Chronic Neutropenia

Mavorixafor Beyond WHIM Syndrome

September 27, 2022

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Event Outline

01 Welcome

02 Overview of Chronic Neutropenia

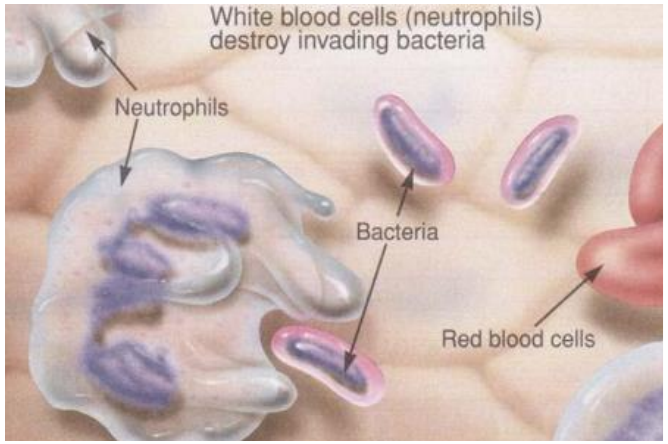
03 Insights into Current Treatment Paradigm

04 Phase 1b Clinical Trial Objectives and Results

05 Future Potential of Mavorixafor in CN Disorders

06 Conclusion and Q&A

Chronic Neutropenia (CN): a Severe Condition with Significant Unmet Needs



Neutrophils circulate in blood & are critical for fighting infections

Risk of Infections Increases with Lower Neutrophil Counts (Neutropenia)

Neutropenia Category	Blood Neutrophil Levels (ANC) – cells/uL
Lower Limit of Normal	>1,500
Mild	1,000 to 1,499
Moderate	500 to 999
Severe	Below 500

Image source: "Understanding Severe Chronic Neutropenia: A handbook for patients and their families," SCNIR 2017; Table data and information on infection risk: https://neutropenianet.org/what-is-neutropenia/

Disease Definition

Persistent, low levels of circulating neutrophils

- Severe, chronic (>3 months) neutropenia carries mortality risk due to infections
- Various types/etiologies of CN disorders: idiopathic, cyclic, congenital, autoimmune

Unmet Need

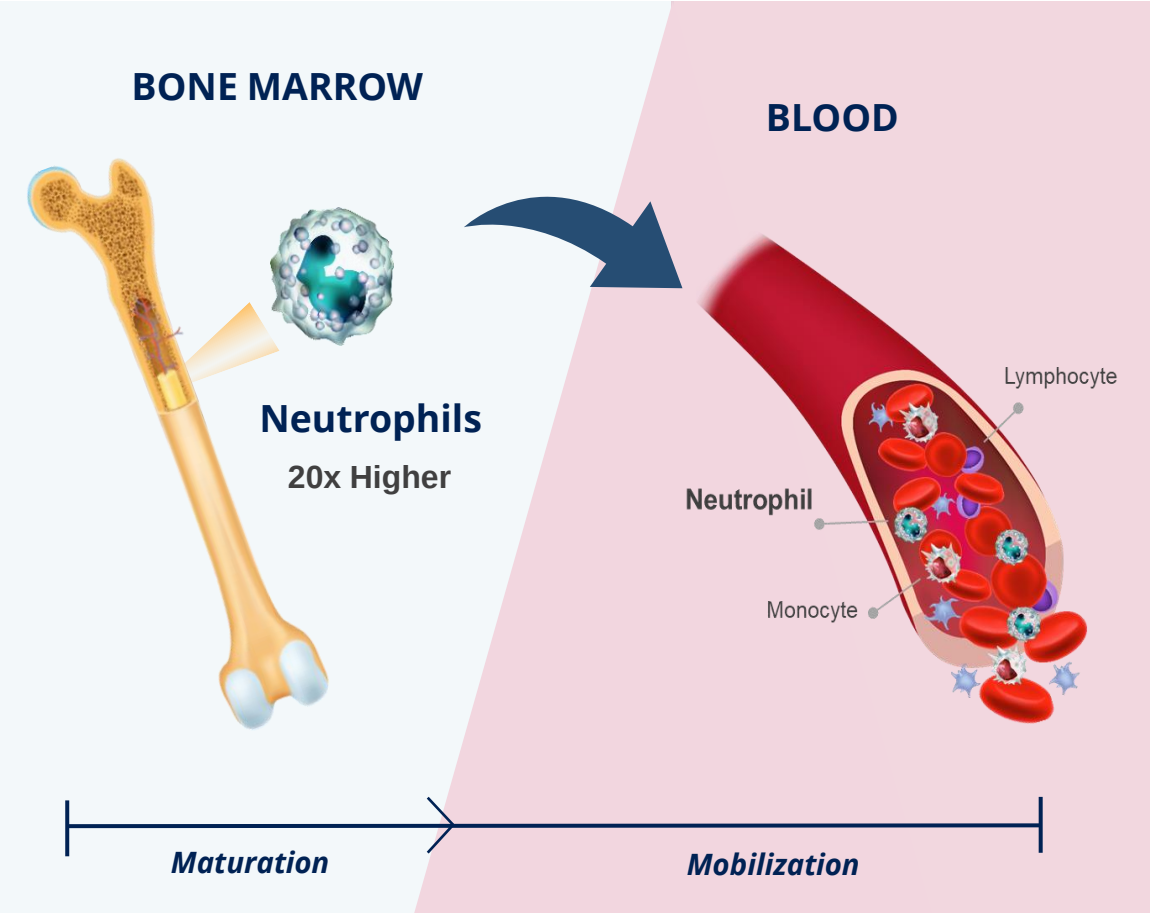
Only one Rx option: daily injectable recombinant granulocyte colony stimulating factor (G-CSF)

