Mavorixafor for Patients with Chronic Neutropenic Disorders Treated with G-CSF: Preliminary Response Data and G-CSF Dose Reduction in an Ongoing Phase 2, Open-Label, Multicenter Study Support Reduction in G-CSF Dosing

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Julia T. Warren, MD, PhD[1,2]; Kathryn E. Dickerson, MD, MS[3]; Anjali A. Sharathkumar, MBBS, MD, MS[4]; Jolan E. Walter, MD, PhD[5]; David B. Wilson, MD, PhD[6]; Christophe Arbet-Engels, MD, PhD[7]; Katrina P. Adell, MD[7]; Susan Dubuc, RN, MSN[7]; Rick MacLeod[7]; Katie Peters, MS[7]; Deborah J. Steiner, MD, MS[7]; Murray Stewart, MD[7]; Arthur G. Taveras, PhD[7]; Kelly Walkovich, MD[8]

[1]Division of Hematology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [3]Division of Hematology and Oncology, Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX, USA; [4]Stead Family Department of Pediatrics, Carver College of Medicine, University of Iowa Health Care, Iowa City, IA, USA; [5]Division of Allergy & Immunology, Department of Pediatrics, Morsani College of Medicine, University of South Florida at Johns Hopkins All Children's Hospital, St. Petersburg, FL, USA; [6]Department of Pediatrics, Washington University School of Medicine, St. Louis, MO, USA; [7]X4 Pharmaceuticals, Inc., Boston, MA, USA; [8]C.S. Mott Children's Hospital, Ann Arbor, MI, USA

Scan for more information on the study

Background

- Chronic neutropenia (CN) includes blood disorders with heterogeneous causes and presentations, characterized by low levels of neutrophils (ANC <1500/µL for >3 months) leading to increased susceptibility to recurrent and/or severe infections[1]
- Injectable granulocyte colony-stimulating factor (G-CSF) is the only approved therapy for severe chronic neutropenia
  - G-CSF presents unmet needs, with burden posed by frequent injections, side effects (e.g., bone pain), and prolonged use associated with the risk of malignancies in some CN disorders[2]
- Mavorixafor is an investigational oral, highly-selective CXCR4 antagonist that showed:
  - Durable increases in ANC and reduction in frequency and severity of infections; apparent safety and tolerability in a phase 3 trial in WHIM syndrome[3]
  - Substantial ANC increases in a phase 1b trial in chronic neutropenic disorders[54]
- The phase 2 trial of mavorixafor in chronic neutropenic disorders is ongoing; these data will inform the design of the planned phase 3 study in CN[5]
- A phase 3 trial is planned to evaluate the efficacy (positive ANC response, infection rate) and safety of mavorixafor

Objectives

- To report preliminary results for 3 participants enrolled in an ongoing phase 2, open-label, multicenter trial evaluating the safety, tolerability, and proof of concept for efficacy of mavorixafor, alone or with concurrent G-CSF use, in chronic neutropenia disorders (NCT04154488; part 2)

Methods

Primary Objectives	Secondary Objectives	Exploratory Objectives
• Evaluate safety, tolerability, and effect on ANC of 6-month chronic dosing of mavorixafor	• Characterize the multidose PK profile of mavorixafor during 6 months of chronic dosing • Evaluate effect of 6-month chronic dosing of mavorixafor on ALC, WBC, and AMC	• Assess incidence and duration of infection-related events with chronic dosing • Evaluate G-CSF dose reduction in participants treated concurrently with mavorixafor and G-CSF

Figure 1. Primary, secondary, and exploratory objectives for part 2 (phase 2) of clinical trial evaluating mavorixafor for chronic neutropenia. ALC, absolute lymphocyte count; AMC, absolute monocyte count; PK, pharmacokinetic; WBC, white blood cell.

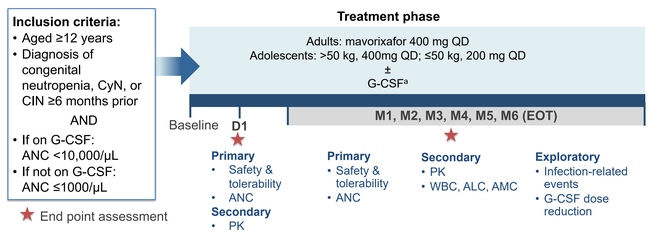


Figure 2. Study design schematic of phase 2 clinical trial (NCT04154488)
ALC, absolute lymphocyte count; AMC, absolute monocyte count; ANC, absolute neutrophil count; CIN, chronic idiopathic neutropenia; CyN, cyclic neutropenia; D, day; EOT, end of treatment; G-CSF, granulocyte colony-stimulating factor; M, month; PK, pharmacokinetics; QD, once daily.
[a]Participants already on G-CSF continued individualized G-CSF dosing for ≥8 weeks. Dose and/or frequency may be reduced based on monthly ANC assessments.

