrophils and $CD34^+$ hematopoietic stem cells specifically. This prompted successful trials of plerixafor in animals and humans for the purpose of $CD34^+$ hematopoietic stem cell mobilization. This is a procedure in which apheresis of donor blood is done to separate and remove $CD34^+$ cells, which allows for immune system reconstitution after high dose chemotherapy for cancer. Plerixafor is effective either by itself or in combination with granulocyte colony-stimulating factor (G-CSF), which is the agent that has traditionally been used for this purpose. In Phase III clinical studies that led to its licensure in the US, it was found that there was a dramatic, statistically significant increase in the percentage of difficult to mobilize (because of prior chemotherapy) individuals who reached the target number of cells collected when plerixafor was used with G-CSF compared to when G-CSF was used alone.(28, 29)

Clinical Pharmacology / Mechanism of Action: Plerixafor is a specific antagonist of the CXCR4 chemokine receptor and blocks binding of its cognate ligand, stromal cell-derived factor-1 (SDF-1 also known as CXCL12). Both SDF-1 and CXCR4 are recognized to play a role in the trafficking and homing of human hematopoietic stem cells (HSCs) to the marrow compartment. Once in the marrow, stem cell CXCR4 can act to help anchor these cells to the marrow matrix, either directly via SDF-1 or through the

induction of other adhesion molecules. Treatment with plerixafor resulted in leukocytosis and elevations in circulating HSC in mice, dogs, and humans.

Pharmacokinetics: Pharmacokinetic studies in normal volunteers and cancer patients have shown that plerixafor is rapidly absorbed after subcutaneous (SQ) injection.(10, 30) Peak plasma concentration is observed at 30-60 minutes after a single 0.24 mg dose and the half-life has been estimated at approximately 5 hours. The drug is eliminated through the kidneys with 70% excreted unchanged in the urine in 24 hours. There are no reported drug-drug interactions, and studies to date have found no interactions with the cytochrome P450 system. In vitro, the drug was negative in tests of mutagenesis. However, in vivo, it has been found to be teratogenic in animals and could be excreted in breast milk. It is therefore contraindicated in pregnant women or nursing mothers. The teratogenicity may be a direct effect of blocking CXCR4 since animal studies have found the receptor to be critical for several aspects of embryogenesis and immune system development.(8,31,32)

Adverse Reactions: The data described herein reflect 2 randomized studies in patients with NHL and MM, in which 301 patients treated with plerixafor in combination with G-CSF were compared to 292 patients who were treated with placebo and G-CSF.(28,29) Side effects attributed to the drug were relatively minor and consisted of mild injection site reactions and gastrointestinal complaints. (Appendix B) In particular, the most common adverse reactions (≥10%) reported in patients who received plerixafor in conjunction with G-CSF were diarrhea, nausea, fatigue, injection site reactions, headache, arthralgia, dizziness, and vomiting.

Gastrointestinal complaints: Nausea, vomiting, and diarrhea were frequently reported in cancer patients treated with both plerixafor and G-CSF, but also may be attributable to the chemotherapy, the apheresis, or the underlying disorder as these have not been a problem in WHIMS patients treated to date.

Injection site reactions: In the randomized studies, 34% of patients with NHL or MM had mild to moderate injection site reactions at the site of subcutaneous administration of plerixafor.(28,29) These included erythema, hematoma, hemorrhage, induration, inflammation, irritation, pain, paresthesia, pruritus, rash, swelling, and urticaria. In contrast, in 2 studies of the drug in WHIMS patients, injection site reactions occurred but consisted only of small, self-resolving areas of erythema and pruritus occurring mainly at doses of 0.08 mg/kg and above.(3, 4) In the patients treated for 6 months with low doses (0.01-0.04 mg/kg) no injection site reactions were observed.(5)

Other adverse events: Mild to moderate systemic reactions were observed in fewer than 1% of patients in cancer studies approximately 30 minutes after plerixafor administration. These events included one or more of the following: urticaria, periorbital swelling, dyspnea, hypoxia, vasovagal reactions, orthostatic hypotension, and/or syncope. Symptoms generally responded to treatments (e.g., antihistamines, corticosteroids, hydration, or supplemental oxygen) or resolved spontaneously (Appendix B), and have not been observed in studies of WHIMS patients.

1.2.1 Summary of Previous Pre-Clinical Studies

In vitro studies have demonstrated that plerixafor is specific for CXCR4 and is a reversible inhibitor of the natural ligand's (SDF-1, aka CXCL12) ability to bind the receptor. Plerixafor has a very similar ability to bind and block the signaling of both wild type and WHIM variants of CXCR4.(2) Long-term administration to mice, rats, and monkeys was found to be safe; however, in high doses (10 times > the highest human dose) in pregnant rats, the drug was found to be teratogenic causing fetal mortality. Also in rats, increased spleen weight was observed after 2 to 4 weeks of daily administration at high doses – 4 times the highest human dose (Appendix B).

1.2.2 Summary of Relevant Clinical Studies

Plerixafor in combination with G-CSF has been used in more than 980 patients enrolled in 16 clinical studies for the purpose of stem cell mobilization as reported by the manufacturer, Genzyme/Sanofi Corp, to the FDA. In one randomized study of 298 patients with NHL where all patients were given 0.24 mg/kg of the drug subcutaneously daily for 1 to 7 days (median, 2 days), 59% of those who received the drug combination were able to achieve the collection goal of 5 million CD34+ cells/kg versus only 20% who received G-CSF alone ($p<0.001$).(28) In a second randomized study, 302 patients with multiple myeloma were mobilized in the same way and 72% achieved the collection goal of 6 million CD34+ cells/kg versus only 34% of those who received G-CSF alone ($p<0.001$).(29) In Phase I studies by McDermott, et al and Dale, et al., 9 adult WHIMS patients were treated with a dose escalation of plerixafor up to the FDA approved dose of 0.24 mg/kg/d and were found to rapidly mobilize all leukocyte subsets to the blood that are decreased in the disease.(3, 4) The lowest dose, 0.02 mg/kg/d, was able to increase the neutrophils to greater than 500 cells/μL of blood which is considered the boundary below which an increased risk of bacterial and fungal infection may occur. One of the 9 had to stop the dose escalation at 0.08 mg/kg because of development of an acute exacerbation of chronic bronchitis and possible pneumonia (4), but both studies concluded that the drug was safe and effective and that this was proof of principle that antagonism of CXCR4 could reverse panleukopenia. However, these studies left open the question as to whether long-term, low dose therapy would be practical, safe, and clinically effective. We have completed a 6-month study of 3 adult WHIMS patients given 0.01-0.02 mg/kg twice/day and found that the leukocyte mobilization effects were durable and that the drug was safe for administration up to 6 months.(5).

Moreover, the frequency of infection was reduced on plerixafor as compared to retrospective data mined for the three years before starting therapy and prospective data collected for one year after ending therapy. No new warts occurred during treatment and multiple existing warts improved or resolved. Although these results are encouraging, the small number of patients studied, limited duration of drug treatment, and retrospective mining of control data leave open to question whether plerixafor is truly efficacious for clinical outcomes in WHIMS. The goal of the current study is to answer this question choosing as the primary endpoint the severity of infections compared between the plerixafor treatment arm and the comparator G-CSF treatment arm using a double-blinded, crossover design. G-CSF is required as a comparator because of its approved use in patients with SCN.

1.3 Description of Comparator Treatment: G-CSF

G-CSF is FDA-licensed and the standard of care for severe chronic neutropenia, and will be used as the control or comparator drug in this study.(24) (see Appendix C.) G-CSF is a recombinant human protein produced in *E. coli* that is identical in amino acid sequence with the exception of an additional *N*-terminal methionine to a naturally occurring cytokine made by human monocytes, fibroblasts, and endothelial cells. G-CSF acts on specific receptors to regulate the proliferation and differentiation of neutrophil progenitors, and augments the bone marrow release and function of mature neutrophils. It has minimal effects on other hematopoietic cell types. Its effect on bone marrow release of neutrophils is mediated in part by interfering with CXCL12 availability at CXCR4.

1.3.1 Summary of Relevant Clinical Studies

In Phase I studies involving 96 subjects with no myeloid malignancies, G-CSF administered at doses of 1 to 70 μg/kg/day resulted in a dose-dependent increase in circulating neutrophil counts.(33-35) Neutrophil counts returned to baseline within 4 days after discontinuation of G-CSF therapy. The absolute monocyte count was reported to increase in a dose-dependent manner in most subjects receiving G-CSF; however, the percentage of monocytes in the differential count remained within the normal range. In all studies to date, absolute counts of eosinophils and basophils were within the normal range following administration of G-CSF. Increases in lymphocyte counts following dosing with G-CSF have been reported in some healthy individuals and subjects with cancer. Daily administration of G-CSF has been shown in a

randomized Phase III trial to be safe and effective in children and adults with severe chronic neutropenia, resulting in sustained increases in the neutrophil count and decreases in infection-related morbidity.(24) In particular, daily treatment with G-CSF led to significant beneficial changes in the incidence and duration of infection, fever, antibiotic use, and oropharyngeal ulcers in this setting.(24) The lower incidence and duration of infections was associated with decreased episodes of hospitalization, diarrhea, nausea, fatigue, and sore throat. In that study, the G-CSF dose was adjusted to maintain a median ANC between 1500 and 10,000 cells/mm^3. Overall, response to G-CSF was observed in 1 to 2 weeks. The median ANC after 5 months of G-CSF therapy was 7460/mm^3 (range, 30/mm^3 to 30,880/mm^3).

Mild-to-moderate bone pain was reported in approximately 33% of subjects with severe chronic neutropenia treated with G-CSF in clinical trials. (see Appendix C) This symptom was readily controlled with non-narcotic analgesics. Generalized musculoskeletal pain was also noted in a higher frequency of subjects treated with G-CSF. Palpable splenomegaly was observed in approximately 30% of subjects. Abdominal or flank pain was observed infrequently, and thrombocytopenia (<50,000/mm^3) was noted in 12% of subjects with palpable spleens. Fewer than 3% of all subjects underwent splenectomy, and most of these had a pre-study history of splenomegaly. Fewer than 6% of subjects had thrombocytopenia during G-CSF therapy, most of whom had a pre-existing history of the condition. Thrombocytopenia was managed by discontinuing or reducing the dose of G-CSF. An additional 5% of subjects had platelet counts between 50,000/mm^3 and 100,000/mm^3, with no associated serious hemorrhagic sequelae. Epistaxis was noted in 15% of subjects treated with G-CSF, which was associated with thrombocytopenia in 2% of the subjects. Anemia was reported in approximately 10% of subjects, but, in most cases, it appeared to be related to frequent diagnostic phlebotomy, chronic illness, or concomitant medications. Other AEs infrequently observed and possibly related to G-CSF therapy were injection site reaction, rash, hepatomegaly, arthralgia, osteoporosis, cutaneous vasculitis, hematuria/proteinuria, alopecia, and exacerbation of some pre-existing skin disorders (e.g., psoriasis). Cytogenetic abnormalities, transformation to myelodysplastic syndrome (MDS), and acute myeloid leukemia (AML) have been observed in subjects treated with G-CSF for severe chronic neutropenia.

As of 31 December 1997, data have become available from a post marketing surveillance study of 531 subjects with severe chronic neutropenia who had an average follow-up of 4 years. Based on analysis of these data, the risk of developing MDS and AML appears to be confined to the subset of subjects with congenital neutropenia. A life-table analysis of these data revealed that the cumulative risk of developing AML or MDS by the end of the 8^{th} year of treatment with G-CSF in subjects with congenital neutropenia was 16.5%, which represents an annual rate of approximately 2%. Cytogenetic abnormalities, most commonly involving chromosome 7, have been reported in subjects treated with G-CSF who had previously documented normal cytogenetics. It is unknown whether the development of cytogenetic abnormalities, MDS, or AML is related to chronic daily administration of G-CSF or to the natural history of congenital neutropenia. It is also unknown if the rate of conversion in subjects who have not received G-CSF is different from that of individuals who have received it. Routine monitoring through regular complete blood count (CBC) is recommended in all subjects with severe chronic neutropenia.

1.4 Scientific Rationale and Clinical Justification

Published evidence and the package insert of G-CSF suggest that long term, high dose G-CSF therapy may be associated with the development of leukemia and myelodysplasia in SCN patients.(36) Whether or not this would occur in WHIMS patients is currently unknown, but is one reason to consider alternative therapies. In addition, patients have been described who due to G-CSF receptor mutations or the development of anti-G-CSF antibodies fail to respond to G-CSF with an increased ANC.(37) In addition, our anecdotal experience is that WHIMS patients experience severe bone pain with the normal dosing of G-CSF perhaps due to their increased retention of mature neutrophils in the marrow

(myelokathexis). Lastly, G-CSF is not an effective treatment for warts, the signature infection in WHIMS, which might be better addressed with mechanism-based therapy such as plerixafor.

Our Phase 1 study has provided preliminary evidence that low dose plerixafor b.i.d. is safe and effective over 6 months in mobilizing leukocytes to the blood, reducing infection frequency (Figure 1) and reducing wart burden; however, this study was not designed, controlled or powered to establish efficacy of plerixafor treatment for the main clinical endpoints in the disease (recurrent infections and warts) or to compare its efficacy to G-CSF, the FDA approved therapy for SCN.(5)

1.5 Preliminary Report of Unexpected Adverse Events in this Study

As of May 2017, sixteen subjects have been randomized in this study of which nine have received at least some of both study drugs.

1.5.1 An Incident of a New Psoriasis-like Rash

A subject experienced a worsening rash (psoriasis-like) beginning a week after commencing the 1st study drug and the symptoms resolved after switching to the alternate study drug and topical steroid treatment.

1.5.2 Joint Pain (Arthralgia) and an Incident of Reactive Arthritis

Some subjects with a prior history of joint pain (arthralgia or arthritis) prior to enrollment experience a recurrence or worsening of their symptoms with G-CSF and/or with the study drug(s). However, one subject who had no prior history of joint pain or G-CSF treatment, experienced pain and swelling in his wrist, hands, and knees and had to be discontinued from both study drugs and treated with oral steroids. Soon after the pain began, the subject tested positive for urethral chlamydia which causes reactive arthritis. Thus it may be that the subject's symptoms were exacerbated by the increased circulating neutrophil levels caused by both drugs.

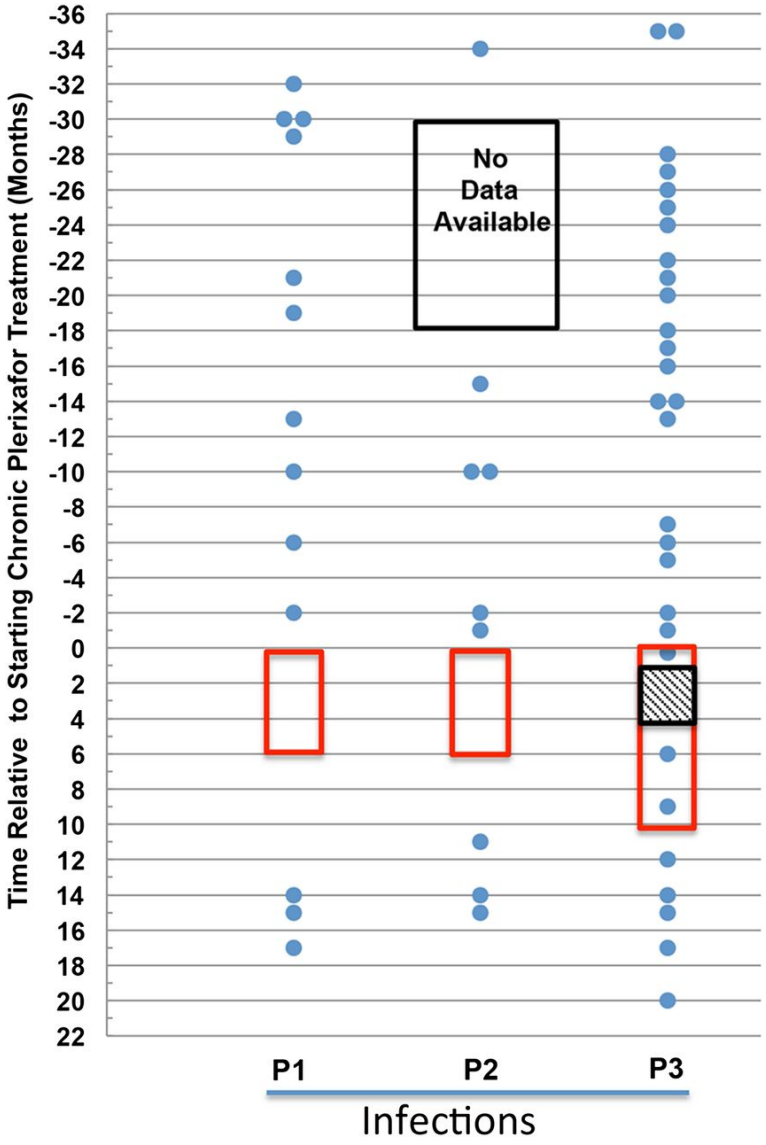

Figure 1: Plerixafor May Reduce Infection Incidence in Patients with WHIMS.