- Infection risks remain, although improved
- High likelihood of debilitating side effects
- Increased cancer risk in certain populations
- Burden of administration

SIGNIFICANT OPPORTUNITY FOR AN ORAL EFFICACIOUS THERAPY WITH GOOD TOLERABILITY

CXCR4 Plays A Key Role in Maturation & Mobilization of Neutrophils

Mature neutrophil pool in bone marrow is 20 times higher than in circulation[1]



Neutrophils are retained in the bone marrow (BM) by the CXCL12/CXCR4 axis creating a "reserve"

- More than 100 billion neutrophils exit the BM per day[2]
- Vast majority are held in reserve

Downregulation of CXCR4 leads to maturation of neutrophils and mobilization into the blood

- G-CSF down-regulates CXCR4 expression[3]
- CXCR4 antagonism inhibits signaling[4]

1. Bainton DF (1980) The cells of inflammation: a general view. In Weissmann G (ed) *The Cell Biology of Inflammation*, vol 2, pp 1–25. Amsterdam: Elsevier/North-Holland 2. Furze RC, et al, *Immunology*. 2008 3. Kim HK, et al, *Blood*. 2006. 4. Mosi, RM, et al, *Biochem Pharmacol*, 2012

Mavorixafor

Realizing the Potential of CXCR4 Antagonism in an Oral Capsule

Mavorixafor: the only oral CXCR4 antagonist in development

- A small molecule with high potency and selectivity
- Demonstrated ability to increase the mobilization of white blood cells, including neutrophils, from bone marrow to bloodstream
- Durable half-life supporting once-daily dosing
- Potential utility across broad range of chronic neutropenic disorders with high unmet needs

Safety Profile To Date Supports Chronic Use

- >200 patients/subjects treated to date
- Prior Phase 2 trial in WHIM syndrome:
  - Median treatment duration at 400 mg = 184 weeks
  - Low-grade adverse events reported (most commonly reported adverse events include: dyspepsia, nausea, dry mouth, conjunctivitis)

Patent Protection Expected Through 2038 and Beyond

Injectable G-CSF is the Only Approved Therapy for CN Disorders

Treatment Has Significant Challenges, Limitations, and Risks

Injections of G-CSF

- Approved for idiopathic, cyclic, and congenital severe CN
- Up to twice-daily to increase neutrophil counts and reduce severe neutropenia, infection risk
- Recommended starting dose 5-6 mcg/kg twice daily
- Often dosed by “down-titration” and at reduced frequencies
- Multiple visits to optimize dose & side effects

Challenges for patients on G-CSF

- Increased risk of myelodysplastic syndromes (MDS)[1]
- 70% with bone-pain impacting compliance and quality of life[2]

G-CSF For Injection

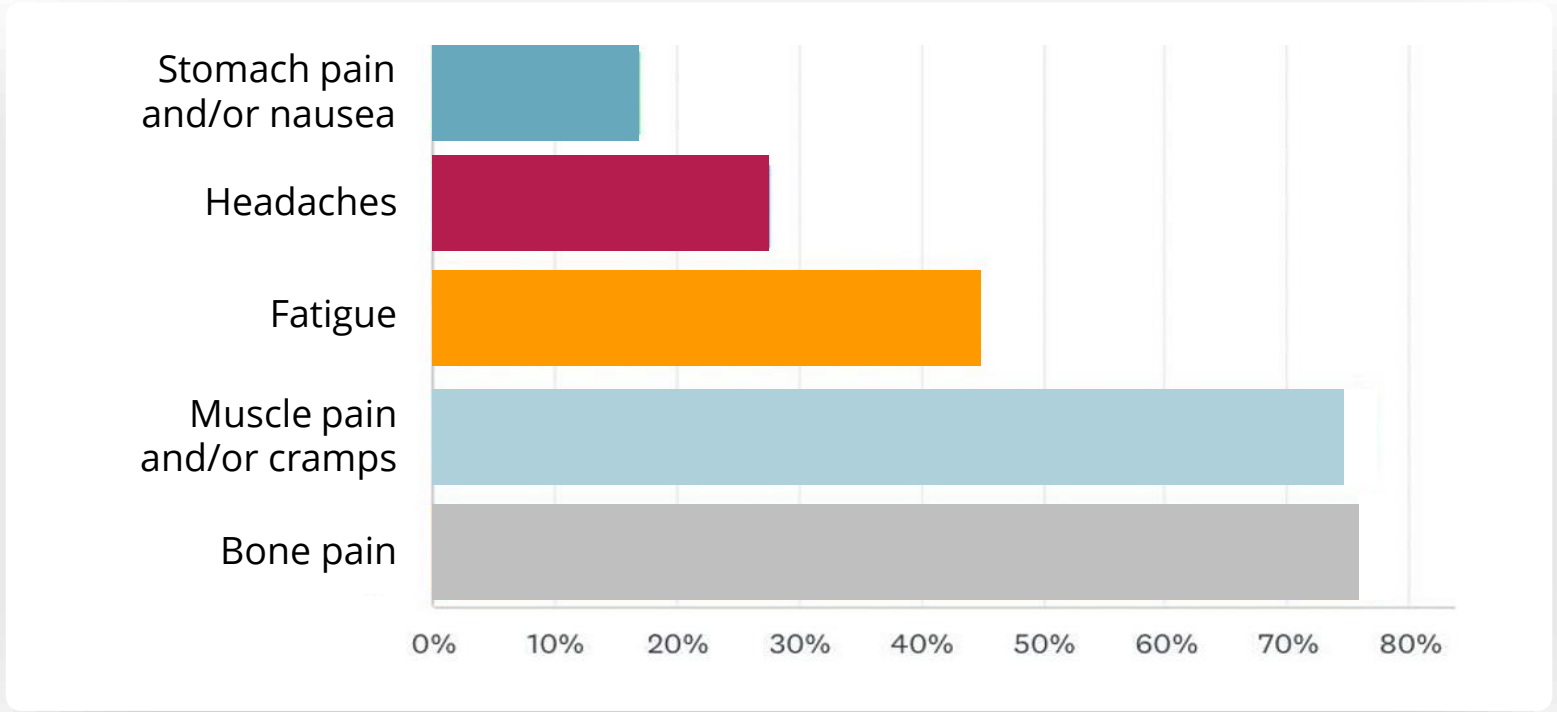
Indicated for Idiopathic, Cyclic and Congenital Severe Neutropenia

