

Evaluating the Safety and Efficacy of Mavorixafor, an Oral CXCR4 Antagonist, in Participants with Primary Chronic Neutropenic Disorders: Results from the Phase 2 Study

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Background

- Primary chronic neutropenia (CN) is characterized by abnormally low levels of circulating neutrophils and increased infection risk. Primary CN can be severe, with recurrent infections requiring antibiotics and hospitalizations, and can cause a significant impact on quality of life for patients and their families.¹⁻³
 - Congenital CN, including cyclic and severe CN, is caused by inherited genetic mutations, is typically diagnosed in childhood, and can result in isolated neutropenia or neutropenia as part of a syndrome.
 - Acquired CN, also called chronic idiopathic neutropenia (CIN), leads to shortened neutrophil lifespans due to either antineutrophil antibodies or an unknown cause.
- There is one FDA-approved treatment indicated for severe chronic neutropenia: injectable granulocyte colony-stimulating factor (G-CSF).⁴
 - Injectable G-CSF has been available for approximately 30 years and has considerably improved these patients' clinical outlook. Despite this, the reported side effects include bone pain and splenomegaly, thrombocytopenia, glomerulonephritis, vasculitis, and osteoporosis.⁵⁻⁷
 - Long-term treatment with G-CSF, especially at high doses, is correlated with an increased risk of myelodysplastic syndrome and leukemia in patients with congenital neutropenia.^{7,8}
 - Due to dose limiting toxicity and risks associated with long-term high-dose G-CSF exposure, patients do not always receive the optimal daily dosing regimen.
 - Some patients with infrequent dosing strategies and those patients who are unable to tolerate optimal G-CSF dosing may have gaps in protection and may be vulnerable to infections.
- Once daily mavorixafor, an oral CXCR4 antagonist approved by the US FDA in 2024 for patients ≥12 years of age with WHIM syndrome, increases the number of circulating mature neutrophils and lymphocytes.^{9,10}
- As CXCR4 antagonism has demonstrated efficacy in patients with CXCR4 gain of function variants,⁹ and the CXCR4-CXCL12 pathway plays an essential role in granulopoiesis, neu-trophil trafficking, and neutrophil homeostasis, regulating the development and egress of white blood cells, including neutrophils, from the bone marrow into the periphery,^{11,12} we hypothesize that mavorixafor may provide beneficial treatment effects for other primary CN disorders.

Neutropenia Severity Grades	NIH Classification ¹³	Absolute Neutrophil Count (ANC)
Severe (Grade 4)		< 500 cells/μL
Moderate (Grade 3)		500–1,000 cells/μL
Mild (Grade 2)		1,000–1500 cells/μL
Non-clinical (Grade 1)		1,500 = Lower Limit of Normal (LLN)

Objective

Assess the safety and efficacy of once daily mavorixafor oral therapy, alone and with injectable G-CSF, in participants with primary CN in an open-label phase 2 study.

Methods

- The study enrolled participants ≥12 years of age with absolute neutrophil count (ANC) ≤1000 cells/μL (<10,000 cells/μL if on G-CSF) and a diagnosis of CIN, congenital neutropenia (exclusive of cyclic presentation), or cyclic neutropenia (ie, congenital neutropenia with a cyclic presentation).
- Participants received oral, once-daily mavorixafor as monotherapy or in combination with injectable G-CSF (with the option for dosage reduction after 2 months if ANC remained >500 cells/μL) for a 6-month period.
- Participants with an infection requiring antibiotics or who took systematic antibiotics within 4 weeks before Day 1 were excluded.
- Safety assessments:
 - Treatment emergent adverse events (TEAEs) using Common Terminology Criteria for Adverse Events.
 - Clinical laboratory parameters, vital signs, and electrocardiograms.
- Efficacy: assessed via ANC measurements
 - ANC increases >500 cells/μL are considered clinically meaningful.^{1,14,15}
- Neutrophil function: Whole blood samples from a subset of participants were analyzed to measure blood neutrophil responses to bacterial challenge (opsonized *E. coli*) by reactive oxygen species (ROS) generation assay and phagocytosis assay.

Phase 2 Study: Assessing Safety, Durability of ANC Levels Over 6-Month Period



Results

STUDY POPULATION & PARTICIPANT DISPOSITION

- A total of 23 participants were enrolled in the study, of whom 20 participants completed the study and 3 participants discontinued.
- The overall mean age was 33.7 years; 2 participants were aged <18 years.