The data for each patient are presented in separate columns. Each infection is represented as a dot and plotted by the month it occurred in relation to the start of plerixafor therapy. The time on plerixafor is bounded by the red box. Note that data for P2 were unavailable for the 12 month period marked by the black box. For P3, the hatched box represents a gap in plerixafor administration for the purpose of clinical care. G-CSF was administered to patients P1 and P2 both before and after plerixafor treatment, whereas P3 received G-CSF for ~1 month after plerixafor.

2 STUDY OBJECTIVES

2.1 Primary Objective

Compare the severity of infection during treatment with plerixafor and G-CSF.

2.2 Secondary Objectives

1) Compare component measures of infections.
2) Measure the control of warts with plerixafor versus G-CSF.
3) Demonstrate the safety of plerixafor and G-CSF as long-term therapy.
4) Compare the symptoms of chronic infections.
5) Compare quality of life (QOL).
6) Compare drug tolerability and subject drug preference.
7) Compare the increase of leukocyte levels from baseline.

2.3 Exploratory Objectives

Measure type, location, and cause of infections.

3 STUDY DESIGN

3.1 Description of the Study Design

This is a Phase III, double-blinded, randomized, crossover study evaluating plerixafor SQ b.i.d. versus G-CSF SQ b.i.d. in children and adults 10 to 75 years of age with a clinical diagnosis of WHIMS, with a history of recurrent infections and a non-synonymous mutation in the C-tail of CXCR4. Subjects who are pregnant or have a history of hematopoietic cancer or life threatening cardiac arrhythmia are excluded.

Interested subjects come to the NIH-CC and sign the study consent, which initiates the Initial Evaluation period of the protocol, during which eligibility criteria are evaluated. Eligible subjects commence this approximately 4-12 week period during which unblinded b.i.d. G-CSF treatment is continued or offered, if the subject is not already receiving it, and dose is adjusted if necessary to achieve an ANC between 500-1500 cells/μL of blood. Subjects start completing a daily Memory Aid submitting to the NIH-CC once per week. The Memory Aid includes their G-CSF treatment, any new or persistent symptoms, use of prophylactic antibiotics, and IVIg treatments. Subjects also report use of any other medications, incidence and duration of fever, new infections, incidence & duration of antibiotic treatments, and any hospitalizations. Another purpose of this evaluation period is to ensure that subjects are able to comply with required study procedures. At completion of the evaluation period, subjects are randomized to begin either plerixafor or G-CSF treatment. Subjects shall hold G-CSF 2 days in advance of commencing study medication. The next phase of the study is the Equilibration Period of 8 weeks, during which the blinded study drug dose is adjusted for a target ANC of 500-1500 cells/μL with the ANC count measured approximately every 2 weeks at a subject's local medical facility. After this, the study drug dose is continued for 52 weeks, during which the dose may be adjusted to maintain the ANC between approximately 500-7500 cells/μL. Also, in this treatment period clinical events are counted and subjects visit the NIH-CC approximately every 4 months for a comprehensive assessment of chronic infections, warts and immune status. Between NIH-CC visits, subjects visit their local medical facility or local provider approximately midway between NIH-CC visits to have blood drawn for CBC/ANC prior to the morning dose of study drug and for treatment of new or worsening infections. CBC/ANC is monitored at the NIH-CC for safety and the need for additional dose adjustments as determined by the Principal Investigator and applied by the unblinded independent pharmacist. Subjects unable to tolerate a study drug will be switched to the alternate study agent according to rules specified below in the Statistics (section14).

After completing the 1st year of treatment, there is a 2-day washout period before a subject crosses over to the alternate study drug for the 2nd year of treatment that is again preceded by an 8-week Equilibration period. After completing the 2nd treatment, there is a 2-day washout period, after which subjects are offered the opportunity to restart G-CSF therapy. There is then a 1-month G-CSF Equilibration and subjects continue to maintain their diaries and to visit their local medical facility for blood draws approximately every two weeks. A study completion visit at the NIH-CC occurs approximately 5 to 6 months after the end of the second year of treatment.

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary endpoint is infection severity, which is measured as a composite of multiple weighted parameters according to rules defined in Appendix D.

3.2.2 Secondary Endpoints

1) Component measures of infections; incidence and duration of infections, fevers, antibiotic treatments, and hospitalization.
2) Control of warts as defined by at least a 50% reduction in numbers, areas or size of existing warts and by the number of new warts.
3) Blood count and immunological parameters.
4) Clinical measures of chronic infections.
5) Treatment side effects,
6) Quality of life scores.
7) Treatment preference.

3.2.3 Exploratory Endpoint

Identify causative organisms and locations of infections in WHIMS subjects.

4 STUDY POPULATION

4.1 Subject Selection and Recruitment Plan

The study is open to patients with WHIMS from 10-75 years of age who may benefit from the study's proposed treatments. WHIMS is a rare genetic disease with approximately 60 patients identified as of 2014 worldwide in the medical literature. We began seeing WHIMS patients in 2006, and as of May, 2014 have a cohort of 24 patients, with 50% of these patients accrued in 2012 and 2013. Sixteen of these 24 patients meet the eligibility criteria for this protocol, which is powered for 20 patients to finish the protocol. Additional potential recruits for this study include patients referred by clinical researchers at NIH, by academic institutions worldwide, and by local health care providers, as well as patient self-referrals. A recruitment letter may be sent to relevant health providers to stimulate accrual. The study will also be listed in ClinicalTrials.gov. We expect to screen 30 patients (accrual ceiling) in order to enroll and randomize 20 patients.

4.2 Inclusion Criteria

Subjects are eligible to enter the study if they meet all of the following criteria:

1) Age $\geq$10 and $\leq$75 years.
2) Heterozygous mutation in the C-tail of CXCR4 in addition to a clinical diagnosis of WHIMS.
3) Documented neutropenia with a baseline ANC below 1500 cells/μL of blood.
4) History of severe and/or recurrent infections.
5) Willingness to interrupt G-CSF medication, 2 days prior to study drug injection.
6) Must have a local medical provider for medical management.
7) Must be willing to provide blood, plasma, serum, and DNA samples for storage.

8) All study subjects must agree not to become pregnant or impregnate a female. Women of childbearing potential must agree to take appropriate steps to avoid becoming pregnant for the duration of the study. Participants in whom pregnancy is biologically possible must use at least 2 study approved methods of contraception, one of which must be a barrier method, and must continue contraception until 5 months after stopping the study drug:
   - Male or female condoms with a spermicide,
   - Diaphragm or cervical cap with spermicide,
   - Intrauterine device,
   - Contraceptive pills or patch, Norplant, Depo-Provera or other FDA-approved contraceptive,
   - Male partner with vasectomy and documented aspermatogenic sterility.
9) Willingness to comply with the study medications, visits, and procedures, as deemed necessary by the principal investigator (PI).

4.3 Exclusion Criteria

If any of the following exclusion criteria are met, a subject will not be enrolled in this study:

1) Neutropenia due to maturation defects in the myeloid lineage or a type of neutropenia, which in the investigator's opinion, is unlikely to improve from the medication administered in this study.
2) Pregnant or breast-feeding women.
3) Known hypersensitivity to plerixafor, G-CSF, or any components of the products.
4) Predisposition to or history of life-threatening cardiac arrhythmia.
5) Requiring dialysis or having markedly impaired renal function with a Creatinine Clearance (CrCl) <15 mL/min (Appendix E).
6) Condition that in the investigator's opinion places a subject at undue risk by participating in the study.

4.4 Justification for Exclusion of Pregnant or Breast Feeding Women

Pregnant women are excluded from this study because the effects of plerixafor on the developing human fetus are unknown with the potential for teratogenic or abortifacient effects. Lactating women are excluded because plerixafor may be excreted in the breast milk and could be potentially harmful to breast-fed infants. Women of childbearing potential must have a negative pregnancy test prior to receiving plerixafor.

4.5 Justification for Exclusion of Children <10 Years of Age

Subjects younger than 10 years of age will be excluded from the study. Although WHIMS is a rare congenital immunodeficiency disorder that affects all age groups, plerixafor has known effects on fetal development in animal models.(8,32,38) These are related to early localization of cells during fetal development; therefore, we feel that age 10 provides a wide safety window for completion of early development and allows us to treat children who may have the most to gain from this treatment in the future. Children as young as 2 months of age have been treated with single high dose (0.24 mg/kg/d) plerixafor for stem cell mobilization without serious side effects and chronic G-CSF use is safe in children.(39,40)

5 STUDY AGENT AND INTERVENTIONS

5.1 Drug Acquisition

5.1.1 Plerixafor: Provided by Manufacturer

Plerixafor is FDA-approved for hematopoietic stem cell mobilization in cancer and is the study drug. It is manufactured by Genzyme/Sanofi Corp., Cambridge, MA, USA. The manufacturer supplies the drug, which is investigational in this study, at no cost.

5.1.2 G-CSF: Obtained Commercially

G-CSF is an FDA-approved drug manufactured by Amgen and is the comparator drug in this study because it is FDA-approved for the treatment of SCN. Drug will be sourced commercially and purchased per the NIH-CC policy.

5.2 Disposition and Dispensation

The study drug and the comparator drug are dispensed through the NIH-CC's pharmacy.

5.2.1 Formulation, Packaging, and Labeling

5.2.1.1 Plerixafor Packaging from Manufacturer

Plerixafor injection is a sterile, preservative-free, clear, and colorless to pale yellow isotonic solution for subcutaneous injection. Each mL of the sterile solution contains 20 mg of plerixafor. Each single-use vial is filled to deliver 1.2 mL of the sterile solution containing 24 mg of plerixafor and 5.9 mg of sodium chloride in water for injection. Storage at room temperature is recommended at 25°C (77°F) with excursions from 15°C-30°C (59°F - 86°F).

5.2.1.2 Plerixafor Repackaging for Study and/or Shipment to Study Participants

Plerixafor vials from the manufacturer will be repackaged by Integrity Bio, Inc into pre-set low-dose volumes between 0.01-0.20 mL in sterile syringes for subject self-injection. The syringe provided to the subject will contain a dose ranging between 0.01-0.04 mg/kg. The upper limit dose of 0.04 mg/kg in this study is low compared to the FDA-approved dose for HSC mobilization (0.24 mg/kg) and was set at this level because our treatment goal is to reduce CXCR4 signaling to normal from 2X normal, the typical level for WHIMS variants of CXCR4, not to zero. Syringes will be shipped periodically to the subject who will store them at refrigeration temperature until injected.

5.2.1.3 G-CSF Packaging from Manufacturer

G-CSF is a sterile, clear, colorless, preservative-free liquid for parenteral administration containing filgrastim at a specific activity of $1.0 \pm 0.6 \times 10^8$ U/mg (as measured by a cell mitogenesis assay). The product is available in single-use vials and prefilled syringes. The single-use vials contain either 300 µg or 480 µg filgrastim at a fill volume of 1.0 mL or 1.6 mL respectively. Refrigerated storage is recommended at 2°C - 8°C (36°F - 46°F), but vials can be left at room temperature for up to 24 hours. Drug should not be exposed to direct sunlight.

5.2.1.4 G-CSF Repackaging for Study and/or Shipment to Study Participants

G-CSF vials from the manufacturer will be repackaged by Integrity Bio, Inc into pre-set volumes of between 0.01-0.65 mL in sterile syringes for subject self-injection. The syringe and dose provided to a subject will range between 0.01-2.0 µg/kg. If randomized to the plerixafor arm, the dose may be temporarily reduced during the transition to accommodate potential residual synergistic effects of the drugs between the treatment arms. Syringes will be shipped periodically to the subject, who will store them at refrigeration temperature until injected.

5.2.2 Labeling of Study Drug

Syringes containing the repackaged plerixafor or G-CSF shall be labeled per NIH Pharmacy policy. An investigational use statement ("Caution: New Drug – Limited by Federal [USA] Law to Investigational Use") will also be labeled.

5.3 Study Agent Storage and Stability

Study Drug will be repackaged from the manufacturer package to the study drug configuration prior to shipment and stored by the subjects at refrigerator temperature until use. The NIH verified that plerixafor is stable when stored in syringes at room or refrigerated temperatures for at least 6 months. Refer to the package inserts (Appendix B & Appendix C) and the abstract from the American Association of

Pharmaceutical Scientists conference
(http://abstracts.aaps.org/Verify/aaps2013/postersubmissions/T2294.pdf).

5.3.1 Storage at NIH-CC

Manufacturer-packaged drugs will be stored as indicated by the manufacturer until repackaging into syringes. Repackaged drug syringes will be tested for sterility and stability, and stored at refrigerator temperature and shipped to the subject home address on a periodic basis with appropriate packaging to prevent extremes of temperature.

5.3.2 Shipment to Participants' Home

Subjects receive their study drug approximately once a month or as required. Shipments are prepared by the NIH Pharmacy and sent via a rapid courier or provided to subjects on their visits to the NIH-CC.

5.4 Study Agent Preparation and Administration

5.4.1 Subject Preparation and Self-Injection

Subjects self-administer the study drug subcutaneously every 12 hours at about the same time each day.

5.4.2 Subject Memory Aid: Injection Site, Injection Volume, Adverse Reactions

Participants are asked to record the quantity injected, the site of injection, and any adverse reaction from the injection (see Appendix F). Subjects are instructed to seek medical attention and inform study staff or the NIH-CC of any adverse events that are life threatening, require immediate medical attention, or limit their ability for self-care.

5.5 Dose-Adjustment and Therapeutic Schedule

The study drug dose is adjusted based on the subject's Absolute Neutrophil Count (ANC) to maintain the pre-morning dose ANC count at approximately between 500-1500 cells/μL during the Equilibration period. Consideration of concurrent infection or other factors that might increase the ANC will be factored into ongoing clinical decisions to adjust the study medication dose. Blinding will be maintained by having the PI or designee make these decisions for both drugs without knowing which drug the subject is currently receiving and then having an independent pharmacist who is un-blinded select the drug, dose, and shipment based on the subject's randomization.

5.6 Study Product Accountability Procedures

5.6.1 Plerixafor

The PI is responsible for ordering, receipt, and return of plerixafor from/to the manufacturer. NIH-CC's pharmacy is responsible for storing, repackaging, labeling, and shipping plerixafor to the subject.

5.6.2 G-CSF

NIH-CC's pharmacy is responsible for sourcing and ordering G-CSF from suppliers and for repackaging, labeling, and shipping G-CSF to the subject.

6 STUDY SCHEDULE AND ACTIVITIES

A schedule of procedures and evaluation for the study is shown in Appendix A.

6.1 Recruitment

Candidates are interviewed to confirm their diagnosis of WHIMS and provided a copy of the study's Informed Consent. A history of recurrent infections and neutropenia, documented CXCR4 mutation, or a newly identified mutation made by analyzing specimens obtained from the subject are required to determine eligibility. Subjects interested in the study are scheduled for a screening visit at NIH-CC.

6.2 Screening

Subjects who have reviewed and signed the informed consent undergo the following procedures.

6.2.1 Labs and Procedures

After reviewing and signing the Informed Consent, subjects undergo the following procedures:

- Pregnancy test for women of childbearing potential.
- Viral Screen: HIV, HTLV-1 and 2, Hepatitis B and C.
- CBC with diff, Chemistries (Acute Care Panel, Creatine Kinase, Hepatic Panel, Mineral Panel, Total Protein, Lactate Dehydrogenase, Uric Acid), erythrocyte sedimentation rate (ESR).
- Prothrombin time (PT), partial thromboplastin time (PTT), Vitamin B-12 & Folate, and Urinalysis.
- Echocardiogram (within the last 5 years for adult) must be reviewed and approved by the PI.
- EKG.

6.2.2 Assessment of Overall Health

The following procedures are required to assess the subject's overall health and safety in the study:

- Weight.
- Vital signs (temperature, heart rate, and blood pressure).
- Medical History including history of infections and warts.
- Medication History including allergies, concomitant medications, IVIg & G-CSF treatments, and prophylactic antibiotics.
- Contraception counseling as appropriate.
- Physical Exam.
- Encourage subjects and their local providers to contact the study coordinator and PI at the onset (or suspected onset) of an infection.