No alternative therapies except for bone marrow transplantation

1. Dale et al *Support Cancer Ther* 2006 Jul 1;3(4):220-31: 2. Michniacki et al, *Blood* (2019) 134 (Supplement_1): 3449; Neupogen label

100-Patient Survey[1] Results:

Significant Challenges with G-CSF



The Patient Experience

91 experienced with G-CSF

- 51 surveyed could tolerate continuing G-CSF treatment:
  - 76% (39) of them noted bone pain as a side effect
  - 75% (38) patients noted muscle pain and/or cramps as a side effect

1. August 2022 Savvy Cooperative Survey Results: *Neutropenia Patient Perspective*

Significant Potential Across CN Disorders Studied in Phase 1b Trial

~50,000 Estimated Chronic Neutropenia Patients in the U.S.[1]

Idiopathic

~40,000

Most commonly diagnosed chronic neutropenia

Not attributable to drugs or specific infectious, inflammatory, autoimmune or malignant causes

Cyclic

~5,000

Typically, a 21-day cycle

Autosomal-dominant disorder

Can be caused by ELANE mutations

Congenital

~2,000

Rare hematological genetic diseases

Can be caused by ELANE and other mutations

Often resistant to G-CSF

1. U.S. Prevalence Based on ICD-10 Code Research, Average Across 3 Years (2018, 2019, & 2021); >90% greater than 18 years of age, ~2/3 female, mixed G-CSF use

Objectives of X4's Phase 1b Study in Chronic Neutropenic Disorders

PRIMARY STUDY OBJECTIVES

Assess mavorixafor treatment for **safety** and ability to **increase absolute neutrophil count (ANC)** across a range of chronic neutropenic disorders (**idiopathic, cyclic, congenital**)

Three Exploratory Sub-Analyses:

Mavorixafor Monotherapy in Those with Neutropenia

Assess if mavorixafor normalizes ANC levels in neutropenic patients as a monotherapy (in those off G-CSF)

Mavorixafor + G-CSF in Those with Neutropenia

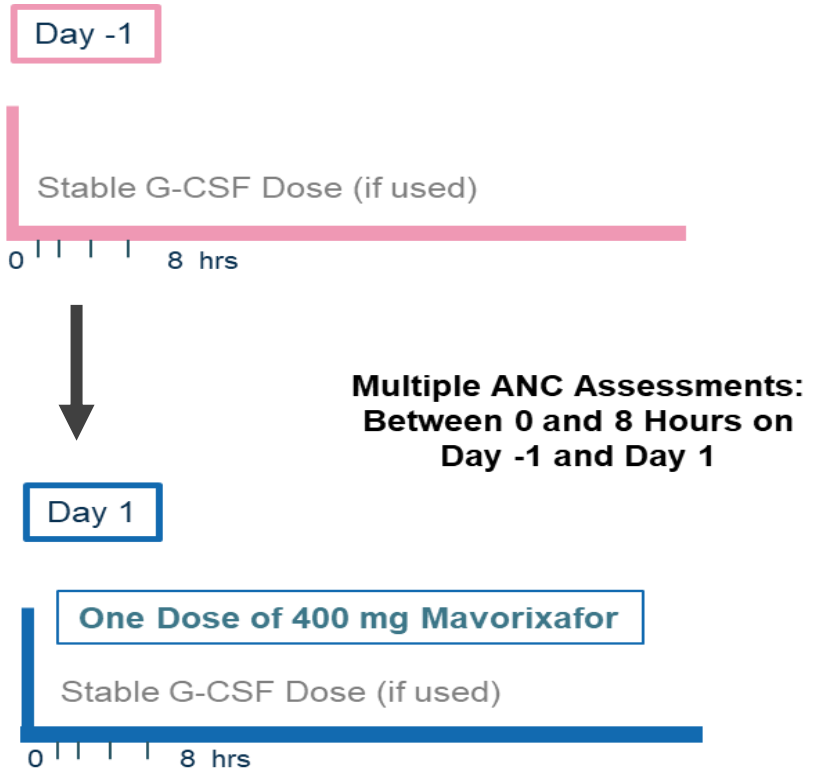
Assess if mavorixafor normalizes ANC levels in neutropenic patients in combination with G-CSF (in those on G-CSF)