Type of Primary Chronic Neutropenia		Sex and Age	
CIN	15	Sex	Male 10
Congenital Neutropenia	6		Female 13
Cyclic Neutropenia	2	Mean Age	34

Enrolled Participants (N = 23)	Mavorixafor (n = 10)	Mavorixafor + G-CSF (n = 13)
Discontinued (n = 3)	Mavorixafor (n = 2)	Mavorixafor + G-CSF (n = 1)
Completed Study (n = 20)	Mavorixafor (n = 8)	Mavorixafor + G-CSF (n = 12)
	Stable G-CSF Dose (n = 3)	Adjusted G-CSF Dose (n = 9)

SAFETY

- Mavorixafor was generally well tolerated as therapy without concurrent G-CSF and in combination with G-CSF over the 6-month study.
- Overall safety profile consistent with prior studies.
- No new safety issues observed when dosed in combination with G-CSF.
- No deaths and no drug-related serious adverse events (SAEs).
- Treatment-related TEAE were experienced by 17 (73.9%) participants.
- Majority of Treatment-related TEAEs were Grade 1 and Grade 2.
- Most frequent treatment-related TEAEs were GI related (nausea and diarrhea) and led to 3 discontinuations in total (all early in study execution).

TREATMENT-RELATED GASTROINTESTINAL TEAEs

Parameter, n (%)	Mavorixafor Without G-CSF (n = 10)	Mavorixafor With G-CSF (n = 13)	Overall (n = 23)
Nausea	5 (50.0)	4 (30.8)	9 (39.1)
Diarrhea	3 (30.0)	4 (30.8)	7 (30.4)
Dyspepsia	2 (20.0)	1 (7.7)	3 (13.0)
Vomiting	2 (20.0)	1 (7.7)	3 (13.0)
Abdominal pain/ Abdominal pain upper	1 (7.7)	2 (15.4)	3 (13.0)

- Treatment-related Gastrointestinal TEAEs were experienced by 14 (60.9%) participants.
- The majority of these GI TEAEs occurred within the first 2 weeks of treatment.
- Most (59% [20]) of the GI TEAEs were not treated with symptom-directed therapy.
- Symptom-directed therapy was used by 7 (30%) participants and included food, Tums, or some prescription GI therapies.
- Three participants (1 with CIN and concurrent G-CSF, 1 with CIN and no concurrent G-CSF, 1 with cyclic neutropenia and no concurrent G-CSF) discontinued due to Grade 1 or 2 GI TEAEs.
 - Two of these 3 participants were taking concomitant medications with known GI side effects, potentially confounding assessment of relatedness.
- No discontinuations following successful clinician/participant education on possible GI effects that typically resolve over time.

Abbreviations: ANC = absolute neutrophil count; CN = chronic neutropenia; CIN = chronic idiopathic neutropenia; G-CSF = granulocyte colony-stimulating factor; GI = gastrointestinal; LLN = lower limit of normal; NIH = National Institutes of Health; ROS = reactive oxygen species; SE = standard error; TEAE = treatment emergent adverse events; WHIM = warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis.

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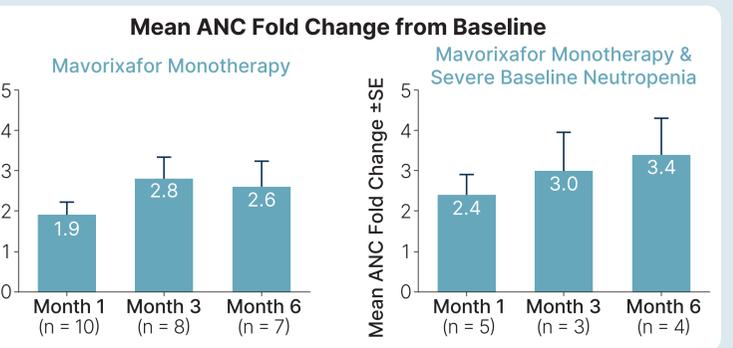
A Phase 3 trial is currently enrolling @clintrials.gov NCT06056297 in 80 international locations. The purpose of this study is to demonstrate the efficacy and evaluate the safety and tolerability of mavorixafor in participants with congenital or acquired primary autoimmune and idiopathic chronic neutropenic disorders who are experiencing recurrent and/or serious infections as assessed by demonstrating its clinical infection benefit and increased levels of circulating neutrophils.

Tricia Gooljarsingh, VP of Medical Affairs, X4 Pharmaceuticals is attending EHA and is available to speak further about this study. Contact: tricia.gooljarsingh@x4pharma.com.