6.3 Initial Evaluation and Baseline Assessment Period

It is important to assess and document a subject's health and ensure they are trained and prepared prior to commencing the first study dose. This Initial Evaluation and Baseline Assessment period is targeted to be about 2 to 20 weeks or the length of time a subject requires being trained and stable on their low-dose G-CSF self-injections and able to visit the NIH-CC to commence the first study dose (Section 6.4). Procedures for baseline assessment may be completed anytime prior to the first dose, furthermore some labs may be drawn and analyzed at the subject's local medical facility (Section 6.3.12).

6.3.1 Measurement of Immunological Markers

The following procedures are performed to assess the subject's immunological markers:

- Quantitative Immunoglobulins
- Leukocyte Phenotyping
- Antibody levels for Diphtheria and Tetanus.

6.3.2 Evaluations: Dermatology, GYN, Dentistry, ENT, Audiology, and Clinical Photography

Due to the prevalence of infections and the risk of HPV in patients with WHIMS, dermatologic, gynecologic, dental, ENT, and audiology evaluations, and photographs of infections and warts on the body surface, will be arranged for subjects prior to commencing their first study treatment, and at the end of each their study drug treatments periods. These evaluations are not mandatory; a subject may refuse to participate in any of the assessments. These evaluations are not meant to replace care provided by a subject's local provider(s).

6.3.3 Additional Evaluations if Clinically Indicated (e.g. PFT and CT of Chest and Sinus)

Some of our WHIMS patients experience frequent respiratory infections some of which result in bronchiectasis and may be debilitating. For these subjects, pulmonary function tests (PFT), sputum

cultures, CT or X-ray of the chest and sinus, as well as a pulmonary consult with possible bronchoscopy may be arranged to treat and evaluate the status of their infections. These evaluations are not mandatory; a subject may refuse to participate in any of the assessments.

6.3.4 Baseline Measure of Bone Density and Spleen Size

- Dual-energy x-ray absorptiometry (DEXA) scan.
- Ultrasonography of the spleen.

6.3.5 Research Blood

Research blood will be collected as required and may include the following: ~10 mL of EDTA anti-coagulated blood (1 purple top), ~10 mL of serum (1 tiger top), and 30-60 mL of heparinized blood (3-6 green tops). The blood will be collected for various purposes, including DNA/RNA isolation, EBV-transformed cell line creation, serum/plasma storage, flow cytometry, cytokine measurements, and drug levels.

6.3.6 Wart and/or Skin Biopsy (optional)

Wart and or skin biopsies may be requested for diagnosis and research from subjects but will be optional. An experienced provider will perform the procedure. Local anesthetics will be used for the biopsy site; no conscious sedation or general anesthesia will be given. The risks of skin/wart biopsy include local pain, bleeding, infection, and the potential for scar and keloid formation. Antibiotics and oral analgesics will be used to manage pain and infection. The histologic response to plerixafor offers generalizable knowledge about the pathophysiology and treatment of this condition.

6.3.7 Bone Marrow Biopsy (optional)

Subjects will have the option of having bone marrow biopsy/aspiration done for research purposes, which could be done either as outpatient or inpatient. Local anesthetics will be used for the biopsy site and IV conscious sedation may be offered to subjects for comfort; these agents may result in transient local discomfort initially and occasionally be associated with allergic reactions. General anesthesia will only be given if the participant is admitted for the procedure. The primary risks of bone marrow biopsy include local pain, bleeding, and infection. Antibiotics and oral analgesics will be used to manage pain and infection if necessary.

6.3.8 Quality of Life Assessment of Period Prior to the Study

Subjects will participate in the quality of life surveys (Section 7.9) with the first survey conducted early in the Initial Evaluation and Baseline Assessment period, after a subject has been screened, in order to reflect their experience prior to interventions caused by this study.

6.3.9 IVIg and Prophylactic Antibiotics

Subjects on IVIg and prophylactic antibiotics prior to enrollment maintain their treatments, as clinically indicated, throughout the study. Though unlikely, it is also possible that subjects may be initiated on these treatments during the study if clinically indicated. A subject's use of IVIg and prophylactic antibiotics will be tracked in the subject Memory Aid (Section 6.3.12).

6.3.10 Determining a Minimum Effective Dose for G-CSF

In the US, the FDA-approved treatment for SCN is G-CSF and we expect many of the WHIMS subjects enrolled in this study to be on daily or every other day treatment with G-CSF prior to enrollment. For this study, we need to determine the Minimum Effective Dose (MED) of b.i.d G-CSF injection to achieve an ANC of 500-1500 cells/μL. Enrollees, not on b.i.d G-CSF or with an ANC less than the lower limit of the target ANC range will have G-CSF initiated or adjusted in this period prior to being randomized.

6.3.11 Preparing for Study Drug Shipments and Study Drug Administration at Home

Subjects will be trained on receiving, storage, preparation, and self-administration of the study/comparator drugs. These procedures are reviewed and customized as necessary for each subject at their screening visit. To verify the practicability of these procedures, a medication kit containing the comparator drug (G-CSF) may be shipped to the subject in this period.

6.3.12 Training and Practice for Submissions of Completed Subject Memory Aid

During the initial evaluation and baseline assessment period, subjects have ample time to practice and become proficient at completing and submitting their clinical Memory Aid (Sections 7.4-7.6). The information collected will assist in monitoring a subject's response to b.i.d G-CSF (Section 6.3.10) and their proficiency at completing the Memory Aid. Subjects will not be randomized to commence study treatment unless they demonstrate two successful submissions and express confidence at completing the Memory Aid.

6.3.13 Select a Local Medical Facility for Blood Draws at a Subject's Home Locale

Subjects require access to a local medical facility so that we can monitor their response, in between visits to the NIH-CC, to home administration of G-CSF or plerixafor. Labs from these facilities will be requested during initial evaluation to determine the optimum dose for b.i.d G-CSF (Section 6.3.10), during equilibration to adjust their study dose (Section 6.5.1), and during treatment to ensure that their response to the study drug dose remains optimum (Section 6.6.2). We will work with each subject to ensure that a local medical facility is available for these purposes and all required study procedures are paid by the NIH.

6.4 Randomization and Initiation of the First Study Dose

After completing their evaluation and baseline assessment (Section 6.3), subjects are randomized to start with either plerixafor or G-CSF for the first year to be followed by the alternate drug for the 2nd year. The NIH Pharmacy will conduct randomization and neither the subjects nor study staff will be aware of which study drug a subject is assigned.

6.4.1 Washout Period Prior to the First Study/Comparator Dose (at least 2 days prior to 1st dose)

All baseline assessments of infection and warts shall be completed prior to a subject receiving their first study/comparator drug injection. Subjects withhold their G-CSF or study/comparator drug injection at least 2 days prior to the first day of the study/comparator drug injection (Day 0).

6.4.2 Assessment of Overall Health (within 2 days prior to the 1st dose)

A clinical assessment similar to what was conducted at baseline (Section 6.2.2) should be repeated within 2 days prior to commencing the first study dose.

6.4.3 Confirm Study Drug Shipment/Injection, Memory Aid, Local Labs, and Reporting Infections

Review and confirm with the subject the processes established for receiving, storing, or administering the study drug, completing and submitting the Memory Aid, and obtaining blood draws at their local medical facility. Review and confirm process for reporting infections, diagnosis, and forwarding the information from their local provider.

6.4.4 Lab Draw Prior to Injection of the 1st Study/Comparator Dose

- CBC with diff, Chemistries (Acute Care Panel, Creatine Kinase, Hepatic Panel, Mineral Panel, Total Protein, Lactate Dehydrogenase, Uric Acid), erythrocyte sedimentation rate (ESR).
- Quantitative Immunoglobulins
- Leukocyte Phenotyping
- Pregnancy test for women of childbearing potential

- Research Blood.

6.4.5 Day of the First Study/Comparator Dose (Day 0)

The subject administers the morning dose at NIH-CC while being observed by research personnel to confirm that the subject is proficient with self-administered subcutaneous (SQ) injection.

6.4.5.1 Prior to Injection

- Orthostatic measurements (i.e. pulse and blood pressure taken in the supine, sitting, standing, position approximately 2 minutes apart) within 1 hour prior to study drug injection.
- Labs: CBC with diff, chemistries, and ESR (optional if previous labs are within 24h).
- Research Blood

6.4.5.2 After Study Drug Injection

- Orthostatic measurements 60 min (+/- 20 min) after study drug injection.

6.4.5.3 Procedures Prior to Leaving NIH-CC

- Subjects are supplied with study drug kit and a supply of the study/comparator drug.
- Counsel subjects with symptomatic or measured orthostasis (decrease in blood pressure > 20 mm Hg systolic or increase in pulse >20/min) to exercise additional caution with home dosing.
- Confirm the schedule and procedure for CBC blood draws at the subject's local medical facility.
- Confirm procedures for subject receipt of study/comparator drug, storage, and administration.
- Confirm procedures for subject submission of reports on newly diagnosed infections and treatments by their local provider. Encourage subjects to contact the study coordinator or PI at the onset (or suspicion) of an infection.
- Confirm Subject Memory Aid: completion, schedule, and method of submission to NIH-CC.

6.5 Equilibration Period for the Treatment (8 weeks)

After administering the initial study dose at NIH-CC subjects continue injecting the study/comparator medication at home. The first 8 weeks of injection is considered the Equilibration period with ANC measured every 2 weeks (+/- 7 days) at the subject's local medical facility.

6.5.1 Blood Draws at Subject's Local Medical Facility Every 2 Weeks

Subjects visit their local medical facility every 2 weeks (+/- 7 days) for blood draws prior to the morning dose.

6.5.2 Dose May be Adjusted to Maintain ANC Between 500-1500 cells/µL

ANC readings are reviewed at the NIH-CC and the study drug dose may be increased for ANC < 500 cells/µL and decreased for ANC>1500 cells/µL. However, any decision to adjust must take into consideration a subject's clinical course and status. Dose changes are implemented at the next scheduled shipment of study/comparator drug to the subject.

6.6 Treatment Period (52 weeks)

At completion of the Equilibration period, subjects commence a 52 week treatment period with a constant dose unless ANC <500 cells/µL, in which case the dose may be increased, or ANC >7500 cells/µL absent concomitant infections that may elevate the ANC, in which case the dose will be decreased. Subjects visit NIH-CC at the start of treatment and every 4 months (+/- 31 days) of treatment for a comprehensive assessment of chronic infections, warts and immune status. Between NIH-CC visits, subjects visit their local facility or provider at least once, midway between NIH-CC visits, to have blood drawn for CBC/ANC or as needed for treatment of new or worsening infections. The 1st treatment period ends with the End of Treatment (EOT) visit.

6.6.1 Assessments at NIH-CC Every 4 Months

Subjects visit NIH-CC every 4 months (+/- 31 days) after start of the Treatment Period for a comprehensive assessment of their health and safety, pregnancy status if applicable, immunological markers, chronic infections, and warts.

6.6.1.1 Labs

- Pregnancy test for women of childbearing potential.
- CBC with diff, Chemistries (Acute Care Panel, Creatine Kinase, Hepatic Panel, Mineral Panel, Total Protein, Lactate Dehydrogenase, Uric Acid), erythrocyte sedimentation rate (ESR).

6.6.1.2 Assessment of Overall Health and Safety

A clinical assessment similar to what was conducted at baseline (Section 6.2.2) should be repeated at each 4-month visit to the NIH-CC.

6.6.1.3 Measurement of Immunological Markers

The following procedures are performed to assess the subject's immunological markers:

- Immune Status (basic): Quantitative Immunoglobulins
- Leukocyte Phenotyping

6.6.1.4 Evaluations and Consults for Assessment of Infections

Subjects may be scheduled for assessment as determined at the baseline visit or as clinically indicated by the PI for worsening of infections and/or warts, as described in Sections 6.3.2 and 6.3.3.

6.6.1.5 Research Blood

As with the baseline assessment visits, research bloods may be collected at each visit to the NIH-CC including blood drawn at peak - e.g. approximately 3 hours after the morning study drug injection.

6.6.1.6 Quality of Life Assessment

Subjects will participate in quality of life surveys (Section 7.9) with the first survey conducted early in the Initial Evaluation and Baseline Assessment period and at each 4-month visit to the NIH-CC.

6.6.1.7 Skin and Wart Biopsies (optional)

As with the baseline assessment visits, skin and or wart biopsies may be proposed for research purposes.

6.6.2 CBC w/diff, ESR, and Chemistries Every 2 Months at Subject's Local Medical Facility

Subjects visit their local medical facility once (at 2 months +/- 31 days) in between their scheduled NIH-CC visits for monitoring of their ANC and changes in blood counts (e.g. anemia or thrombocytopenia). Changes in kidney function and serum electrolytes (chemistry) and ESR (optional) will also be requested and the results transmitted to NIH-CC. The blood draw for these tests should be performed prior to the morning dose of study drug.

6.6.3 Visits to a Subject's Local Provider for New or Worsening Infections

Subjects continue visits to their local provider for routine exams and for treatment of new or worsening infections. Because the study measures the frequency and severity of infections, it is important that subjects submit documentation of infection either through a medical record of their visit or through their provider completing a brief form specifying the diagnosis, treatment, and the result of microbial cultures (Appendix G). Subjects and their local providers are encouraged to contact the study coordinator or PI at the onset of infection related events.

6.6.4 End of Treatment (EOT) Visit for a Study Drug

The last visit to the NIH-CC during the treatment period constitutes the End of Treatment Visit (EOT) where a subject ceases injection of the study or comparator drug and the subject's response to the year's treatment is assessed:

- All assessments to measure the study drug safety and efficacy are completed.
- Subject returns all unused study drug to the NIH-CC.

In addition to the procedures conducted at the 4-month visits during treatment, the following procedures are conducted at the EOT visit:

- EKG,
- Dual-energy x-ray absorptiometry (DEXA) scan,
- Ultrasonography of the spleen,
- Vitamin B12 and Folate,
- Antibody levels for Diphtheria and Tetanus.

6.7 Reverting to a Subject's Pre-study Treatment

After completing both study treatments, subjects revert to their pre-study treatment regimen and are offered G-CSF. Subjects continue to submit their diaries and their ANC results to NIH-CC until the Study Completion visit. Adjustments to G-CSF dose may be made according to ANC during this phase. Subjects of child bearing potential shall continue to maintain at least two forms of contraception.

6.7.1 Washout Period (2 Days)

Subjects reverting back to G-CSF treatment should delay restarting G-CSF for at least two days in order to minimize the possibility of drug interaction between plerixafor and G-CSF.

6.7.2 Monitoring the G-CSF Dose (1-2 Months)

To accommodate potential synergistic drug interactions between plerixafor and G-CSF, a subject's initial G-CSF dose will be reduced and their ANC monitored at 2-week intervals (+/- 7 days) for the first month and at 2-month (+/- 31 days) intervals thereafter, or as clinically indicated.

6.7.3 Study Completion Visit

The study completion visit occurs approximately 5 to 6 months after the EOT visit of the 2nd treatment period. The assessments for this visit are described in Section 6.6.1.

6.8 Early Completion of Treatment Due to Unwillingness or Inability to Receive Study Agent

If for any reason a subject is unwilling or unable to continue receiving the study agent during the Dose Equilibration or Treatment periods, including reasons such as 1) an inability to maintain a minimum ANC level considered safe, defined as ANC greater than or equal to 500 cells/μL, 2) a refusal to continue with the study agent, or 3) a Grade 3 or 4 Toxicity to the study agent, a subject would terminate that phase of the study and proceed to the next phase. Data handling for patients who fail to complete both arms of the study is detailed in the Statistics section (Section 14).

7 STUDY PROCEDURES AND EVALUATIONS

7.1 Absolute Neutrophil Count (ANC)

A primary goal in WHIMS treatment is the correction of neutropenia. The Absolute Neutrophil Count (ANC) is measured as a component of a Complete Blood Count (CBC) test. Normally between 1500-7500 cells/μL, most WHIMS patients without G-CSF, Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF), or plerixafor treatment will have a Baseline ANC between 0-500 cells/μL.

7.1.1 Time of Day Measurement for ANC: Prior to Study Dose

The ANC level is measured prior to a study dose. Since plerixafor and G-CSF are administered twice daily, the ANC should be measured prior to a dose to measure the minimum ANC level approximately 12 hours after a study dose.