Mavorixafor + G-CSF in Those with ANC >1,500 to Assess Potential for G-CSF Taper

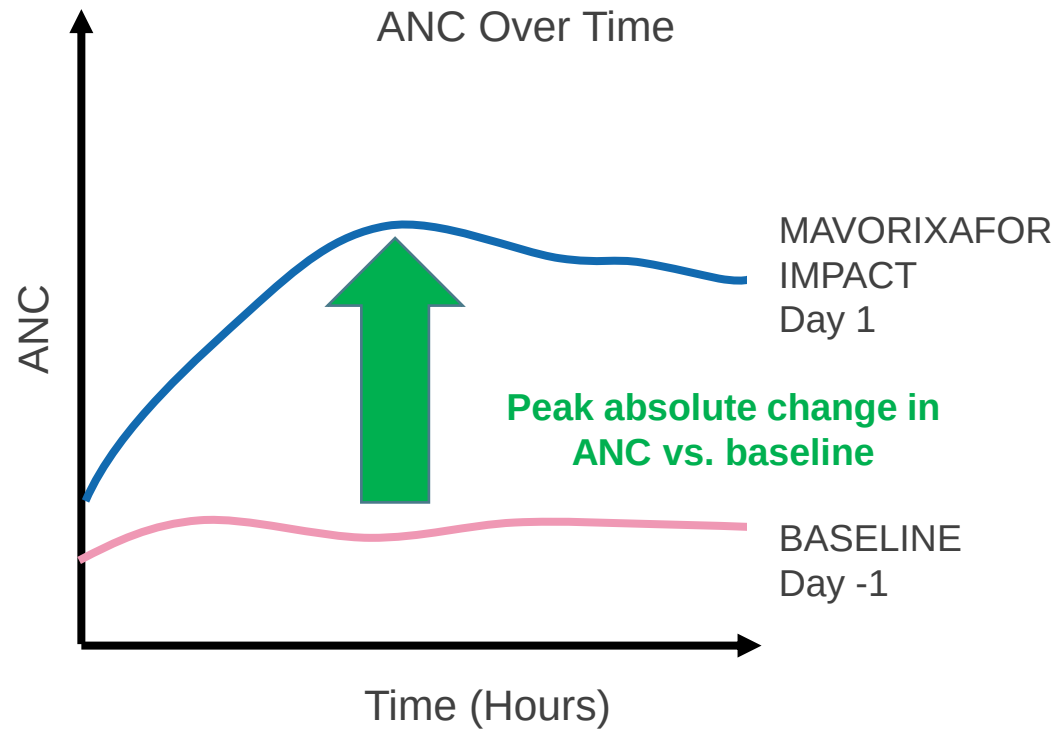
Assess if mavorixafor increases ANC levels in those treated with G-CSF and ANCs >1,500 at baseline to support future study of reducing or discontinuing G-CSF treatment

Measuring Maximum ANC Increase After Single Oral Dose of Mavorixafor

Trial Design



Trial Measurements



Baseline value defined as average ANC over Day-1

Phase 1b CN Trial Demographics & Safety Summary

	Overall	Idiopathic	Congenital	Cyclic
# Patients	25	16	6	3
Mean Age	36	37	32	41
Male/Female	10/15	6/10	1/5	3/0
On/Off G-CSF	18/7	10/6	5/1	3/0
Baseline G-CSF Dose for Those Treated Median (mcg/kg/day)*	1.09	0.56	1.09	1.09

