

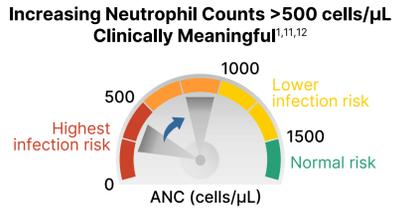
Mavorixafor, an Oral CXCR4 Antagonist, Allows for Granulocyte-Colony Stimulating Factor Dose De-Escalation in Phase 2 Trial Participants with Primary Chronic Neutropenia

Julia T. Warren^{1,2}, Kathryn E. Dickerson³, Jan E. Walter⁴, Katrina Adell⁵, Xiaoxi Li⁵, Sam Wilson⁵, Henry Wu⁵, Deborah J. Steiner⁵, Christophe Arbet-Engels⁵

¹Department of Pediatrics, Division of Hematology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; ²Division of Pediatric Hematology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; ³Department of Pediatrics, Division of Hematology/Oncology, University of Texas Southwestern Medical Center, Dallas, TX; ⁴Department of Pediatrics and Medicine, Morsani College of Medicine, University of South Florida, Tampa, FL, USA; ⁵X4 Pharmaceuticals, Boston, MA, USA

Background

- Primary chronic neutropenia (CN) is defined as a reduction in the absolute neutrophil count (ANC) below normal levels lasting for at least 3 months and is associated with increased susceptibility to infections that can be life-threatening.¹⁻³
 - » Congenital CN, including cyclic and severe congenital neutropenia, are caused by 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 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, reported side effects include bone pain, 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 dosage 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.
- Treatment options for primary CN that provide the opportunity to limit or eliminate injectable G-CSF is a critical unmet medical need.
- Once-daily mavorixafor, an oral CXCR4 antagonist approved by the US FDA in 2024 for patients ≥12 years of age with WHIM syndrome,^{9,10} was recently evaluated for safety and efficacy in a Phase 2 study of primary CN participants.
- A subset of participants entered the Phase 2 study already treated with subcutaneous G-CSF
 - » It was not known whether participants and providers would opt to reduce or eliminate G-CSF following initiation of mavorixafor treatment.



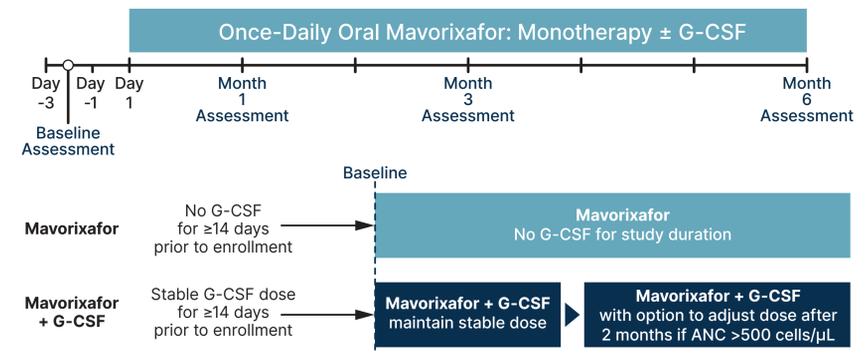
Objective

Assess whether treating participants with primary CN (CIN or congenital) with once daily mavorixafor oral treatment safely enables the reduction of injectable G-CSF dosage while maintaining clinically targeted ANC levels.

Methods

- Study enrolled participants ≥12 years of age with 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) to receive oral, once-daily mavorixafor for 6 months.
- For participants treated with concurrent G-CSF, investigators had the option of G-CSF dosage reduction after 2 months if the ANC remained >500 cells/µL, with the method of G-CSF dosage adjustment per investigator discretion.
- 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.

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



Results

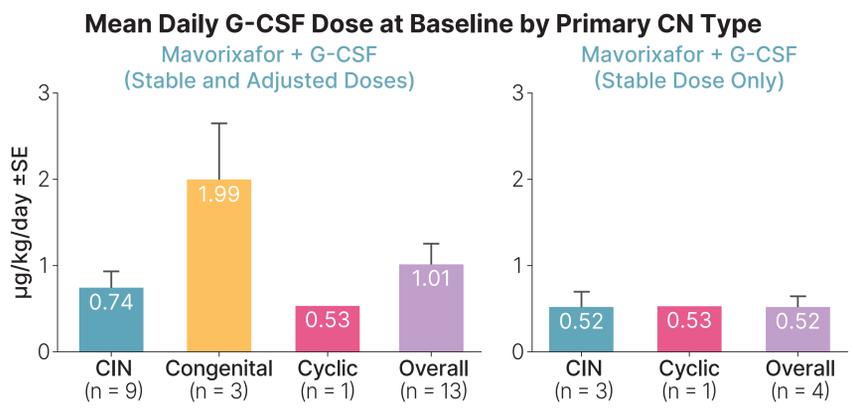
STUDY POPULATION AND PARTICIPANT DISPOSITION

- A total of 23 participants were enrolled in the study, 13 of whom (5 male and 8 female) were treated with G-CSF.
- The overall mean age of the G-CSF-treated participants was 32.5 years.