7.1.2 Target ANC during 8 week Equilibration Period (500 – 1500 cells/µL)

ANC is measured approximately every 2 weeks in this 8-week period and the dose will be adjusted for a target ANC approximately between 500-1500 cells/µL that we have found to be achievable with well-tolerated low-dose plerixafor in our preliminary studies of patients with WHIMS.

7.1.2.1 Subjects with a Baseline ANC > 500 cells/µL

Subjects will be excluded if they do not have neutropenia (Baseline ANC>1500 cells/µL); however, if they do have neutropenia, but their baseline ANC average is greater than the target ANC=500 cells/µL, then they will be given the minimal dosage of both drugs specified by the study in Section 7.1.4) with downwards adjustment possible if they exceed the maximum ANC (7500 cells/µL). Baseline ANC is assessed on at least two measurements on separate days, when a subject is not on G-CSF, plerixafor, or experiencing an acute infection.

7.1.2.2 Subjects Unable to Attain ANC >500 cells/µL During Equilibration, Despite Maximal Dose

The target ANC of 500 cells/µL is accepted as safe in the medical literature. Therefore, for participants whose baseline ANC is <500 cells/µL, we will administer up to the maximal dose for the study (0.04 mg/kg b.i.d. for plerixafor or 2 µg/kg b.i.d. for G-CSF), that is needed to increase the ANC to a minimum of 500 cells/µL and to maintain it at this level as a minimum. If in the dose equilibration period a study subject fails to attain an ANC of 500 cells/µL on the maximum dose cited above, they would be declared a failure on that treatment, stop receiving that treatment, and commence "early" crossover and washout process for switching to the 2nd Treatment, or if failing to respond during the 2nd Treatment, a subject would terminate all study treatments, revert to their pre-study treatment regimen if appropriate or desired, and continue to the Study Completion Visit.

7.1.3 Target ANC during the 52 week Treatment Period (500 – 7500 cells/µL)

After completing the Equilibration period, subjects commence a 52-week treatment period with the goal of a constant dose optimized for the subject. During the treatment period, this dose will only be increased for ANC <500 cells/µL or decreased for ANC >7500 cells/µL, in 2 consecutive measurements on separate days, absent infections that may elevate the ANC.

7.1.4 Dose Range for Low-Dose Treatment

The doses prescribed in this study are significantly lower than the maximum doses that have been used in humans for stem cell mobilization. The maximum current approved dosage for plerixafor = 0.24 mg/kg/day and this is given on up to 4 consecutive days for apheresis (Appendix B). SCN (most of which is due to ELANE mutations) has been treated with G-CSF= 2.3 to 40 µg/kg/day (Appendix C). The dose ranges in this study were selected based on our prior experience with the dosages that are effective in patients with WHIMS in reaching the target biomarker window of 500<ANC<1500:

G-CSF: 0.25 - 2.0 µg/kg twice per day,
Plerixafor: 0.01 - 0.04 mg/kg twice per day.

The dose for plerixafor will be reduced for renal impairment. (Appendix E)

We already have experience treating 16 WHIM patients with low dose daily G-CSF for extended periods with excellent compliance. In our 6 month Phase 1 study of plerixafor in WHIMS, the drug was well-tolerated and compliance was excellent. Interestingly, we observed that the ANC declined more slowly than expected after stopping plerixafor, taking 2-3 weeks to reach the subject's baseline, and that the response to G-CSF once at baseline was greater than expected.(5) Therefore, subjects

assigned G-CSF in the 2nd year treatment in the present study will be started on a lower dose in the Equilibration Period than the optimum dose defined during the evaluation period. The dose will then be adjusted if necessary, as guided by the ANC response.

7.2 Adjusting the Study Dose to Meet ANC Goals

A subject's dose is increased for ANC below 500 cells/μL, and maintained for ANCs up to 1500 cells/μL during the 8-week Equilibration period and for ANCs up to 7500 cells/μL during the 52-week treatment period. Doses of either drug may be reduced if the steady-state counts exceed the upper ANC thresholds in the absence of an acute infection. Two sequential ANC values on different days prior to the morning study drug dose will be used at the times indicated in the protocol to make study drug dose adjustments.

7.2.1 Initial Study/Comparator Drug Doses during Equilibration Period

G-CSF - without a known history of treatment with G-CSF:	0.5 μg/kg b.i.d.
G-CSF - with a history of G-CSF dosing:	Specified by PI prior to randomization.
G-CSF - after recent treatment with plerixafor	Specified by PI prior to randomization.
Plerixafor:	0.01-0.04 mg/kg twice per day.

7.2.2 Adjustment for ANC <500 cells/μL

G-CSF: Increase dose to a maximum of 2.0 μg/kg b.i.d.
Plerixafor: Increase dose to a maximum of 0.04 mg/kg b.i.d.

7.2.3 Adjustment for ANC between 500 – 1500 cells/μL in the Equilibration Period

G-CSF: Maintain dose.
Plerixafor: Maintain dose.

7.2.4 Adjustment for ANC > 1500 cells/μL in the Equilibration Period

G-CSF: The G-CSF dose may be reduced after review of a subject's clinical course.
Plerixafor: The plerixafor dose may be reduced after review of a subject's clinical course.

7.2.5 Adjustment for ANC > 7500 cells/μL in the Treatment Period

G-CSF: G-CSF dose may be reduced after review of a subject's clinical course.
Plerixafor: The plerixafor dose may be reduced after review of a subject's clinical course.

7.3 Immune Status: Leukocyte Immunophenotypes

Leukocyte numbers available from the CBC (ANC, etc.) will be averaged for each 1-year treatment period with either the Study Drug or Comparator Drug and statistical comparison will be performed as part of the secondary endpoints. Lymphocyte flow cytometry results (CD19+, CD4+, CD8+, etc.) will be averaged from the 4, 8, and 12 month visits to the NIH-CC for each agent and statistical comparison will be performed as part of the secondary endpoints. Changes in leukocyte numbers will also be analyzed by length of time on the Study Drug or Comparator Drug.

7.4 Medication Compliance: Study Drug and Prophylactic Antibiotics

7.4.1 Subject Memory Aid

It is important to track a subject's compliance with the study drug, IVIg, and prophylactic antibiotics. Compliance is likely to affect a subject's susceptibility to infection. Considering the duration of study participation, incomplete entries can be expected; therefore, we encourage frequent communications with study subjects in an effort to collect all details concerning adverse events, infections, missed doses of study agent and other concomitant medications taken. The references to diary card have been changed to memory aid as this is more of a tool the subjects can use in addition to information gathered by the study team via frequent communication with subjects such as via phone calls, emails, and phone texts, especially whenever a new infection, unusual side effects or a change in medication or dose occurs.

7.4.1.1 IVIg Treatment and Dose
Subjects record the Date and Dose of the most recent IVIg infused.

7.4.1.2 Record Temperature for Fevers
Subjects record their highest temperature for the day if they have a fever (defined as oral temperature ≥38.3°C. Subjects are encouraged to visit their local provider if they develop a fever.

7.4.1.3 Compliance with Prescribed Prophylactic Antibiotics
Subjects record changes to their use of prophylactic antibiotics.

7.5 Study Drug Side Effects and Toxicity

7.5.1 Subject Memory Aid
The most common side effects expected of the study drugs are listed in the Memory Aid (Appendix F) for subjects to rate. Subjects also have the option of specifying additional side effects. The rating scale described below is based on CTCAE v4.0. Please note the following definitions for Activities of Daily Living (ADL):

Instrumental ADL: Preparing meals, shopping, using telephone and managing money etc.

Self-care ADL: Bathing, dressing, feeding, using toilet, taking medications and not bedridden.

7.5.1.1 Injection Site Reaction
Subjects inject the study drug subcutaneously twice per day and record the Injection Site Reaction defined as "intense adverse reaction (usually immunologic) developing at the site of an injection, for the period between injections.

Not Injected:	Subject did not inject the drug.
1 - Tenderness	Tenderness with or without associated symptoms (warmth, redness, itching).
2 - Pain	Pain; lipodystrophy; edema (swelling); phlebitis (inflammation of a vein).
3 - Ulceration	Ulceration or necrosis; severe tissue damage; operative intervention indicated.
4 - Life-threatening	Life-threatening consequences; urgent intervention indicated.

7.5.1.2 Bone (Skeletal) Pain: back, arms and legs
Subjects may complain of pain after treatment, likely due to leukocyte mobilization. Bone pain: marked deep aching or throbbing discomfort in the back, arms, and legs. Subjects rate their worst pain for the day.

1 - Mild	Mild pain.
2 – Moderate	Moderate pain; limiting Instrumental ADL.
3 - Severe	Severe pain; limiting Self-care ADL.

7.5.1.3 Other Pain: shoulder, abdominal etc.
The study drug may cause enlargement of the spleen, which may result in shoulder or abdominal pain. Subjects should record any pain not related to bone pain.

1 - Mild	Mild pain.
2 - Moderate	Moderate pain; limiting Instrumental ADL.
3 - Severe	Severe pain; limiting Self-care ADL.

7.5.1.4 Headache
Subjects may complain of headache, a sensation of marked discomfort in various parts of the head. Subjects record their worst symptoms for the day.

1 - Mild	Mild pain.
2 - Moderate	Moderate pain; limiting Instrumental ADL.

3 – Severe	Severe pain; limiting Self-care ADL.

7.5.1.5 Dizziness

Subjects may complain of dizziness - disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning, or rocking. Subjects record their worst symptoms for the day.

1 - Mild	Mild unsteadiness or sensation of movement.
2 - Moderate	Moderate unsteadiness or sensation of movement; limiting Instrumental ADL.
3 – Severe	Severe unsteadiness or sensation of movement; limiting Self-care ADL.

7.5.1.6 Nausea

Subjects may experience nausea - a queasy sensation or an urge to vomit - that may be related to the study drug. Subjects tabulate their symptoms for that day.

1 – Mild	Loss of appetite without alteration in eating habits.
2 – Moderate	Oral intake decreased w/o significant weight loss, dehydration or malnutrition.
3 – Severe	Inadequate oral caloric/fluid intake; tube feeding, TPN; hospitalization indicated.

7.5.1.7 Vomiting

Subjects may experience vomiting - a reflexive act of ejecting the contents of the stomach - that may be related to the study drug. Subjects tabulate their symptoms for the day.

1 - 1 to 2 episodes	1-2 episodes (separated by 5 minutes) in 24 hrs.
2 – 3 to 5 episodes	3-5 episodes (separated by 5 minutes) in 24 hrs.
3 – 6 or more	≥6 episodes (separated by 5 minutes) in 24 hrs.
4 – Life-threatening	Life threatening consequences, urgent intervention required.

7.5.1.8 Diarrhea

Subjects may experience diarrhea – frequent and watery bowel movement - that may be related to the study drug. Subjects tabulate their symptoms for the day.

1 – Increase <4 stools	Increase of 1-4 stools per day over baseline.
2 – Increase 4-6 stools	Increase of 4-6 stools per day over baseline.
3 – Increase >=7 stools	Increase >=7 stools per day; incontinence; hospitalization indicated. Limiting Self-care ADL.
4 – Life-threatening	Life threatening consequences, urgent intervention required.

7.5.1.9 Subject Specifies Other Symptoms or Adverse Events.

Subjects can specify other study drug reactions and rate the severity for that day.

1 – Mild	Mild symptoms; intervention not indicated (required).
2 – Moderate	Minimal, local or noninvasive intervention indicated; limiting Instrumental ADL.
3 – Severe	Medically significant but not immediately life-threatening. Hospitalization indicated, disabling; limiting Self-care ADL.
4 – Life-threatening	Life threatening consequences; urgent intervention required.

7.5.2 CBC, Chemistries, ESR, and Pregnancy for Women of Childbearing Potential

In addition to ANC and the CBC w/diff, we may request additional labs including blood chemistries, and ESR. These standard clinical tests will allow us to monitor for changes in blood counts (anemia or thrombocytopenia), changes in kidney or liver function, serum electrolytes, and blood glucose. For women of childbearing potential, a urine or serum pregnancy test will be conducted.

7.5.3 Splenic Enlargement

There is a possibility of splenic enlargement with both drugs: very rare cases of splenic rupture have been reported in patients following the administration of G-CSF (Appendix C) and rats given high doses of plerixafor were found to have splenic enlargement (Appendix B).

7.5.3.1 Spleen Ultrasonography

Since WHIMS patients may develop splenomegaly prior to therapy, a spleen ultrasonography will be performed prior to the first study dose and at the end of each treatment period. Additional sonograms may be performed at subsequent visits if clinically indicated.

7.5.3.2 Spleen Assessment as part of Physical Examination at Research Assessment

Assessment of the spleen will be part of the physical exam at NIH-CC visits every 4 months.

7.5.4 Electrocardiogram

An electrocardiogram (EKG) will be performed during screening to serve as baseline and to rule out preexisting cardiac arrhythmia. EKG will be repeated at the EOT visit for each treatment arm.

7.5.5 Echocardiogram

If an echocardiogram (ECHO) has not been performed in the previous 5 years on a subject or the results of such a test cannot be obtained, this non-invasive cardiac testing will be performed to look for congenital cardiac malformations or cardiac conditions that would predispose a subject to life threatening arrhythmia.

7.5.6 Dual-energy X-ray Absorptiometry (DEXA) Scans

To monitor for the loss of bone density, dual-energy x-ray absorptiometry (DEXA) scans will be performed prior to the first study dose and at the end of each treatment period.

7.6 Rate and Severity of Infections

7.6.1 Subject Memory Aid: Symptoms of Infections

7.6.1.1 Incidence and Severity of Fever

Subjects should report symptoms of chills or fevers and take their oral temperature as required. The highest temperature measured that day should be recorded. Subjects are encouraged to visit their local provider if they develop a fever.

7.6.1.2 Number of Days with Fever

Each day a subject reports an elevated oral temperature at any time during the day above 38.3°C is counted as a day with fever.

7.6.1.3 Change in Severity of Chronic Infection

WHIMS patients often experience ongoing chronic infections with the type, symptom, and severity varying amongst the patients. We plan to identify and measure changes in the severity of these infections.

7.6.1.4 Visits to Local Provider for Medical Exam or Treatment

Subjects should record visits at their local facility for medical exams or treatments.

7.6.1.5 Incidence and Duration of Antibiotic for Treatment

Subjects should specify any antibiotic prescribed or taken to treat an infection and record the medication activity for that day. The duration of antibiotic use is based on the number of days from the start date to the end date of treatment recorded in the Memory Aid. A missed day or missed partial day is included in the duration.

7.6.2 Clinical Diagnosis and Treatment of Infections

While enrolled in the study, subjects continue visits to their local medical provider for clinical care, as per their routine prior to enrollment. The diagnosis and treatment results of their infection should be submitted to NIH-CC using either or both of the following methods:

7.6.2.1 Local Provider Completes a Diagnosis and Treatment Form (option 1)

The local provider completes the Diagnosis and Treatment form:

- Date of Visit,
- Chief Complaint, Onset of Symptoms,
- Diagnosis, New/Chronic/Recurrent/Exacerbation,
- Infection: Site, Type (viral, fungal, bacterial, etc..), Suspect Causative Organism,
- Treatment Prescribed, and
- Results of related Laboratory Tests or Cultures,
- Outcome of Infections (Resolved, Resolved with residual Symptoms, Ongoing),
- Provider will be encouraged to contact study staff.

Localized infection sites that are contiguous will be considered as 1 single infection. A sample form that can be used by the study coordinator, PI, or local care provider is shown in Appendix G.

7.6.2.2 Subject or Provider forwards Documents Relating to the Infection (option 2)

Subject obtains or requests a copy of their medical records related to the infection to be sent to NIH-CC.

7.6.3 ENT and Audiology Evaluation at NIH-CC

Subjects with a history of ear or sinus infections are scheduled for Audiology and ENT at baseline and completion of each study drug treatment. Additional consults may be scheduled as medically necessary.

7.6.4 Dental and Oral Evaluation

Subjects are scheduled for assessment of dental caries, periodontal disease, and HPV at baseline and completion of each study drug treatment. Additional consults may be scheduled as medically necessary.