Phase 1b Trial in CN Disorders

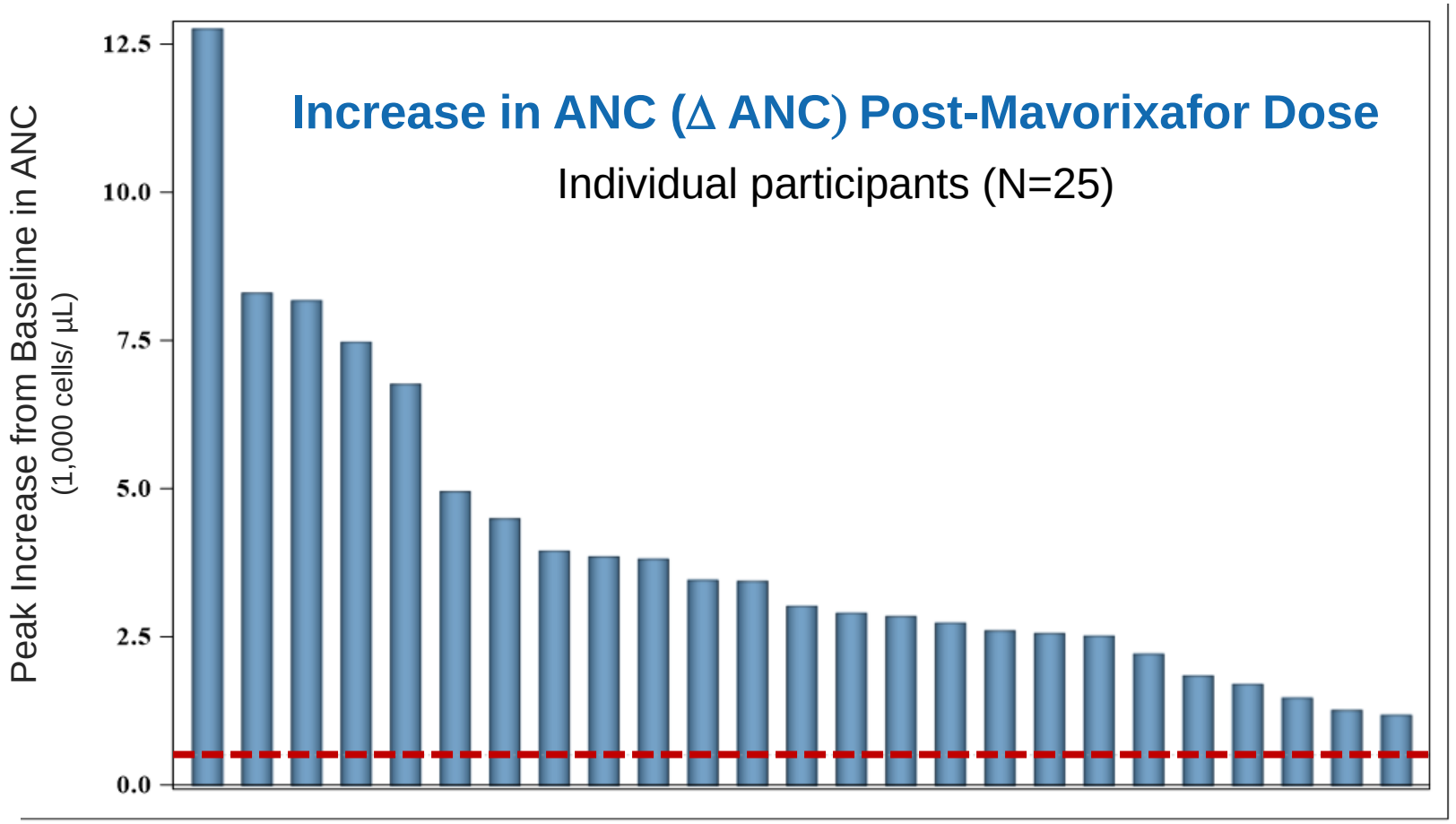
Safety Profile

- Single dose treatment mavorixafor 400 mg
- All low-grade treatment-emergent adverse events
- No treatment-related serious adverse events reported

**Among 7 patients not on G-CSF, one had baseline ANC value above 1,500 cells/uL*

Primary Objective: 100% of Patients Responded

Response defined as increase in ANC >500 cells/ µL[1]

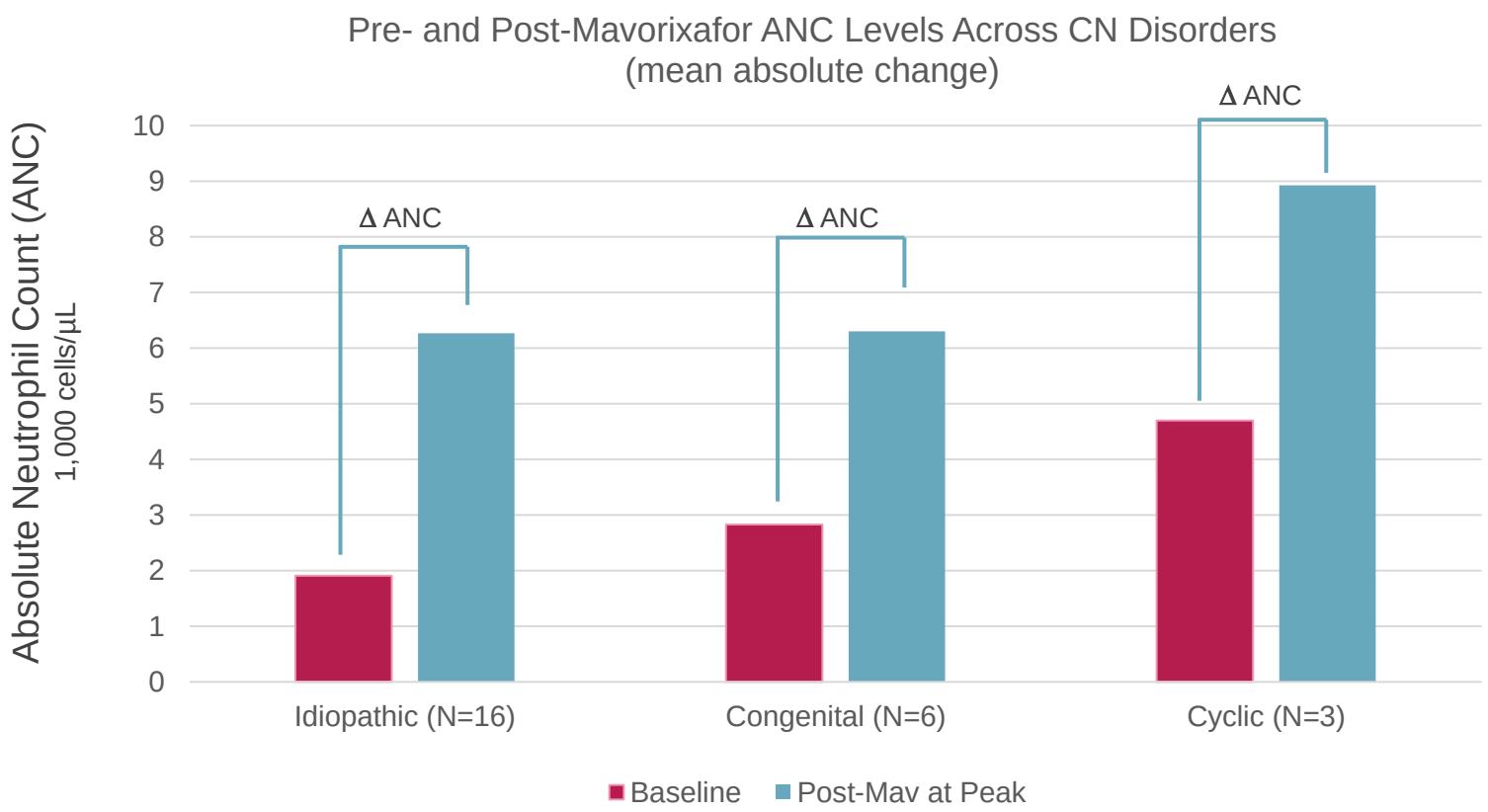


- **All participants responded**
  - Suggests bone marrow reserve of neutrophils can be accessed
- Responses exceeded 500 cells/µL for every individual participant

1. Increase of at least 500 cells/µL corresponds to improvement in at least one grade (e.g. severe neutropenia improves to moderate neutropenia).