- Hematologic parameters, including ANC, were assessed over 8 hours on day 1 and at months 1, 3, and 6. At months 2, 4, and 5, hematologic parameters were assessed within 2 to 4 hours of dosing to reduce trial burden

Participant Disposition: Study Flow Diagram for Phase 2 Clinical Trial (NCT04154488)

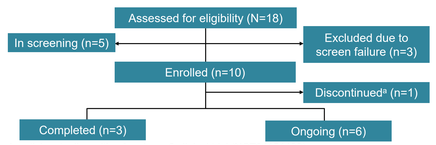


Figure 3. Flow diagram of participants disposition for phase 2 clinical trial (NCT04154488).
[a]Participant withdrew consent.

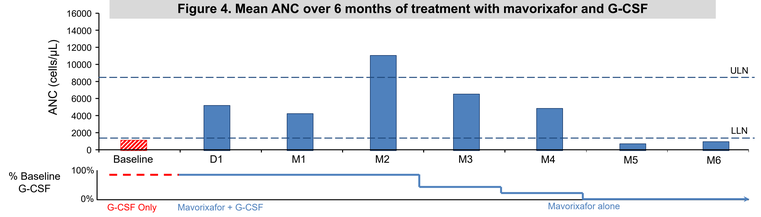
- Only preliminary results for the 3 participants who have completed the study as of September 28, 2023 are presented

Results

Participant 1: Mavorixafor Allows for Exploratory G-CSF Dose Reduction in a Participant With Chronic Idiopathic Neutropenia

Background: 24 year-old female with CIN, pre-study G-CSF dosing: 0.74 µg/kg/dose QOD

Figure 4. Mean ANC over 6 months of treatment with mavorixafor and G-CSF



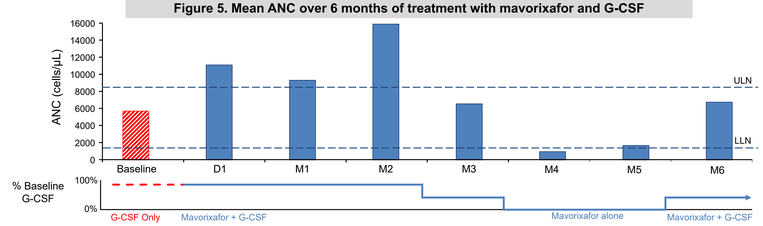
Summary:
- Baseline ANC in mild neutropenia range
- Normalization of ANC with mavorixafor in addition to G-CSF maintained through 4 months, including with ≥75% baseline G-CSF dose reduction (through decreases in dosage and frequency), as determined by the treating physician

ANC, absolute neutrophil count; CIN, chronic idiopathic neutropenia; D, day; G-CSF, granulocyte colony-stimulating factor, LLN, lower limit of normal; M, month; QOD, every other day; ULN, upper limit of normal.
Note: Normal ANC: ≥1500 to 8500 cells/µL; Severe CN: ANC <500 cells/µL; Moderate CN: ANC ≥500 and <1000 cells/µL; Mild CN: ANC ≥1000 and <1500 cells/µL.

Participant 2: Mavorixafor Allows for Exploratory G-CSF Dose Adjustment in a Participant With Chronic Idiopathic Neutropenia

Background: 20 year-old female with CIN, pre-study G-CSF dosing: 0.38 µg/kg/dose QD

Figure 5. Mean ANC over 6 months of treatment with mavorixafor and G-CSF



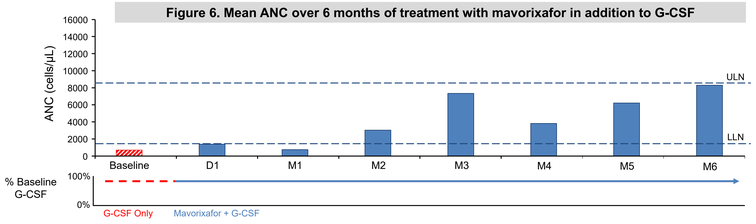
Summary:
- Baseline ANC in normal range
- Mavorixafor, in addition to G-CSF, increased ANC (3500 – 10,000 cells/µL)
- Normal or near-normal ANC maintained with 50% baseline G-CSF dose reduction (through decreases in dosage and/or frequency) and cessation, as determined by the treating physician after M2
- Treating physician increased G-CSF dose to 50% of baseline after M5 due to CN presentation (history of gingivitis)

ANC, absolute neutrophil count; CIN, chronic idiopathic neutropenia; D, day; G-CSF, granulocyte colony-stimulating factor; LLN, lower limit of normal; M, month; QD, once daily; ULN, upper limit of normal.
Note: Normal ANC: ≥1500 to 8500 cells/µL; Severe CN: ANC <500 cells/µL; Moderate CN: ANC ≥500 and <1000 cells/µL; Mild CN: ANC ≥1000 and <1500 cells/µL.