7.6.5 PFT for Subjects with Chronic Respiratory Infections

WHIMS patients frequently suffer from repeated pulmonary infections that result in bronchiectasis and chronic bronchitis. Subjects may undergo pulmonary function tests during screening and at the end of each treatment period. In addition, subjects with a history of respiratory infections may be scheduled for a pulmonary consult at screening to optimize their therapy. Additional consults can be scheduled if needed for new or worsening infections/lung function

7.7 Monitoring Warts

7.7.1 Photos of Infections and Warts

For subjects with warts who consent to clinical photography, a comprehensive photo set encompassing an overview of the external surface of the body will be taken at baseline and at the end of each treatment period, including detailed photographs of the hands and feet, which are typical sites for warts in WHIM patients. Detailed photos may be taken of particular warts and other types of skin infections, including infections in the anogenital areas if applicable. The photos will serve as the measure of the number and severity of infection. To ensure consistent measurements, a similar set of photos will be taken at subsequent visits to the NIH-CC.

7.7.2 Recording the Quantity and Severity of Warts

A case report form will be utilized to document the type, appearance, and location of the warts, photographs of the warts, treatments of existing warts, appearance of new warts, and representative warts/wart areas of interest will be quantified and tracked at each visit to the study center.

7.7.3 Dermatology Evaluation
Subjects will be evaluated by dermatology at baseline and at the completion of each study drug. Additional consults may be scheduled if requested by dermatology or for new or worsening cutaneous infections.

7.7.4 GU/GYN Evaluation
Subjects will be scheduled for a genitourinary or gynecology exam at baseline and at the completion of each study drug. Additional exams can be scheduled if requested by GU/GYN or for new or worsening infections.

7.8 Specimen Preparation, Handling, and Shipping
As the transmission of human immunodeficiency virus (HIV) and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate precautions will be employed by all personnel involved in the drawing of blood and the shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the NIH.

7.9 Quality of Life (SF36 v2)
Subjects will complete a validated Quality of Life questionnaire (SF-36, version 2) at Baseline and at the 4, 8, 12 month visits to NIH-CC during the treatment period. At completion of the second treatment period, subjects will be asked whether they prefer the first drug they received or the second.

7.10 Request for Excess Tissue
Tissue removed for medical indications at the NIH or elsewhere that is not required for a subject's medical care and would otherwise be discarded, with the subject's permission, may be requested to be sent to the NIH for pathologic or research purposes.

8 POTENTIAL RISKS AND BENEFITS

8.1 Potential Risks of plerixafor
The dose for plerixafor in this study is 0.01-0.04 mg/kg SQ twice per day is 3 to 12 times less than the FDA-approved and commonly prescribed dose of 0.24 mg/kg per day when used in combination with G-CSF for hematopoietic stem cell mobilization. The most common adverse reactions (ARs; ≥10%) associated with plerixafor at 0.24 mg/kg/day in combination with G-CSF administered subcutaneously to subjects with cancer at doses that were over 3-12 fold higher than the dose that will be used in the current study include diarrhea, nausea, fatigue, injection site reactions, headache, arthralgia, dizziness, and vomiting.

Injection site reactions: A temporary urticaria-like, pruritic, raised and erythematous lesion can occur at the injection site and is common with higher doses than will be used in this study. These reactions typically resolve within minutes with no treatment. Prolonged reactions if problematic will be treated with standard medical therapies such as topical corticosteroids, oral antihistamines, etc.

Musculoskeletal Pain: Musculoskeletal pain may affect bones, muscles, ligaments, tendons, or nerves and may include one or a combination of the following types of pain: Bone Pain (deep dull pain from the back, legs, and arms), Joint Pain or Arthralgia (pain and/or swelling in the joints), Back Pain, and or Pain in the Extremities.

Gastrointestinal side effects: Various side effects related to gastrointestinal function have been reported after doses of 0.24 mg/kg including abdominal pain, diarrhea, constipation, nausea, and vomiting, all at

higher rates than in subjects given placebo. In general, these have not resulted in the need to stop the medication.

Excessively high white counts (leukocytosis): Because of the mechanism of action of this medication, it is expected that white blood cell counts will rise. However, normal volunteers have not risen above 25,000 cells/μL of blood after 1 day of treatment at 0.24 mg/kg/day. The subjects likely to be enrolled in this study generally have low circulating WBC and are unlikely to develop leukocytosis. As an additional safety measure, we are starting participants at a low dose of study medication and can lower it if indicated by a high ANC count (>7500 cells/μL).

Thrombocytopenia and bleeding: Lower platelet counts (thrombocytopenia) have been reported with administration of both study/comparator drugs, but no serious bleeding events have been reported for plerixafor to date.

Splenic enlargement: An increase in spleen size has been shown to occur in rats treated with plerixafor at proportionately higher doses than will be used here. Although this has not been reported as causing any severe problems in humans, we will monitor for clinical signs of problems by asking subjects about left shoulder or left upper quadrant abdominal pain at NIH-CC visits. If these occur, the subject will be evaluated by medically appropriate imaging and the study drug may be stopped at the discretion of the PI. In addition, spleen size will be monitored by ultrasound as specified in Appendix A.

Cardiac Arrhythmia: In one human study, 2 HIV-infected patients developed a non-life threatening cardiac arrhythmia consisting of frequent premature ventricular contractions.(10) Individuals who are at high risk for life threatening arrhythmia based on EKG or cardiac problems detected on ECHO or who have a past history of life threatening cardiac arrhythmia will be excluded from this study.

Paresthesia: In one human study, some HIV-infected patients developed some transient perioral or peripheral numbness that resolved with discontinuation of the drug. The patients affected were treated with doses considerably higher than will be used in this study and the problem may have been related to other medications, which HIV-infected patients commonly use, or HIV itself.

Exacerbation of Chronic Bronchitis/Pneumonia: One of three WHIM subjects treated with plerixafor in our previous 6 month Phase 1 trial developed an acute exacerbation of chronic bronchitis and a pneumonia during treatment.(5) However, this is already common in untreated WHIMS patients, so cannot be considered a risk of plerixafor. WHIM patients often develop bronchiectasis as they age as a result of repeated lung infections. This may lead to poor clearance of sputum and chronic bronchitis with frequent exacerbations and chronic colonization of the sputum with bacterial and fungal pathogens typical for cystic fibrosis patients, (i.e., Pseudomonas, Stenotrophomonas, and Aspergillus). Increased circulating neutrophils from either plerixafor or G-CSF could contribute to thickened sputum, which may worsen this chronic problem. If subjects have chronic respiratory symptoms, sputum culture for these bacteria as well as tuberculosis and atypical mycobacteria will be obtained at the screening visit. Subjects who suffer from this disease complication may receive pulmonary consultation and have their pulmonary treatment regimen optimized prior to randomization and study drug initiation. This pulmonary regimen may include drug treatments such as inhaled or nebulized beta adrenergic agonists, anticholinergic medications, hypertonic saline, prophylactic antibiotics, or DNase enzymes, and physical stimulation of the cough reflex with breathing devices or treatments to improve sputum clearance.

Varicella Zoster Infection: During chronic plerixafor therapy we observed reactivation of herpes zoster in one of three subjects.(5) The subject was treated with oral acyclovir and the infection resolved completely within days.

8.2 Potential Risks for G-CSF

Allergic-type Reactions: Allergic-type reactions occurring on initial or subsequent treatment have been reported in <1 in 4000 of subjects treated with G-CSF. These have generally been characterized by systemic symptoms involving at least two body systems, most often skin (rash, urticaria, facial edema), respiratory (wheezing, dyspnea), and cardiovascular (hypotension, tachycardia). Some reactions occurred on initial exposure. Reactions tended to occur within the first 30 minutes after administration and appeared to occur more frequently in subjects receiving intravenous G-CSF. Rapid resolution of symptoms occurred in most cases after administration of antihistamines, steroids, bronchodilators, and/or epinephrine. Symptoms recurred in more than half the subjects who were rechallenged.

Splenic Rupture: Splenic rupture, including exceedingly rare fatal cases, has been reported following the administration of G-CSF. Individuals receiving G-CSF who report typical left upper abdominal and/or shoulder pain will be evaluated for an enlarged spleen or splenic rupture. In addition, spleen size will be monitored by ultrasound as specified in Appendix A.

Musculoskeletal Pain: Musculoskeletal pain may affect bones, muscles, ligaments, tendons, or nerves and may include one or a combination of the following types of pain: Bone Pain (deep dull pain from the back, legs, and arms), Joint Pain or Arthralgia (pain and/or swelling in the joints), Back Pain, and or Pain in the Extremities.

Acute respiratory distress syndrome (ARDS): ARDS has been reported in patients receiving G-CSF, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Subjects receiving G-CSF who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, G-CSF should be withheld until resolution of ARDS or discontinued. Subjects will receive appropriate medical management for this condition.

Alveolar Hemorrhage: alveolar hemorrhage manifesting as pulmonary infiltrates and hemoptysis requiring hospitalization has been reported in healthy donors undergoing peripheral blood progenitor cell mobilization. Hemoptysis resolved with discontinuation of G-CSF.

Growth Factor for Tumor: G-CSF is a growth factor that primarily stimulates neutrophils. However, the possibility that G-CSF can act as a growth factor for any tumor type cannot be excluded.

Immunogenicity: As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in subjects receiving G-CSF has not been adequately determined. While available data suggest that a small proportion of subjects developed binding antibodies to G-CSF, the nature and specificity of these antibodies has not been adequately studied. Cytopenias resulting from an antibody response to exogenous growth factors have been reported on rare occasions in subjects treated with other recombinant growth factors. There is a theoretical possibility that an antibody directed against G-CSF may cross-react with endogenous G-CSF, resulting in immune-mediated neutropenia; however, this has not been reported in clinical studies or in post-marketing experience. Subjects who develop hypersensitivity to G-CSF may have allergic or hypersensitivity reactions to other *E coli*-derived proteins.

Cutaneous Vasculitis: Cutaneous vasculitis has been reported in subjects treated with G-CSF. In most cases, the severity of cutaneous vasculitis was moderate or severe. Most of the reports involved subjects with severe chronic neutropenia receiving long-term G-CSF therapy. Symptoms of vasculitis generally developed simultaneously with an increase in the ANC and abated when the ANC decreased. Many subjects were able to continue G-CSF at a reduced dose.

Aortitis - inflammation of the aorta: Aortitis has been reported in patients who received G-CSF. Symptoms may include fever, abdominal pain, feeling tired, and back pain.

The following AEs have been identified during post-approval monitoring of G-CSF: splenomegaly, splenic rupture, ARDS, alveolar hemorrhage and hemoptysis, sickle cell crisis, cutaneous vasculitis, aortitis, Sweet's syndrome (acute febrile neutrophilic dermatosis), decreased bone density and osteoporosis in pediatric severe chronic neutropenia subjects receiving chronic treatment with G-CSF.

8.3 Risks and Discomforts of Phlebotomy

Subjects will undergo repeat blood sampling on several occasions during the initial phase of the study and during the treatment period. For research blood purposes, each venipuncture will be for 3 mL to 120 mL of blood in adults. Phlebotomy for blood tests may cause pain, lightheadedness/fainting, or lead to the formation of a small subcutaneous hematoma caused by blood leaking from a punctured blood vessel. The hematoma causes only minor discomfort; it is not dangerous and requires no treatment other than reassurance to the subject. There is also a small risk of infection at the site of the needle puncture, which can be readily treated with antibiotic therapy. At the time of enrollment, each subject will be asked about their participation in other research studies to ensure that the amount of blood drawn does not exceed the limits allowed for adult subjects by the NIH Clinical Center (Medical Administrative Series Policy #: M95-9: Guidelines for Limits of Blood Drawn for Research Purposes in the Clinical Center. Available at: http://cc-internal.cc.nih.gov/policies/PDF/M95-9.pdf

8.4 Risks and Discomforts of Skin or Wart Biopsies

Wart or skin biopsies may be requested for diagnosis and research from subjects but will be optional. An experienced clinician will perform the procedure. Unless the procedure is being performed in conjunction with a clinically indicated surgery, only local anesthetics will be used to prepare the biopsy site. The risks of wart biopsy include local pain, bleeding, infection, and the potential for scar and keloid formation. Antibiotics and oral analgesics will be used to manage pain and infection. The differences in the immune response during plerixafor and G-CSF treatment offers generalizable knowledge about the pathophysiology and treatment of this condition and knowledge of infecting types of HPV and the presence of other co-infecting viruses may have clinical implications for the subject (i.e., risk of cancer development is increased with "high risk" HPV types).

8.5 Risks and Discomforts of Bone Marrow Biopsy

Subjects have the option of having bone marrow biopsy done for research purposes, which could be performed as an outpatient procedure. Local anesthetics will be used to prepare the biopsy site and IV conscious sedation may be offered to subjects for comfort; these agents may result in transient local discomfort initially and occasionally be associated with allergic reactions. General anesthesia will only be given if the participant is admitted for the procedure. The primary risks of bone marrow biopsy include local pain, bleeding, and infection. Antibiotics and oral analgesics will be used to manage pain and infection.

8.6 Risks of Stopping G-CSF

Subjects receiving G-CSF at the time of randomization will have the agent stopped for two days prior to receiving the first dose of study drug. This short washout period is to avoid the possibility of synergy between G-CSF and plerixafor. The risk of infection during the two day washout period is unlikely to be significantly increased. Moreover, the subjects will be closely monitored at the NIH-CC as outpatients during this period.

8.7 Potential Benefit

G-CSF is an FDA-approved treatment for neutropenia and has been shown to reduce infection in congenital neutropenia.(24) (Appendix C) Plerixafor is a specific antagonist of CXCR4 and provides a novel molecularly targeted potential therapy for WHIMS. Recent Phase I dose-escalation studies of

plerixafor in a total of 9 subjects demonstrated that the drug mobilizes not only neutrophils but also all other leukocyte subsets that are decreased in the blood of WHIMS patients.(3, 4) Furthermore, low-dose therapy with plerixafor alone for 6 months in 3 subjects resulted in a reduction of infections, no new warts and possible improvement of existing warts, and no safety concerns.(5) This collective experience appeared to be an improvement compared to pre and post study treatments of the same subjects with G-CSF.

8.7.1 Reduced Infections

G-CSF has been shown to be effective in alleviating neutropenia and reducing infection in patients with chronic neutropenia (24) and there is some limited anecdotal and retrospectively controlled evidence that plerixafor may also have clinical benefits. The aim of this study is to define which drug is superior in WHIMS patients. The crossover design ensures that all subjects are able to receive both treatments: subjects without prior treatment with either agent may experience improved outcomes from either treatment, while subjects previously on G-CSF may obtain benefits with plerixafor.

8.7.2 Improved Drug Tolerability

In our clinical experience treating WHIMS patients with G-CSF and plerixafor, we have identified low dose ranges able to maintain the ANC within the target range for the present study of 500-1500 cells/microliter, which is considered in the literature as 'safe'. At these doses, we have observed no toxicity attributed to either plerixafor or G-CSF and both appear to be well-tolerated.

8.7.3 Control of Warts

Limited evidence suggests that during chronic treatment with plerixafor in WHIMS patients, warts are improved in appearance and size and seem not to recur which is different from the patient's prior experience on/off G-CSF therapy. This may indicate a beneficial effect of plerixafor treatment in HPV disease.(5) This study is designed to further investigate and validate this preliminary result.

8.7.4 Increased Leukocyte Response

Preliminary published evidence suggests that plerixafor is capable of increasing all leukocytes measured that are diminished in the circulation of WHIMS patients (neutrophils, CD4+/CD8+ lymphocytes, B cells, and monocytes) in contrast to G-CSF, which increased mainly neutrophils.(3-5) It is currently unknown whether the increased circulating leukocytes convey the expected benefits in terms of reducing infection or improving the immune system function and this study is designed to further investigate and validate this.

9 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

9.1 Intended Use

Sample collection, handling, storage, and shipment will follow NIH-CC policies and procedures. We will make a summary of radiology and laboratory results available to subjects and their local physicians. Samples and data collected under this protocol may be used to study the causes of primary immunodeficiency, the consequences thereof, and its treatment. Genetic testing to determine the cause of the underlying disorder will be performed utilizing another appropriate protocol and will not be performed as part of this protocol.

9.2 Storage and Tracking

Access to stored samples will be limited using either a locked room or a locked freezer. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data. Samples and data acquired will be tracked using software designed for this purpose.

9.3 Sharing of Samples and Data
Other investigators at the NIH or outside may wish to study these samples and/or data. In that case, IRB approval must be sought prior to any sharing of samples and/or data. Any clinical information shared about the sample would similarly require prior IRB approval.

9.4 Reporting Loss or Unanticipated Destruction of Samples
Any loss or unanticipated destruction of samples or data (for example, due to freezer malfunction) that is a Serious Protocol Deviation or compromises the scientific integrity of the data collected for the study, will be reported to the National Institute of Allergy and Infectious Diseases (NIAID) IRB.