Primary Objective Results: Oral Mavorixafor Increased ANC By >3,000 cells/µL

Consistent, large increases seen across all CN disorders studied (idiopathic, congenital, cyclic)



Idiopathic
Δ ANC of ~4,200 cells/µL

Congenital
Δ ANC of ~3,400 cells/µL

Cyclic
Δ ANC of ~4,200 cells/µL

Baseline value defined as average ANC over Day-1

Exploratory Sub-Analyses: Patient Numbers and Baseline Profiles

25 Participants: 3 Sub-Groups (no overlap between groups)

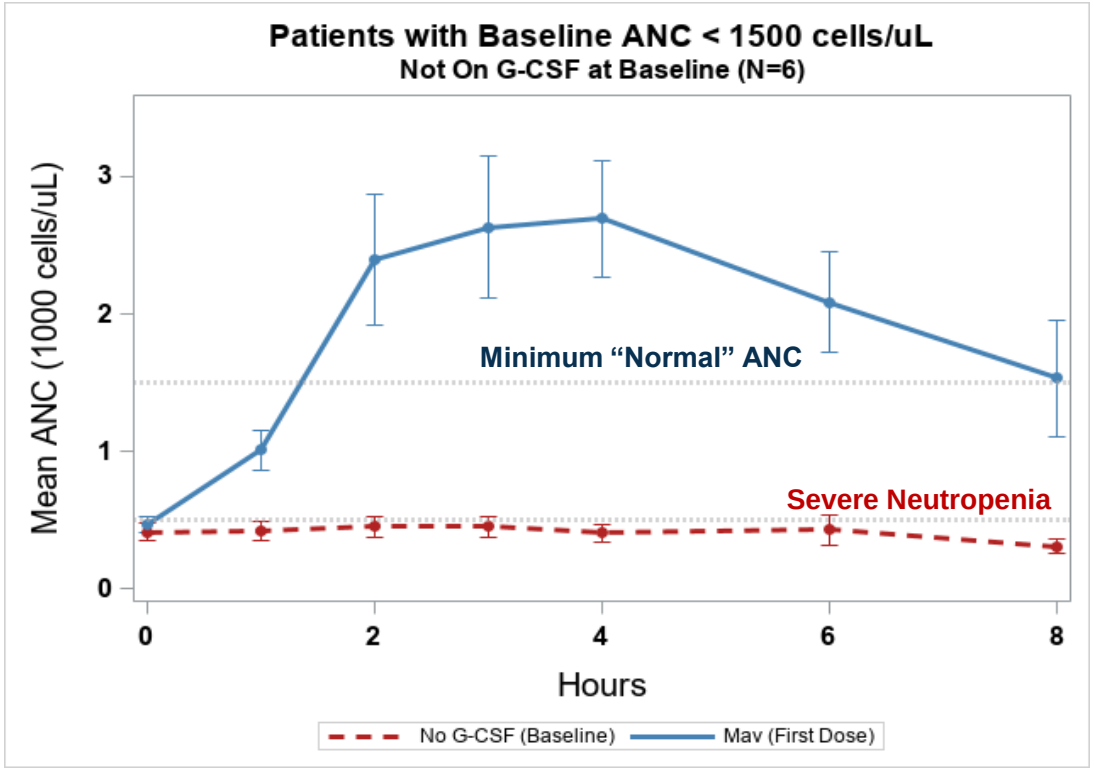
N = 6	N = 8	N = 11*
Assess impact of mavorixafor monotherapy in neutropenic patients	Assess impact of mavorixafor + G-CSF in neutropenic patients	Assess impact of mavorixafor + G-CSF in patients with ANC >1,500 to support G-CSF taper
Severe Neutropenia at Screening Mean ANC = 420 cells/µL No G-CSF	**Moderate Neutropenia at Screening** Mean ANC = 1,000 cells/µL G-CSF: 0.91 mcg/kg/day	**Normal ANC at Screening** Mean ANC = 4,300 cells/µL G-CSF: 1.09 mcg/kg/day