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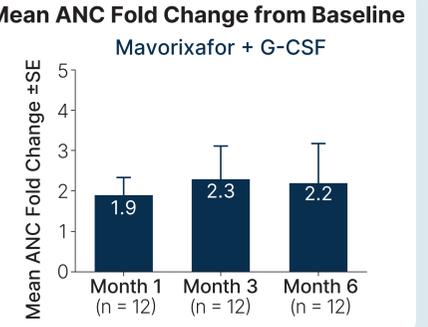
Mavorixafor Without Concurrent G-CSF Durably and Meaningfully Increased Mean ANC Beginning at 1 Month and Continuing through 3 and 6 Months

- At 6 months, the cohort of participants treated with mavorixafor without concurrent G-CSF who completed the study showed overall improvement in ANC
 - achieved mean ANC of ~1200 cells/μL resulting in a shift from moderately neutropenic to mildly neutropenic range.
 - ~2.6-fold change in mean ANC from baseline.
- Participants with severe neutropenia (i.e. ANC < 500 cells /μL) at baseline treated with mavorixafor without concurrent G-CSF show ~3-fold change in mean ANC from baseline at 3 and 6 months.



Mavorixafor with Concurrent G-CSF (Stable-Dose and Dose-Reduced) Durably Maintained Mean ANC Above LLN from Baseline Through 6 Months

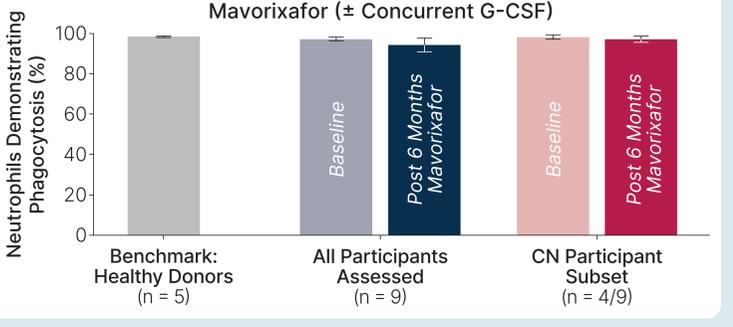
- The cohort of participants treated with mavorixafor with concurrent G-CSF, including those with reduced doses of G-CSF
 - maintained mean ANC above LLN from Baseline through 6 months.
 - showed ~2-fold change in mean ANC from baseline.
- In the cohort of participants with moderate ANC (≥500 and <1500 cells/μL) at baseline, mavorixafor with concurrent G-CSF (stable-dose and dose-adjusted) resulted in ~8- and ~6-fold changes in mean ANC at Months 3 and 6, respectively.
- Given the option, investigators in consultation with participants chose to substantially reduce injectable G-CSF therapy in 9 of 12 eligible participants.
 - 89% (8 of the 9) had G-CSF adjusted at the earliest possible timepoint (following Month 2 visit).
 - Three participants completely withdrew from any G-CSF treatment before Month 6.
 - The cohort of participants with reduced G-CSF maintained normal mean ANC.



Functionality Assessments in a Subset of Mavorixafor-treated Participants Demonstrate Neutrophils Capable of Phagocytosis and ROS Generation

- 9 study participants were included in the functionality assessments:
 - 5 with CIN and 4 with congenital CN.
 - 4 were treated with mavorixafor without concurrent G-CSF, 5 with mavorixafor with concurrent G-CSF.
- The mean percentage of neutrophils capable of phagocytosis remained comparable to healthy donor controls after 6 months of mavorixafor therapy.
- The mean percentage of neutrophils performing ROS functions¹ was also comparable to healthy donors in all participants (n=9), including congenital neutropenia participants (n=4). (Data not shown.)
- Results were similar for the participants with CIN and participants with congenital CN.

Neutrophil Functionality Before and During Mavorixafor Therapy



Conclusions

- Treatment with mavorixafor, alone or with stable dosage or dosage-adjusted G-CSF was generally well tolerated and resulted in meaningful and durable increases in ANC levels in participants with primary CN regardless of subtype or severity.
- G-CSF use was substantially reduced, suggesting that mavorixafor treatment may permit G-CSF dosage reductions, which could minimize exposure to G-CSF and its possible side effects, potentially improving patients' quality of life and possibly contributing to lowering the long-term risk of malignancy correlated with chronic, higher-dose G-CSF use in the subset of congenital CN patients predisposed to malignancy.^{7,15,17} Further research is needed.
- The functional assays show mavorixafor-treated CN participants' neutrophils are capable of phagocytosis and ROS generation, supporting the potential of mavorixafor to reduce in-infection rate in CN patients, the demonstration of which is one of the primary objectives of the ongoing CN Ph3 trial (with the co-primary endpoint of annualized infection rate).
- Observed increases in ANC in participants with primary CN supports the hypothesis that the mobilization of white blood cells from the bone marrow enabled by the CXCR4 antagonist mavorixafor has a restorative effect on the fine balance of neutrophil homeostasis.
- Further investigation is required to more fully understand the tolerability and efficacy profile of mavorixafor in primary chronic neutropenia; a Phase 3 trial (NCT06056297) is currently enrolling in 80 international locations to assess the ability of mavorixafor to elevate neutrophils and reduce annualized infection rate in participants with certain moderate to severe primary neutropenias.