9.5 Disposition of Samples

9.5.1 Request by Study Participant
Subjects may decide at any point not to have their samples stored. The PI will destroy or assure the destruction of all known remaining samples and report what was done to both the subject and to the IRB. This decision will not affect the subject's participation in other protocols at NIH.

9.5.2 At Completion of Study
At the completion of the protocol (termination), samples will either be destroyed, or after IRB approval, transferred to another existing protocol.

10 REMUNERATION PLAN FOR SUBJECTS
Study subjects and their families will not receive any per visit reimbursement for the clinical trial. However for optional procedures performed for research purposes only, $120.00 will be paid for each wart and/or skin biopsy, and $200 paid for each bone marrow biopsy.

11 ASSESSMENT OF SAFETY

11.1 Documenting, Recording, and Reporting Adverse Events
At each contact with the subject, information regarding AEs will be elicited by appropriate questioning and examinations and they will be:

- Immediately documented in the subject's medical record/source document.
- Recorded in Clinical Research Information Management System, and
- Reported as outlined below (e.g., IND sponsor, IRB, FDA).

11.2 Definitions
Adverse Event (AE)
An AE is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participating in the research, whether or not considered related to the research.

Adverse Reaction (AR) or Adverse Drug Reaction (ADR)
An AE that is caused by an investigational agent (drug or biologic).

Suspected Adverse Reaction (SAR)
An AE for which there is a reasonable possibility that the investigational agent caused the AE. 'Reasonable possibility' means that there is evidence to suggest a causal relationship between the drug and the AE. A SAR implies a lesser degree of certainty about the causality than an AR, which implies a high degree of certainty.

Serious Adverse Event (SAE)

A serious AE (SAE) is an AE or any untoward medical occurrence that at any time results in 1 or more of the following outcomes:

- Death
- Life threatening event (immediate threat to life) event
- An inpatient hospitalization or prolongation of an existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly or birth defect,
- A medically important event*

*Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that may not be immediately life threatening or result in death or hospitalization, but they may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed above.

Unexpected Adverse Event
An AE is unexpected if it is not listed in the Investigator's Brochure or Package Insert (for marketed products) or is not listed at the specificity or severity that has been observed. It is the responsibility of the IND Sponsor to make this determination.

Serious and Unexpected Suspected Adverse Reaction (SUSAR)
A SUSAR is a Suspected Adverse Reaction that is both Serious and Unexpected.

Unanticipated Problem (UP)
An UP is any event, incident, experience, or outcome that is

1. Unexpected in terms of nature, severity, or frequency in relation to:
   - The research risks that are described in the IRB-approved research protocol and informed consent document, investigator's brochure, or other study documents; and
   - The characteristics of the subject population being studied; and
2. Possibly, probably, or definitely related to participation in the research; and
3. Places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Per the IND sponsor, an AE with a serious outcome will be considered increased risk.

Unanticipated Problem That Is Not an Adverse Event (UPnonAE)
Unanticipated problem that is not an Adverse Event (UPnonAE): An unanticipated problem that does not fit the definition of an adverse event, but which may, in the opinion of the investigator, involve risk to the subject, affect others in the research study, or significantly impact the integrity of research data. Such events would be considered a non-serious UP. For example, we will report occurrences of breaches of confidentiality, accidental destruction of study records, or unaccounted-for study drug.

Protocol Deviation
Any change, divergence, or departure from the IRB approved study procedures in a research protocol. Protocol deviations are designated as serious or non-serious and further characterized as

1. Those that occur because a member of the research team deviates from the protocol.
2. Those that are identified before they occur, but cannot be prevented.
3. Those that are discovered after they occur

Serious Protocol Deviation: A deviation that meets the definition of a Serious Adverse Event or compromises the safety, welfare or rights of subjects or others.

Non –compliance: The failure to comply with applicable NIH HRPP policies, IRB requirements, or regulatory requirements for the protection of human subjects. Non-compliance is further characterized as

1. Serious: Non-compliance that
    a. Increases risks, or causes harm, to participants
    b. Decreases potential benefits to participants
    c. Compromises the integrity of the NIH-HRPP
    d. Invalidates the study data
2. Continuing: Non-compliance that is recurring
3. Minor: Non-compliance that, is neither serious nor continuing.

11.3 Investigator Assessment of Adverse Events

If a diagnosis is clinically evident (or subsequently determined), the diagnosis rather than the individual signs and symptoms or lab abnormalities will be recorded as the AE. All AEs occurring after enrollment through the final study visit will be documented and recorded, and those not related to disease progression will be reported as described below in Section 11.4 and Section 11.5.

A laboratory abnormality should be reported as an AE if it requires an intervention. Interventions include, but are not limited to, discontinuation of treatment, dose reduction/delay, additional assessments, or concomitant treatment. In addition, any medically important laboratory abnormality may be reported as an AE at the discretion of the investigator. This could include a laboratory result for which there is no intervention but the abnormal value suggests disease or organ toxicity.

The investigator will evaluate all AEs with respect to the seriousness (criteria listed above), severity (intensity or grade), and causality (relationship to the study agent and relationship to research) according to the following guidelines.

11.3.1 Severity

The investigator will grade the severity of each AE according to the "Common Terminology Criteria for Adverse Events (CTCAE)" (v 4.0):
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Severity grading for clinical events not found in the toxicity table will be graded according to the following grading scale:

1. *Grade 1 (Mild):* Events causing no or minimal interference with usual social and functional activities.
2. *Grade 2 (Moderate*): Events causing greater than minimal interference with usual social and functional activities.
3. *Grade 3 (Severe):* Events causing inability to perform usual social and functional activities.
4. *Grade 4 (Potentially Life-Threatening)*: Events causing inability to perform basic self-care functions OR medical or operative intervention is indicated to prevent permanent impairment, persistent disability, or death. *Note: A severity assessment of "potentially life-threatening" event is not necessarily the same as a life-threatening event, when used as an "SAE" criterion. The latter means that the event is an immediate threat to life as opposed to a potential threat to life.*
5. *Grade 5 (Death)*.

11.3.2 Causality

Causality (likelihood that the event is/is not related to the study agent) will be assessed considering the factors listed under the following categories:

Definitely Related

- Reasonable temporal relationship.
- Follows a known response pattern.
- Clear evidence to suggest a causal relationship.
- There is no alternative etiology.

Probably Related

- Reasonable temporal relationship.
- Follows a suspected response pattern (based on similar agents).
- No evidence of a more likely alternative etiology.

Possibly Related

- Reasonable temporal relationship.
- Little evidence for a more likely alternative etiology.

Unlikely Related

- Does not have a reasonable temporal relationship.

OR

- Good evidence for a more likely alternative etiology.

Not Related

- Does not have a temporal relationship.

OR

- Definitely due to an alternative etiology.

Note: Other factors (e.g., dechallenge, rechallenge) should also be considered for each causality category, when appropriate. Causality assessment is based on available information at the time of the assessment of the AE. The investigator may revise the causality assessment as additional information becomes available.

11.4 Investigator Reporting Responsibilities to the Sponsor

11.4.1 Adverse Events

Line listings, frequency tables, and other summary AE data will be submitted to the IND sponsor when needed for periodic safety reviews, review of IND annual reports, review of IND safety reports, and preparation of final study reports.

11.4.2 Serious Adverse Events

All SAEs (regardless of relationship and whether or not they are also UPs) must be reported on the Safety Expedited Report Form (SERF) and sent to the Sponsor Clinical Safety Office (CSO) by fax or e-mail attachment. Deaths and immediately life threatening SAEs must be reported to the CSO within 1 business day after the site becomes aware of the event. All other SAEs must be reported within 3 business days of site awareness.

SPONSOR CLINICAL SAFETY OFFICE CONTACT INFORMATION:
OCRPRO Clinical Safety Office
5705 Industry Lane
Frederick, MD 21704
Phone: 301-846-5301

Fax: 301-846-6224
E-mail: rchspsafety@mail.nih.gov

11.4.3 Unanticipated Problems

Unanticipated Problems that are also adverse events must be reported to the CSO and sent by fax or e-mail attachment no later than 7 calendar days of site awareness of the event. UPs that are not AEs are not reported to the Sponsor CSO.
Report all UPs that are also adverse events to the CSO on the NIH Problem Report Form.

11.4.4 Protocol-Specified Events

There are no protocol-specified events.

11.4.5 Pregnancy

Pregnancy itself is not an AE. However, complications from pregnancy are AEs and may be SAEs. Pertinent obstetrical information for all pregnancies will be reported to the CSO via fax or e-mail within 3 business days from the site's awareness of the pregnancy.

Pregnancy outcome data (e.g., delivery outcome, spontaneous, or elective termination of the pregnancy) will be reported to the CSO within 5 business days of the site's awareness of the outcome on a protocol-specified form. In the event of pregnancy, the subject will be followed to term for safety monitoring. In the event of pregnancy:

- Treatment for the subject will be un-blinded;
- If subject is being treated with plerixafor, the study drug will be discontinued;
- If subject is being treated with G-CSF, the study comparator drug may be withheld for the 1st trimester;
- Subject will be advised to notify their obstetrician;
- Pregnancy will be reported to the Data Safety Monitoring Board (DSMB).

11.5 Investigator Reporting Responsibilities to the NIAID IRB

11.5.1 Expedited Reporting

Serious and non-serious Unanticipated Problems, deaths, serious deviations, and serious or continuing non-compliance will be reported within 7 calendar days of investigator awareness. Serious Adverse Events that are possibly, probably, or definitely related to the research will be reported to the NIAID IRB within 7 calendar days of investigator's awareness, regardless of expectedness.

11.5.2 Waiver of Reporting Anticipated Protocol Deviations, Expected UPnonAEs and Deaths

Anticipated deviations in the conduct of the protocol will not be reported to the IRB unless they occur at a rate greater than anticipated by the study team. Expected adverse events will not be reported to the IRB unless they occur at a rate greater than that known to occur in WHIMS. If the rate of these events exceeds the rate expected by the study team, the events will be classified and reported as though they are unanticipated problems. Deaths related to the natural history of WHIMS will be reported at the time of continuing review.

11.5.3 Annual Reports

The following items will be reported to the NIAID IRB in summary at the time of continuing review:

- Serious and non-serious unanticipated problems
- Expected SAEs that are possibly, probably, or definitely related to the research;
- SAEs that are not related to the research;
- All adverse events, except expected AEs and deaths granted a waiver of reporting.
- Serious and Non-Serious Protocol deviations

- Serious, continuing, and minor non-compliance
- Any trends or events that in the opinion of the investigator should be reported.

11.6 Follow-up of Adverse Events and Serious Adverse Events

AEs that occur following enrollment of the subject (by signing the informed consent) are followed until the final outcome is known or until the end of the study. AEs that have not resolved by the end of the study will be recorded as "ongoing", and will be followed until the final outcome is known. If it is not possible to obtain a final outcome for an SAE, the investigator will record the reason a final outcome could not be obtained. SAEs that occur after the end of the study that are reported to and are assessed by the investigator to be possibly, probably, or definitely related must be reported to the CSO, as described above.

11.7 Investigator Initiated Trial (IIT) Sponsor Obligations and Reporting Responsibilities

Serious and unexpected suspected adverse reactions as defined in FDA 21 Code of Federal Regulations (CFR) 312.32 and determined by the IND sponsor will be reported to the FDA as IND safety reports. The IND sponsor will also submit an IND Annual Report of the progress of the investigation to the FDA, as defined in 21 CFR 312.33. AEs that are also UPs will be summarized by the IND sponsor and distributed to investigators.

For this Investigator Initiated Trial (IIT):

- The IIT sponsor (OCRPRO) warrants that the study will be performed in compliance with all applicable local and international laws and regulations, including without limitation ICH E6 guidelines for Good Clinical Practices.
- The IIT sponsor shall be responsible for the respect of all obligations required by applicable local and international laws and regulations.
- The sponsor shall be responsible for ensuring submission of required expedited and periodic reports to the FDA and the NIAID IRB. The IIT sponsor is responsible for providing any "Dear Investigator Letter" (DIL) for new safety finding received from Sanofi group entity to the investigators and Ethics Committee.
- The sponsor must report the following information in English to the Sanofi group entity Pharmacovigilance contact:

  1. Routine transmission of: All Serious Adverse Events (SAEs). These events must be transmitted within 1 working day of the sponsor's awareness or identification of the event.

     Results of any relevant complementary exams performed to obtain the final diagnosis of any SAE (e.g., hospital discharge summary, autopsy, consultation) will be made available to Sanofi group entity upon request.
  2. Other events or periodic reports (e.g. Development Safety Update Report (DSUR)), submitted to the FDA must be transmitted at the time of submission.
  3. Other significant safety issues or findings in a study pertaining to safety of product must be transmitted within 3 working days.
  4. The study report of any IIT must contain a section describing safety review and conclusion.
  5. The reference safety information to be used by the IIT sponsor for evaluation of expectedness of adverse events shall be the current approved product label available in the country.

SANOFI GROUP ENTITY PHARMACOVIGILANCE CONTACT

<u>Fax/email of SAE Reports to Sanofi</u>:

IST/ISS Investigators will notify Sanofi via fax or email, attention Sanofi Pharmacovigilance (PV):

Fax: 908-203-7783 (US)
E-mail:USPVmailbox@sanofi.com

11.8 Halting Criteria for the Protocol

Halting the study requires immediate discontinuation of the study agent administered to subjects and suspension of enrollment in this study until a decision is made whether or not to continue the study agent administration.

The halting criteria include:

1. Two or more subjects experience the same or similar SAEs that are unexpected and are possibly, probably, or definitely related to the study agent, or
2. Any safety issue that the site investigators determine should halt the study.

The IRB, IND sponsor, or the FDA may halt the study at any time following review of any safety concerns. The DSMB may recommend a study halt.

11.8.1 Reporting of Study Halting

If a halting requirement is met, a description of the event(s) or safety issue must be reported by the PI within 1 business day to the sponsor CSO by fax or e-mail. The PI must inform the IRB that a halting requirement has been met.

11.8.2 Resumption of a Halted Study

The IND sponsor, in collaboration with the PI and the DSMB, will determine if it is safe to resume the study. The IND sponsor will notify the PI of this decision. The conditions for resumption of the study will be defined in this notification. The PI will notify the IRB of the decision to resume the study.

11.9 Pausing Criteria for a Subject

The decision to suspend administration of a study agent for a single subject requires discontinuation of study agents administrated to the study subject until a decision is made whether or not to continue the administration of the study agent.

The pausing criteria for a single subject in this study include:

1. A subject experiences an SAE or a grade 3 or greater AE that is unexpected (as determined by the IND Sponsor) and is possibly, probably, or definitely related to the study agent; or
2. Development of any exclusion criteria may be cause for discontinuation; or
3. Any safety issue that the investigator determines should pause administration of the study agent to a single subject. The IND sponsor, in collaboration with the PI, may also pause for an individual subject if a safety concern is identified during routine aggregate data analysis.

11.9.1 Reporting of Pausing for a Subject

If a pausing requirement is met, a description of the AEs or safety issue must be reported by the site investigator via fax or email within 1 business day to the sponsor CSO, PI, the IRB and the DSMB.

11.9.2 Resumption of a Paused Study

The IND sponsor in collaboration with the PI and DSMB will determine if it is safe to resume administration of the study agents to the subject/group. The IND sponsor will notify the site investigators of this decision. The site investigators will notify their local IRB(s) of the decision to resume administration of the study agents prior to resumption.

11.10 Withdrawal Criteria for an Individual Subject

An individual subject will be withdrawn from the study for any of the following:

1. A subject's decision (investigator should attempt to determine the reason for the subject's decision).
2. Any clinical AE, laboratory abnormality, or other medical condition or situation such that continued participation in the study would not be in the best interest of the subject. Subjects will be followed for the duration of the study for indicated safety assessments.
3. Non-compliance with study procedures to the extent that it is potentially harmful to the subject or to the integrity of the study data.
4. A change in the subject's baseline condition after enrollment so that the subject no longer meets the inclusion/exclusion criteria.

11.11 Additional Enrollment for Withdrawn Subjects

Subjects who are not evaluable as described in the Statistics (Section 14) may be replaced with other eligible subjects.

12 SAFETY OVERSIGHT AND MONITORING PLAN

12.1 Safety Review and Communication Plan

A Safety Review and Communication Plan (SRCP) has been developed for the protocol. The SRCP is an internal communications document between the PI and the IND sponsor CSO, which delineates the safety oversight responsibilities of the PI, the CSO, and other stakeholders. The SRCP also includes the overall plan for conducting periodic safety surveillance assessments.