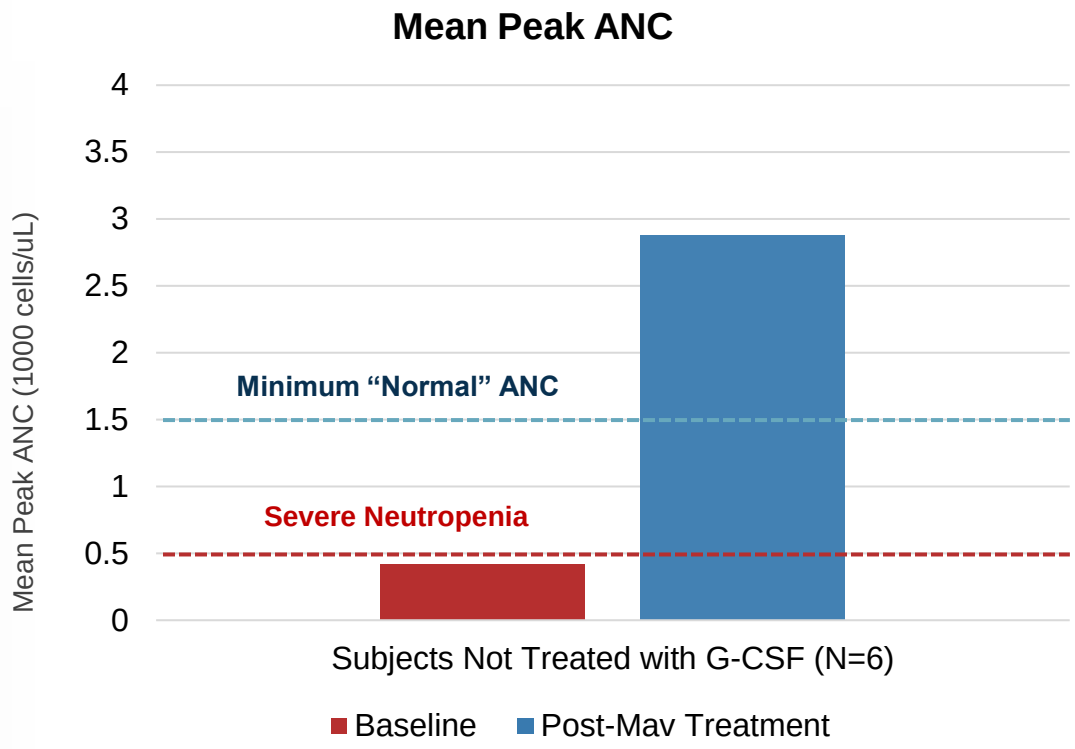
* Includes one participant with congenital neutropenia who was not on G-CSF but had baseline ANC > 1,500 cells/µL.

Sub-Analysis 1: Mavorixafor Monotherapy Normalized ANC in Neutropenic Patients

Kinetics and Mean Increase in ANC

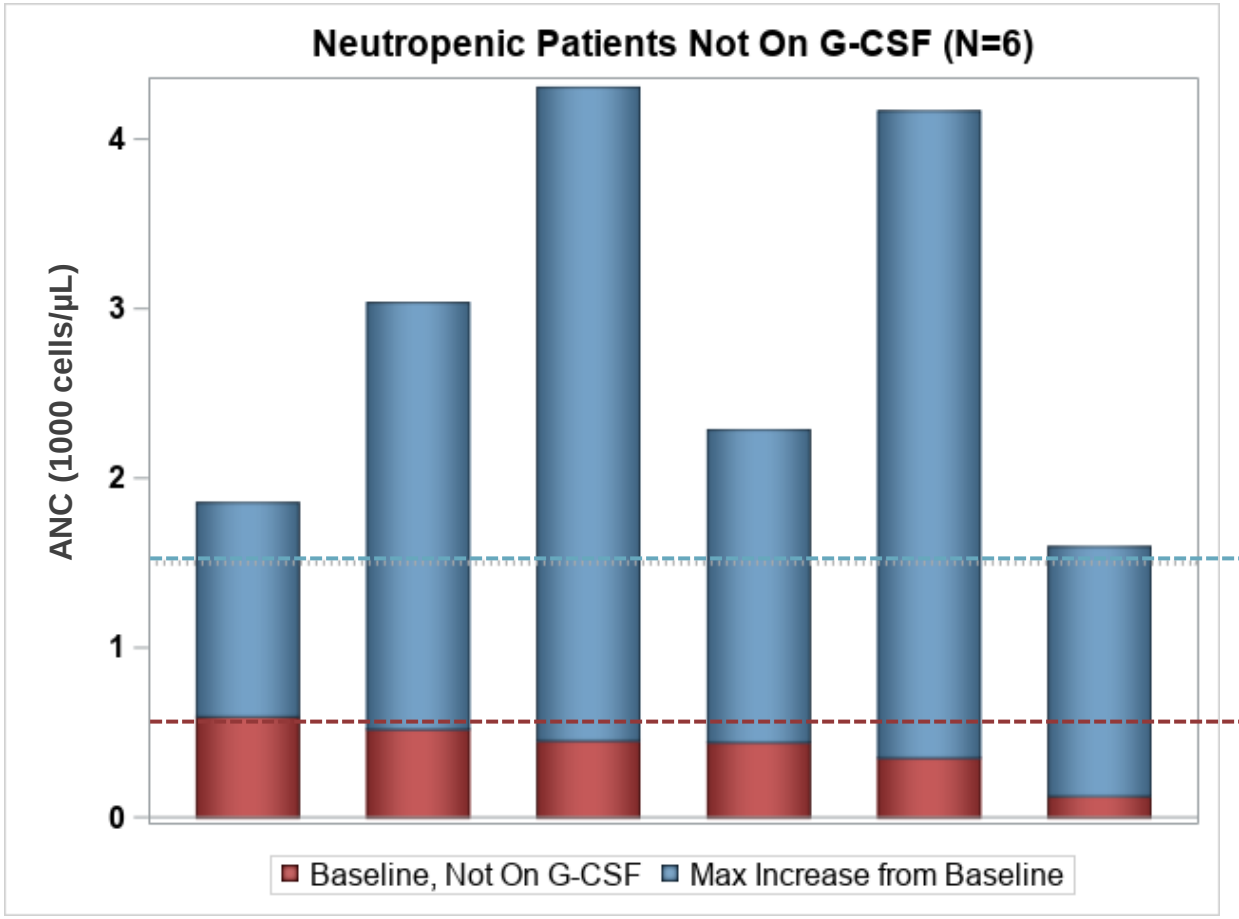
- Mavorixafor normalized ANC levels within 2 hours
- Mean ANC increase of ~2,500 cells/µL across all participants