Participant 3: ANC Maintained within the Normal Range When Mavorixafor is Used in Combination with a Stable G-CSF Dose in a Participant with Cyclic Neutropenia

Background: 39 year-old male with CyN, pre-study G-CSF dosing: 0.53 µg/kg/dose QD

Figure 6. Mean ANC over 6 months of treatment with mavorixafor in addition to G-CSF



Summary:
- Moderate neutropenia at baseline
- Normal ANC maintained from M2 through M6

ANC, absolute neutrophil count; CyN, cyclic neutropenia; D, day; G-CSF, granulocyte colony-stimulating factor; LLN, lower limit of normal; M, month; QD, once daily; ULN, upper limit of normal.
Note: Normal ANC: ≥1500 to 8500 cells/µL; Severe CN: ANC <500 cells/µL; Moderate CN: ANC ≥500 and <1000 cells/µL; Mild CN: ANC ≥1000 and <1500 cells/µL.

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Participants 1, 2, and 3: Infection Events and Safety/Tolerability

Among the 3 participants treated with mavorixafor for 6 months in additional to G-CSF:

Infection reduction
- Four (4) infections were reported within the first 2 months
  - Laryngitis, pharyngitis (Participant 1); nasopharyngitis, cystitis (Participant 2)
- No infections were reported during the following 4 months despite some participants adjusting G-CSF dosing regimen

Safety and Tolerability
- Nineteen (19) adverse events
- No events were serious, and all were Grade 1 (mild) or Grade 2 (moderate)
- None of these events led to mavorixafor dose reduction, interruption, or cessation
- There were no new safety adverse events
- These preliminary data are consistent with the safety and tolerability of mavorixafor in the WHIM program, with mild and moderate gastrointestinal events, such as nausea and vomiting reported

Chronic Neutropenia Community Insights on G-CSF Dosing Adjustments in Addition to an Oral Agent

- Due to substantial disease burden, incorporating patient perspective into the clinical research process can improve patient outcome[6]

CN participant feedback suggests that patients would take an oral medicine in addition to G-CSF if it reduced the dose or frequency of G-CSF, with a strong preference for reduced frequency[a]

Further investigation is needed to determine individual patient G-CSF dosing adjustment, and X4 is working with the scientific and clinical community to design future studies

[a]Preliminary results from a chronic neutropenia engagement survey in partnership with the National Neutropenia Network

> "If I am able to decrease my dosing or the frequency of my injection it would help some of the side effects from G-CSF. I am very willing to take a medication orally to help that!"

> "Taking G-CSF less frequently would allow more flexibility in my life"

> "It would be really helpful to reduce how often I need an injection even if it is only by 25%"

> "It would be very nice to reduce both dose and frequency, or either! It would be absolutely worth it to reduce side effects, or improve medication efficacy"

Conclusions

- Sustained normal ANC levels within the first 3 months observed in all 3 participants
- Preliminary results suggest:
  - G-CSF dosing adjustments (frequency and/or dose) ≥50% can maintain normal or near-normal ANC
  - Early infection event reporting did not demonstrate increased infections with G-CSF reduction
  - No new safety adverse events or concerns with mavorixafor
- Further investigations are warranted to establish guidance on mavorixafor treatment, including optimizing individualized G-CSF dose and frequency adjustments for long-term maintenance of adequate ANC and improvement in clinical presentation
- G-CSF dosing represents an unmet medical need in individuals with chronic neutropenic disorders
  - Preliminary feedback from CN community suggest that G-CSF dose reductions could represent meaningful change to many patients with CN
- Overall, preliminary ANC and infection data support the primary end points of positive ANC response and infection rate, respectively, in the global phase 3 pivotal study

These early phase 2 data for mavorixafor in addition to G-CSF support the CN phase 3 study design and potential G-CSF dosing adjustment

References

1. Fioredda F, et al. *Hemasphere*. 2023;7(4):e872. **2.** Donadieu J, et al. *Expert Rev Hematol*. 2021;14(10):945-960. **3.** Badolato R, Donadieu J. *Hemasphere*. 2023;7(Suppl):e684700a. **4.** Warren J, et al. *Blood*. 2022;140 (Supp 1): 1408–1410. **5.** NCT04154488. Updated October 4, 2023. Accessed November 9, 2023. https://clinicaltrials.gov/study/NCT04154488. **6.** Mercieca-Bebber R, et al. *Patient Relat Outcome Meas*. 2018;9:353-367

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