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)

G-CSF DOSE ADJUSTMENTS

- Baseline G-CSF Dosages
 - At baseline, the mean daily G-CSF dosage was 1.01 µg/kg/day for all 13 participants who had entered the study using G-CSF.
 - Analyzing by primary CN type, the cohort of participants with congenital neutropenia who were using G-CSF had the highest mean daily dosage, of 1.99 µg/kg/day.
 - The mean G-CSF dosages at baseline were lower among the participants who maintained a stable G-CSF dosage throughout the study.



Phase 3 Now Enrolling

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



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

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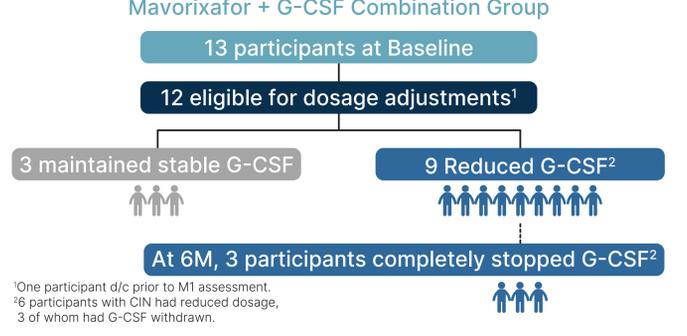
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Disclosures: JTW, KED, and JEW are study investigators and consultants for and receive research funding from X4 Pharmaceuticals, Inc. KED is also a consultant advisor for Agios, unrelated to this work. KA, SD, XL, SW, HW, CAE, and DS are current employees of X4 Pharmaceuticals and/or have equity ownership in X4 Pharmaceuticals.

G-CSF Dosage Reductions

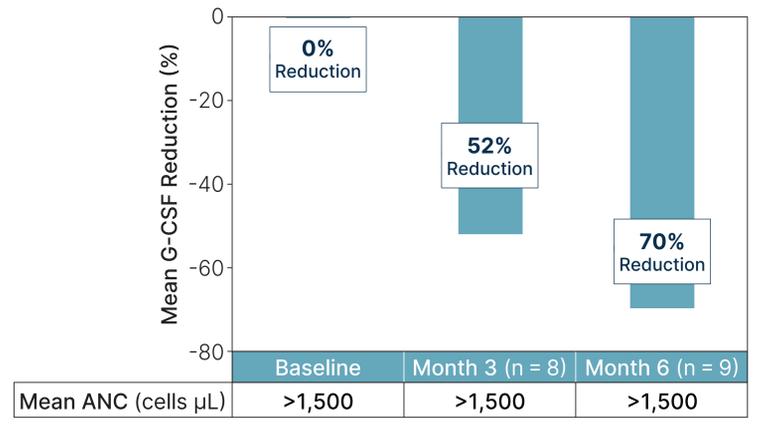
- Given the option, investigators, with their patients, chose to substantially reduce injectable G-CSF therapy for 9 of 12 eligible participants.
 - » 89% (8 of the 9) had G-CSF adjusted at the earliest possible timepoint (following Month 2 visit).
 - » 33% (3 of 9) of participants with dosage adjustments, all with CIN, were taken completely off G-CSF prior to, and remained off at, Month 6 visit.

Disposition of Dosage-Reduction Eligible Participants



- At Month 6, the mean G-CSF dosage reduction was 70% of baseline dosage and mean ANC levels above the lower limit of normal for neutrophil count were maintained.

Mean G-CSF Reduction Over Time



Conclusions

- The majority of participants and investigators were willing and elected to substantially reduce or discontinue injectable G-CSF use with oral mavorixafor treatment. All participants with congenital neutropenia concurrently treated with G-CSF, including one with the ELANE variant, were able to decrease G-CSF while maintaining mean ANC at normal levels.
- 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.^{7,13,14} Further research with patient registry data is needed.
- No new side effects were seen with combination mavorixafor and G-CSF therapy.
- This study provides the first evidence that a significant subset of patients with CIN, or acquired CN, may be able to successfully transition off injectable G-CSF for mavorixafor, providing an oral option to treat chronic neutropenia.
- Future studies are required to understand the optimal timing and pace of G-CSF dosage reduction and drivers of patient/provider willingness to reduce or eliminate G-CSF use.