12.2 Sponsor Medical Monitor

A sponsor medical monitor representing the IND sponsor (OCRPRO), has been appointed for the safety oversight in this clinical study. The sponsor medical monitor will be responsible for performing safety assessments as outlined in a Safety Review and Communications Plan.

12.3 Data and Safety Monitoring Board

The NIAID intramural DSMB will review the IRB-approved protocol, informed consent documents, data and safety monitoring plan and any stopping guidelines of the study prior to initiation and twice a year. The board may convene additional reviews as necessary. The board will review the study data to evaluate the safety, efficacy, study conduct and progress, and scientific validity and integrity of the trial. All SAEs, UPs, and IND safety reports will be reported by the PI to the DSMB at the same time they are submitted to the IRB or IND sponsor. As part of this responsibility, the DSMB members must be satisfied that the timeliness, completeness, and accuracy of the data submitted to them for review are sufficient for evaluation of the safety and welfare of the study subjects. The DSMB may also convene as needed, if stopping criteria are met, or other safety issues arise that the PI and/or NIAID clinical director or designee would like the DSMB to address. The PI will notify the DSMB of any cases of intentional or unintentional unblinding as soon as possible. The PI will notify the board at the time pausing or halting criteria are met and obtain a recommendation concerning continuation, modification, or termination of the study. The PI will submit the written DSMB recommendations and summary reports to the NIAID IRB.

12.4 Procedures for Emergency Unblinding

In the event of a pregnancy occurring during treatment or Grade 4 or 5 toxicity in a participant their drug treatment will be unblinded and the subject and their local physician will be told of their status. Whenever possible the PI and investigators will not be made aware of their treatment status. If this is unavoidable, the IRB, DSMB, and CSO will be notified.

13 CLINICAL MONITORING STRUCTURE

13.1 Site Monitoring Plan

As per International Conference on Harmonization (ICH) Good Clinical Practice (GCP) 5.18, clinical protocols are required to be adequately monitored by the study sponsor. This study monitoring will be conducted according to the NIAID Intramural Clinical Monitoring Guidelines. Monitors under contract to the NIAID/OCRPRO will visit the clinical research site to monitor all aspects of the study in accordance with appropriate regulations and the approved protocol. The objectives of a monitoring visit will be: 1) to verify the existence of signed informed consent documents for each monitored subject; 2) to verify the prompt and accurate recording of all monitored data points and prompt reporting of all SAEs; 3) to compare abstracted information with individual subjects' records and source documents (subjects' charts, laboratory analyses and test results, physicians' progress notes, nurses' notes, and any other relevant original subject information); and 4) to ensure the investigators compliance with the protocol, and completeness and accuracy of the study records. The monitors also will inspect the clinical site regulatory files to ensure that regulatory requirements (Office for Human Research Protections [OHRP]) and applicable guidelines (ICH-GCP) are being followed. During the monitoring visits, the investigator (and/or designee) and other study personnel will be available to discuss the study progress and monitoring visit.

The investigator (and/or designee) will make study documents (e.g., consent forms, and pertinent hospital or clinical records) readily available for inspection by the local IRB, site monitors, and NIAID staff for confirmation of the study data. A specific protocol-monitoring plan will be discussed with the PI and study staff prior to enrollment. The plan will outline the frequency of monitoring visits based on factors such as study enrollment, data collection status, and regulatory obligations.

A monitoring visit will occur after the first five participants have been treated for 6 months in order to ensure completeness of reports sent by outside labs and to verify the presence of Memory Aid forms.

14 STATISTICAL CONSIDERATIONS

14.1 Study Hypotheses

The primary hypothesis is that the Total Infection Severity Score (TISS) will be significantly reduced while on plerixafor compared to GCSF. The TISS score is the sum of the Infection Severity Scores (Appendix D) for all infections during each period (1 year of treatment). Secondary endpoints include infection related parameters, wart response, immunological parameters, and measures of chronic infections, side effects, quality of life, and treatment preference.

14.2 Sample Size Justification

The primary endpoint is the change in the total infection severity score during period 1 minus the total infection severity score during period 2. Retrospective data on 11 subjects treated with G-CSF for one year provided a mean TISS score of 21 with a standard deviation of 10. We conservatively assume that there will be a reduction of 50% between the TISS score during the plerixafor period and the TISS score during the G-CSF period. Table 1 provides some power calculations based on a two group t-test using an alpha = 0.05 two-sided test and setting power at 90%. The groups are defined by their randomization sequence Gp (meaning G-CSF first then plerixafor) or pG (for plerixafor treatment first, followed by G-GSF).

Table 1: **Sample size required to achieve 90% power under different assumptions for the mean response on G-CSF and plerixafor. Power formula based on a two-sided two sample t-test with alpha=0.05 using the period 1 minus period 2 change in TISS scores as the primary outcome. A standard deviation of 10 for the difference is assumed.**

Mean TISS while on G-CSF	Mean TISS while on plerixafor	Percent Reduction in TISS	Mean Change for Gp group	Mean Change for pG group	Mean Difference in changes between groups	Total Sample Size
21	10	52.4%	11	-11	22	12
21	11	47.6%	10	-10	20	14
21	12	42.9%	9	-9	18	16
21	13	38.1%	8	-8	16	20
21	14	33.3%	7	-7	14	24

From Table 1, we see that with 16-20 subjects we can detect 38%-43% reductions in TISS while on plerixafor. Such reductions would be clinically meaningful and we will thus aim to enroll 20 subjects. While the Wilcoxon two sample rank sum test will be used in the analysis to provide some robustness against aberrant TISS scores, the power based on a t-test is a good approximation to the power for a Wilcoxon test. We use the two sample Wilcoxon test instead of the one sample paired difference Wilcoxon test to provide robustness to the possibility of secular trends in the TISS score over the two periods.

14.3 Study Population

Our study population will be genetically proven WHIM patients (known compatible heterozygous CXCR4 mutation) age 10-75 who have a history of recurrent infections and are neutropenic (ANC<1500 at baseline). These individuals would be likely to benefit from either the study drug or the comparator agent. Subjects will be recruited for participation among those being followed at NIH (24 as of May 2014), followed elsewhere in the US or other countries, newly diagnosed by dermatologists, immunologists, gynecologists, urologists, or primary care physicians or self-referred.
As with US subjects, subjects recruited from other countries will receive their routine care and obtain blood counts from their local providers and visit the NIH-CC per study schedule.

14.4 Description of Analysis

14.4.1 Efficacy Analysis – Infection Severity Score (ISS)

Data from a subject's study Memory Aid such as visits to a subject's local medical provider, anti-infective prescriptions, fevers (oral temperature >38.3^{o}C), hospitalization, and diagnoses of infection from the subject's medical provider, are collected, reviewed and scored at the study center by the PI according to specific pre-defined weighting rules (Appendix D) designated the ISS.

14.4.1.1 Infection-related Events

An Infection-related Event is defined by any of the following:

1) Diagnosis of Infection by a Clinician: Subjects are encouraged to visit their local medical provider if they experience symptoms of a new or worsening infection such as fevers, chills, aches, pain, worsened cough, swelling, redness, etc. Subjects record visits to their local medical provider in their Memory Aid and provide documentation of the diagnosis and treatment to the NIH-CC. If a provider clinically diagnoses an infection (i.e. otitis, sinusitis, dental infection, bronchitis, pneumonia, abscess), this is recorded and counted as an Infection-related Event.
2) Presumed Diagnosis of Infection by a Clinician: The precise cause of an infection cannot always be determined. A differential diagnosis of possible infections and/or biomarker indications of an infection will be counted as an infection.
3) Resolution of Infection Symptoms after Treatment with Antibiotics: Subjects with chronic or recurrent infections may have a standing prescription for antibiotics without need to visit their local medical providers prior to initiating treatment. Because subjects record their symptoms of

infection and any antibiotic taken for treatment in their Memory Aid (Appendix F), resolution of likely symptoms of infection (for example fever, pain, or worsened cough) coincident with commencing an antibiotic regimen will be counted as an Infection-related Event even if not diagnosed clinically.

14.4.1.2 Severity of Fever for an Infection-related Event

The highest temperature recorded during an episode of infection is scored as described in Appendix D. Fevers that are of indeterminate origin (i.e. not clearly associated with an Infection) are counted as a fever, but are not included in the ISS.

14.4.1.3 Level of Antibiotic Treatment for an Infection-related Event

The highest level of prescribed antibiotic treatment (topical, oral, or parenteral) for an Infection is scored and described in the Infection Severity Score in Appendix D.

14.4.1.4 Extent of Hospitalization for an Infection-related Event

The highest level of care is scored as described in the Infection Severity Score in Appendix D.

14.4.2 Method of Analysis

For the primary analysis of our data we will use a two-sample Wilcoxon test under a ranking scheme where we form a score for each person

S = (TISS during period 1 – TISS during period 2),

where TISS is the Total Infection Severity Score, which is the sum of all ISSs during a period. For example, if a subject had 3 infections on plerixafor with ISSs of 4, 1, 3 and 2 infections on GCSF with ISSs of 5,1, the score would be (4+1+3) – (5+1) = 8-6=2.

It is possible that not all subjects will have complete follow-up for both periods. We next describe how to handle such subjects. Drug failures are subjects who must discontinue their assigned drug because 1) drug is intolerable and the subject refuses to take the study drug, 2) the ANC is reliably less than 500 cells/µL or 3) an adverse event precludes further study drug administration. Drug failures in treatment period 1 cross over to the opposite arm; drug failures in treatment period 2 receive best available therapy. A drug failure should get the worst rank. Let S* be the largest of the absolute value of the scores for all subjects with complete data. To operationalize giving the worst rank, we will give drug failures during the first period a score of S*+1. If a drug failure occurs during the second period, they receive a score of -(S*+1). Subjects who are drug failures in each period receive a score of 0.

Apart from drug failures, some subjects may drop out of the study for reasons different than the above three. For subjects who drop out in period 2 after at least 3 months of follow-up an adjusted score will be formed.

S = TISS in period 1 - (TISS in period 2)/f

where f is the fraction of intended follow-up attained in period 2 (note that f>=3/12). Based on these scores, we will calculate a permutation p-value using the two-sample Wilcoxon rank test. Subjects who drop out in period 1 or before 3 months of period 2 will be excluded from the primary analysis.

If missing data and drug failures are substantial, different sensitivity analyses will be conducted. These could include discarding all such subjects or developing a model to help allow imputation of missing data, or performing a model based analysis.

All tests will be two-sided with a type I error rate of 0.05.

14.4.3 Interim Analysis

After 10 subjects have data for the primary analysis, an interim analysis will be performed. If the two-sample Wilcoxon test of TISS scores achieves a one-sided permutation p-value of 0.05 or less indicating better TISS scores on G-CSF versus plerixafor, serious consideration should be given to stopping the study for futility.

A subject has data for the primary analysis if

1) They have completed 1 year of plerixafor treatment and 1 year of G-CSF treatment
2) Are a drug failure on either plerixafor or G-CSF (or both)
3) They drop out in period 2 after 3 months of follow-up.

No interim analysis for efficacy is planned; it is difficult for a rank-based procedure to achieve a small p-value after 10 subjects, and we anticipate the study will be entirely or nearly entirely enrolled by the time 10 subjects have complete data for the primary endpoint.

14.4.4 Futility Monitoring

The study will be monitored for operational futility. If fewer than 10 subjects have been enrolled after 2 years (counting time from the first enrollment), or if it is clear earlier that fewer than 10 subjects will be enrolled after 2 years, the study will be closed to further recruitment, and subjects already enrolled may choose to continue on the study or revert to best available medical therapy. If after 3 years the recruitment has plateaued at some level less than 20, the DSMB should consider closing the study to further recruitment while continuing the study of the enrolled subjects until all have data for the primary analysis.

14.4.5 Safety Analysis

The following tables of AEs will be completed after unblinding the study:

- A listing of all SAEs including the treatment arm to which the subject was assigned.
- Frequency tables of AEs by treatment arm, severity, and reported relationship to treatment.

14.4.6 Secondary Analysis

14.4.6.1 Secondary endpoints

Secondary endpoints (incidence of fevers and number of febrile days, incidence of hospitalization and number of hospital days, incidence of antibiotic treatment and number of antibiotic days, number of infections and number of days with infections, number of new visible warts, and the change in severity for existing warts) will follow the same type of analysis as described above with the TISS being replaced by number of fevers, number of febrile days, etc. All tests will be two-sided with a type I error rate of 0.05.

14.4.6.2 Incidence and Duration of Infection-related Event

An infection-related Event will be counted as an incidence of infection. The duration of infection is the number of days the symptoms of infection are present.

14.4.6.3 Incidence and Duration of Fever

Febrile days are defined as days in which the subject's oral temperature $\geq 38.3°C$, at any point during the day (or 24 hour period). Contiguous days of fever will be counted as an incidence of fever. For subsequent fevers to be considered a new/additional incidence of fever, an interval of at least 48 hours without fever related symptoms such as elevated temperature, chills, aches, and fatigue must separate each event of a fever.

14.4.6.4 Incidence and Duration of Antibiotic Treatment

A prescribed treatment with a new antibiotic (oral, IV, or topical) is counted as an incidence of antibiotic treatment. The duration of antibiotic treatment is the number of days a subject is under treatment with an antibiotic other than a prophylactic antibiotic; missing an occasional dose does not invalidate the count for that day. For example if a subject is asked to take a 10 day course of antibiotics for otitis this will count as one episode of otitis and 10 days of antibiotic therapy regardless of whether the subject actually takes all 10 days or misses a day. Additional antibiotic treatments during or after the initial treatment are counted as additional incidences of antibiotic treatment.

14.4.6.5 Incidence and Duration of Hospitalization

An incidence of hospitalization is an admission to a hospital for treatment of an infection or presumed infection. Hospital days are defined as any day that a subject is in a hospital for treatment due to a diagnosis (or presumed diagnosis) of infection. The duration of an infection related event is the number of days the symptoms of infection persists.

14.4.6.6 Severity of Chronic Infections

Subjects with chronic and/or frequently recurring infections record the severity of their symptoms in their Memory Aid. At the Initial Evaluation period prior to randomization and treatment, a baseline of their symptoms is documented and incorporated into their Memory Aid. During treatment, any significant change in baseline such as worsening infection that affects their function or require symptomatic treatment (e.g., over the counter medication) are recorded, as well as any significantly improved symptoms that improves their function or reduces their need for symptomatic treatment (e.g., over the counter medication) are computed as used as a measure of their severity of infection.

14.4.6.7 Use of Prophylactic Antibiotics

At the Initial Evaluation period prior to randomization and treatment, a subject's use of prophylactic antibiotics is documented and incorporated into their Memory Aid. Subjects record their compliance with these prophylactics in their Memory Aid. Changes in prescription or to a subject's use of the prophylactic are recorded. Although this information is not a direct measure of a subject's severity of infection, it is collected to provide background information that may explain confounding or extrinsic factors that may affect a subject's rate and severity of infection. Subjects who are prescribed prophylactic antibiotics will be encouraged to continue them throughout the study so as to minimize any confounding.

14.4.6.8 Control of Warts

Existing warts will be documented at baseline visits prior to treatment with either the study drug or the comparator agent via clinical photographs, if the subject consents. Every 4 months during the treatment period clinical photography will be repeated in areas with new or existing warts. Our main endpoint will be the number of new visible warts occurring during each 52-week treatment period. We will also analyze the size changes of existing untreated warts and the regrowth of treated/removed warts as secondary endpoints. A two-sample Wilcoxon paired difference test will be used for analysis.

14.4.6.9 Change of Leukocyte Blood Counts

Leukocyte numbers available from the CBC (ANC, etc.) will be averaged throughout each 1-year treatment period with either the Study Drug or Comparator Drug and statistical comparison will be performed as part of the secondary endpoints. Lymphocyte flow cytometry results (CD19+, CD4+, CD8+, etc.) will be averaged from the 4, 8, and 12 month visits to the NIH-CC for each agent. In addition both of these averages will be compared to the subject baseline defined as the average of any measurements of G-CSF and plerixafor within 6 months of starting the study at NIH-CC. A two-sample Wilcoxon paired difference test will be used for analysis. Changes in leukocyte numbers will also be analyzed by length of time on the Study Drug or Comparator Drug.

14.4.6.10 Quality of Life and Subject Preference Assessment

The subjects will complete a validated Quality of Life (QOL) questionnaire (SF-36 version 2) during the 4, 8, and 12 month visits in the Treatment period at the NIH-CC, and the responses will be averaged and compared. Changes in QOL scores will also be analyzed by length of time on the Study Drug or Comparator Drug. At completion of the second treatment period, subjects will be asked whether they prefer the first drug they received or the second. A two-sample Wilcoxon paired difference test will be used for analysis.

14.4.7 Randomization

Randomization will be blocked so that after every 4 subjects, 2 will have been assigned initial treatment with G-CSF and 2 will have been assigned initial treatment with plerixafor.

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1 Informed Consent Process

Informed consent is a process where information is presented to enable persons to decide voluntarily whether or not to participate as a research subject. It is an ongoing conversation between the human research subject and the researchers, which begins before consent is given and continues until the end of the subject's involvement in the research. Discussions about the research will provide essential information about the study and will include the purpose, duration, experimental procedures, alternatives, and risks and benefits. Subjects will be given the opportunity to ask questions and have them answered.

Subjects will sign the informed consent documents prior to undergoing any research procedures. Subjects may withdraw consent at any time throughout the course of the study. A copy of the informed consent documents will be given to the subjects for their records. The researcher will document the signing of the consent forms in the subject's medical record. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in the study.

The acquisition of main study informed consent will be documented in the participant's medical records, as required by 21 CFR 312.62. The informed consent form will be signed and personally dated by the participant and the person who conducted the consenting process. The original signed informed consent form will be retained in the subjects' medical chart and a copy of it will be provided to them.

Consent from Non-English Speaking Participants

If a non-English speaking participant is unexpectedly eligible for enrollment, the participant will be provided with the CC Short Written Consent Form for Non-English Speaking Research Participants in the participant's native language and a verbal explanation of the purpose, procedures and risks of the study as described MAS Policy M77-2, NIH HRPP SOP 12 and 45 CFR 46.117(b)(2). The IRB-approved English consent form will serve as basis for the verbal explanation of the study. The investigator will obtain an interpreter unless the investigator is fluent in the prospective participant's language. Preferably, the interpreter will be someone who is independent of the participant (i.e., not a family member). Interpreters provided by the CC will be used whenever possible. The interpreters will translate the IRB-approved English consent form verbatim and facilitate discussion between the participant and investigator.

The IRB-approved English consent form will be signed by the investigator obtaining consent and a witness to the oral presentation. The CC Short Written Consent Form will be signed by the participant and a witness who observed the presentation of information. The interpreter may sign the consent document as the witness and, in this case, will note "Interpreter" under the signature line. A copy of both signed forms will be provided to the participant to take home.

The investigator obtaining consent will document the consent process in the participant's medical record, including the name of the interpreter. Further, all instances of use of the CC Short Written Consent Form will be reported to the IRB at the time of annual review. If the CC Short Written Consent Form is used three times or more for the same language, this will be reported to the IRB immediately.

15.2 Subject Confidentiality

The investigator will ensure that the subjects' anonymity is maintained. Subjects will not be identified in any publicly released reports of this study. All records will be kept confidential to the extent provided by federal, state, and local law. The study monitors and other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator, including, but not limited to, medical records. The investigator will inform the subjects that the above-named representatives will review their study-related records without violating their confidentiality. To maintain subject confidentiality, all laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified only by a coded number to maintain subjects' confidentiality. All records will be kept locked and all computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, FDA, NIAID, OHRP, or the sponsor's designee.

16 DATA HANDLING AND RECORD KEEPING

16.1 Data Management Responsibilities

The investigator is responsible for assuring that the data collected is complete, accurate, and recorded in a timely manner. Source documentation (the point of initial recording of information) should support the data collected in the electronic data system**,** and must be signed and dated by the person recording and/or reviewing the data. All the data should be reviewed by the investigator and signed in ink or electronically.

16.2 Data Capture Methods

Study data will be collected at the study site and maintained in an electronic data system. These forms or systems are to be completed on an ongoing basis during the study. Only authorized individuals shall perform data entry into the electronic data system. Corrections to the electronic data system shall be tracked electronically (password protected or through an audit trail) with the time, date, name of the individual making the correction, and details of the change being made.

16.3 Types of Data

Source documents include, but are not limited to, the subject's medical records, laboratory reports, EKG tracings, x-rays, radiologist's reports, subject's diaries, biopsy reports, ultrasound photographs, progress notes, pharmacy records, and any other similar reports or records of procedures performed during the subject's participation in the study

16.4 Source Documents and Access to Source Data/Documents

Study data will be collected and maintained in NIH-CC electronic records, and the subject's study binder. The PI is responsible for assuring that the data collected are complete, accurate, and recorded in a timely manner. Source documentation (the point of initial recording of a piece of data) should support the data collected, and must be signed and dated by the person recording and/or reviewing the data. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical trial. Source documents include, but are not limited to, the subject's medical records, laboratory reports, progress notes, pharmacy records and any other similar reports or records of procedures performed during the subject's participation in the study. Data from the data system will be collected directly from the subjects during study visits or will be abstracted from the subjects' medical records. Each subject's medical record must record his/her

participation in the clinical trial and study agent (with doses) and any other medical interventions or treatments administered, as well as any adverse reactions experienced during the trial.

To maintain the subjects' confidentiality, access to the data will be limited. Authorized representatives from NIAID and regulatory agencies will be permitted to examine clinical records for the purposes of quality assurance review, audits, and evaluation of the study safety and progress.

16.5 Study Records Retention

The investigator is responsible for retaining all essential documents listed in the ICH GCP guideline. Essential documentation for all the study subjects is to be maintained by the investigators in a secure storage facility for a minimum of 3 years according to NIAID policies. The FDA requires study records to be retained for up to 2 years after marketing approval or disapproval (21 CFR 312.62), or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational agent for a specific indication. These records are also to be maintained in compliance with IRB, state, and federal medical records retention requirements, whichever is longest. All stored records are to be kept confidential to the extent required by federal, state, and local law.

Should the investigator wish to assign the study records to another party and/or move them to another location, the investigator must provide written notification of such intent to OCRPRO/NIAID, with the name of the person who will accept responsibility for the transferred records and/or their new location. Prior to the destruction or relocation of research records, NIAID must be notified in writing and written permission from OCRPRO/NIAID is required.

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APPENDIX A: SCHEDULE OF PROCEDURES AND EVALUATION

Evaluations	Screening, Initial Evaluation Period and Baseline Assessments (Screening & Baseline)		1st Equilibration Period (Day Prior, Day 0, & Local Labs)			1st Year Treatment Period (52 weeks)			2nd Equilibration & 2nd Year Treatment[a]	Reversion to Pre-study Treatment	
	Screening V1 W –(2 to 20)	*Baseline* V2	*Prior to Injection* V3 D -1/0	*1st Dose* V3 D 0	*Local Labs*[a] L 1, 2, 3 W 2, 4, 6 (± 7d)	Evaluation V 4, 5, 6 M 0, 4, 8 (± 31d)	*Local Labs*[a] L 4, 5, 6 M 2, 6, 10 (± 31d)	*EOT* V7 M 12 (± 31d)	2nd Study Drug[b] V 8-12 L 7-12 M13 to 26 (± 31d)	*Local Labs*[a] L 13-15 W 2, 4 (± 7d) M 28 (± 31d)	Study Completion V13 M 30 (± 61d)
Informed consent	X										
Weight	X		X			X		X	X (x5)		X
Vital Signs: Temp, Pulse, Blood Pressure	X		X	X[c]		X		X	X (x6)		X
Pregnancy testing as applicable and contraception counseling as appropriate.	X		X			X		X	X (x5)		X
CBC with Differential	X	L	X		L	X	L	X	X (x5) L (x6)	L	X
ESR and Chemistry[d]	X	L	X	X	L	X	L	X	X (x6)	L	X
Vitamin B12, Folate	X							X	X		
PT/PTT, Urinalysis, Viral Panel[e]	X										
EKG	X							X	X		
Echocardiogram (within 5 years)	X										
History, Medications, Allergies, contraceptive counseling, and Physical Exam	X		X			X		X	X (x4)		X
Review/adjust subject's IVIg, prophylactic antibiotic and G-CSF dose		X									

Ultrasonogram of the spleen, DEXA Scan		X						X	X		
Quantitative Immunoglobulin and Leukocyte Phenotyping. Research blood as required.		X	X			X		X	X (x5)		X
Antibody levels (Includes Tetanus, Diphtheria)		X						X	X		
Photographs of cutaneous Warts (Photo of genital Warts is optional)		X				X		X	X (x4)		X
Standard Consults: Dermatology, Dental, GYN, ENT and Audiology		X						X	X		
Additional Procedures/Consults if clinically indicated: PFT, chest-CT, sinus-CT, etc.		X						X	X		
QOL (SF-36v2) Questionnaire		X				X		X	X (x4)		
Training/Review: Memory Aid, local labs, drug shipment, storage, and administration		X	X								
Randomization		X									
G-CSF or plerixafor stopped at least 2 days prior the 1st day of injection			X						X	X	
Optional: wart, skin, & bone marrow biopsies		O				O		O	O		O
Submission and review of subject Memory Aid		X	X (x4)			X (x26)			X (x30)	X (x10)	
AE monitoring		X	X (x4)			X (x26)			X (x30)	X (x10)	

V=visit; D=study Day; d= days; W=Study Week (from start of 1st injection); M= Study Month; O=Optional; L= may be performed at subject's Local facility; G-CSF=granulocyte colony stimulating factor; CBC=complete blood count; ESR; PT/PTT=prothrombin time/partial thromboplastin time; EKG=electrocardiogram; ENT=ear, nose, and throat; QOL=Quality of Life; AEs=adverse events.

[a] Local Labs: Subjects may obtain their laboratory tests locally and the results sent to the NIH. If practical, provisions will be made for labs to be drawn at a Quest facility, at no cost, and accessible to the subject. ESR test is optional for local lab draws.

[b] Column represents the summation and aggregate of the activities for the Equilibration and Treatment Period of the second (alternate) study drug.

[c] In addition to vital signs, orthostatic pulse and blood pressure should be measured prior to injection and 60 +/- 20m post injection.

[d] Chemistry: NIH -Acute Care Panel, Hepatic Panel, Mineral Panel, Serum Protein, Lactate Dehydrogenase, Serum Uric Acid, & Creatine Kinase, and ESR. For home monitoring (local labs), BUN and creatinine are required. Additional chemistries labs may be requested, and ESR if available may be requested.

[e] This includes HIV, hepatitis B/C. HTLV type 1 and II.

[f] Subjects will be instructed on how to record body temperature, fever, symptoms of infection, and anti-infective treatments/prophylaxis on a daily basis, and how to self-administer the study drugs.

APPENDIX B: FDA APPROVED PACKAGED INSERT: PLERIXAFOR

Plerixafor (Mozobil™) is an FDA approved product. The approved package insert is considered a comprehensive source of safety data. The current version of the package insert is available on the Mozobil™ website (http://products.sanofi.us/Mozobil/mozobil.html).

APPENDIX C: FDA APPROVED PACKAGE INSERT: G-CSF

G-CSF, Neupogen™ (filgrastim) is an FDA-approved drug. The approved package insert is considered a comprehensive source of safety data. The current version of the package insert is available on the Neupogen™ website (http://pi.amgen.com/united_states/neupogen/neupogen_pi_hcp_english.pdf).

APPENDIX D: INFECTION SEVERITY SCORE (ISS)

Type of Infection	***Fever***	***Anti-Infective***	***Hospitalization***	***Total***
	0: No chills/fever	0: No Treatment	0: No Hospitalization	
1: Non-sterile site	1: 38.3 -39º C	1: Topical	1: Emergency Room	
2: Sterile site	2: > 39º C	2: Oral	2: Hospitalized	
		3: Parenteral	3: ICU	
1 to 2	*0 to 2*	*0 to 3*	*0 to 3*	***1 to 10***

These parameters will be used to develop a score for each infection. Non-sterile site infections are those which occur in areas of the body routinely exposed to and colonized by microorganisms such as the oral cavity, bronchioles and upper respiratory tract, nasopharynx, vagina, GI tract, and skin; while, sterile sites would include the lower respiratory tract, blood, muscle, bone, joints, urinary bladder, and other typically sterile locations. Fever will refer to the maximum oral temperature recorded during the infection. Anti-infective treatment is scored based on the highest level of treatment i.e. intravenous antibiotic that is changed to oral would score a 3. Similarly hospitalization will refer to the highest level of care received at any point during the infection. Scores for each parameter will be added and thus the score for any given incidence of infection can range from 1-10.

APPENDIX E: DOSING OF PLEXIFOR IN RENAL IMPAIRMENT

In subjects with moderate and severe renal impairment (estimated creatinine clearance [CrCl] ≤50 mL/min), each dose of plerixafor (Mozobil™) will be reduced by one-third. Because of the renal excretion of the drug, this reduction in subjects with moderate and severe renal impairment is expected to result in similar drug levels compared with subjects with normal renal function.

The following (Cockroft-Gault) formula may be used to estimate Creatinine Clearance (CrCl):

Males:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{weight (kg) X (140 – age in years)}}{\text{72 X serum creatinine (mg/dL)}}$$

Females:

Creatinine clearance (mL/min) = 0.85 X value calculated for males

Since there is insufficient information to make dosage recommendations in subjects on hemodialysis, subjects on dialysis or who have a CrCl <15 ml/min are excluded from this study.

APPENDIX F: SAMPLE SUBJECT MEMORY AID

Study Contact Information: *Email and Phone #*

Date

MM/DD/YY

Complete each question by circling ONE Answer from each row.

Infection Related Treatments

Drug 1	**Route**	**Frequency**	Yes	No
Drug 2	**Route**	**Frequency**	Yes	No
Additional Antibiotics:	*Route:*	*Frequency:*	No	Yes

Study Drug and Side Effects

Morning Injection	**Batch ID**	*Site of Injection*	No		
Evening Injection	**Batch ID**	*Site of Injection*	No		
Morning Injection Site Reaction		None	Tenderness	Pain	Ulceration
Evening Injection Site Reaction		None	Tenderness	Pain	Ulceration
Bone/Skeletal Pain (arms, legs, back)		None	Mild	Affects Function	Affects Self-care
Pain (abdomen, shoulder etc.)		None	Mild	Affects Function	Affects Self-care
Headache		None	Mild	Affects Function	Affects Self-care
Dizziness		None	Unsteadiness	Affects Function	Affects Self-care
Nausea		None	Loss of Appetite	Reduced Oral Intake	Tube Feeding
Vomiting		None	1 to 2	3 to 5	6 or more
Diarrhea		None	Increase 1-4 stools	Increase 4-6 stools	7 or more
Additional Side Effect:		No	Mild	Affects Function	Affects Self-care
Additional Side Effect:		No	Mild	Affects Function	Affects Self-care

Fevers and Infections (please inform study staff)

Record your highest temp for the day	*Enter Temp*			
Missed School/Work due to side effect of study drug	No	Partial Day	Full Day	
Missed School/Work because of Infection	No	Partial Day	Full Day	

Visits to the Doctor

Visit to Doctor for Infection or Side Effects			No	Visit to Doctor	Emergency Room	Hospital
Treatment:	*Route:*	*Frequency:*	Taken	Not Taken		
Treatment:	*Route:*	*Frequency:*	Taken	Not Taken		

Please inform study staff of any events that are disabling or require immediate medical attention.

Notes:

Legend:

Bolded Entries	Prefilled by NIH	
		Subject selects 1 Item per row
Italicized entries	*Optional entries by subject*	

APPENDIX G: EVALUATION OF INFECTION FORM

Directions: Please circle relevant items and fill in underlined sections. Use a different form for each infection unless contiguous and related.

1) Date of Office or ER Visit, Hospitalization:_____

2) Chief Complaint:_____

3) Date of Onset of Symptoms:_____

4) Diagnosis (New / Chronic / Recurrent / Exacerbation): Otitis, Sinusitis, Dental Infection, Pharyngitis, Other oral infection, Bronchitis, Pneumonia, Cellulitis, Cutaneous abscess, Osteomyelitis, Endocarditis, Meningitis, Joint Infection, Gastroenteritis, urinary tract infection, unknown
Other or further information: _____

5) Site of Infection:_____

6) Likely Cause of Infection: Viral, Bacterial, Fungal, Parasite, Unknown,
Other: _____

7) Treatment Prescribed: _____

8) Route of Treatment: Topical, Oral, intravenous

9) Length of Treatment Prescribed (days):_____

Relevant Laboratory Results:

10) Culture/Test Result: _____ pending or not performed.

11) Outcome of Infection: Pending, Unknown, Resolved, Resolved with residual symptoms, Ongoing,
Other:_____

12) Additional Information (optional): _____