Sub-Analysis 1: Mavorixafor Monotherapy Normalized ANC in Neutropenic Participants

Individual Participant Data



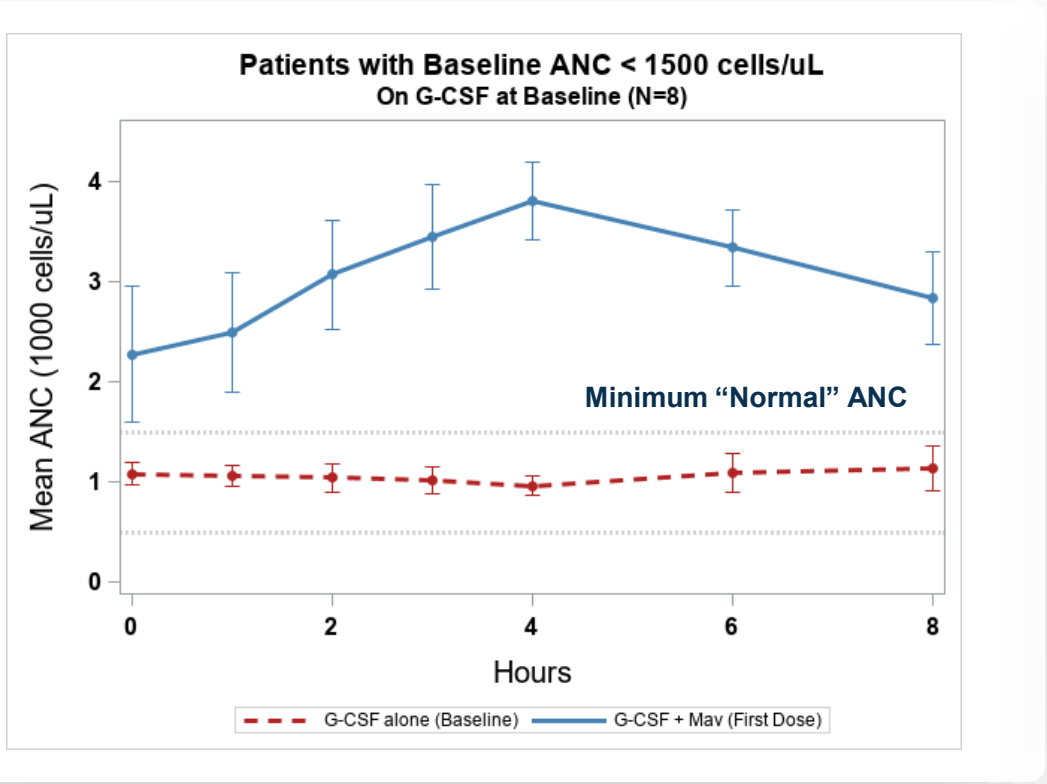
All patients had severe neutropenia pre-treatment

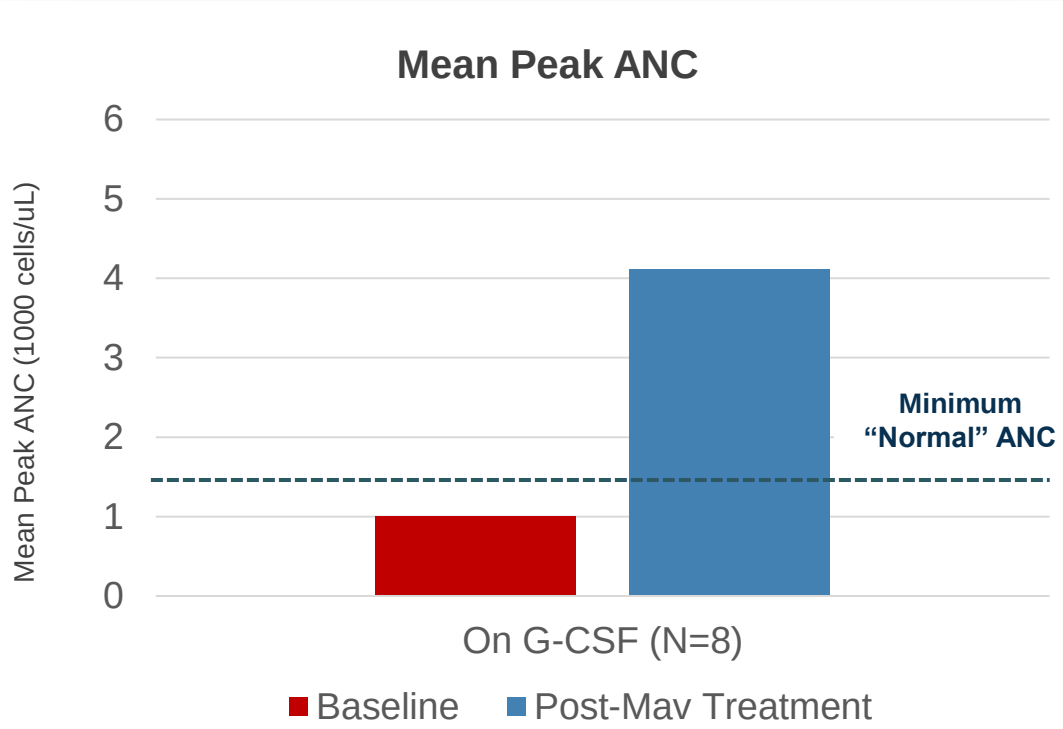
- All (100%) participants responded
- All (100%) achieved normalized ANC levels

Sub-Analysis 2: Mavorixafor + G-CSF Normalized ANC in Neutropenic Participants

Kinetics and Mean Increase in ANC

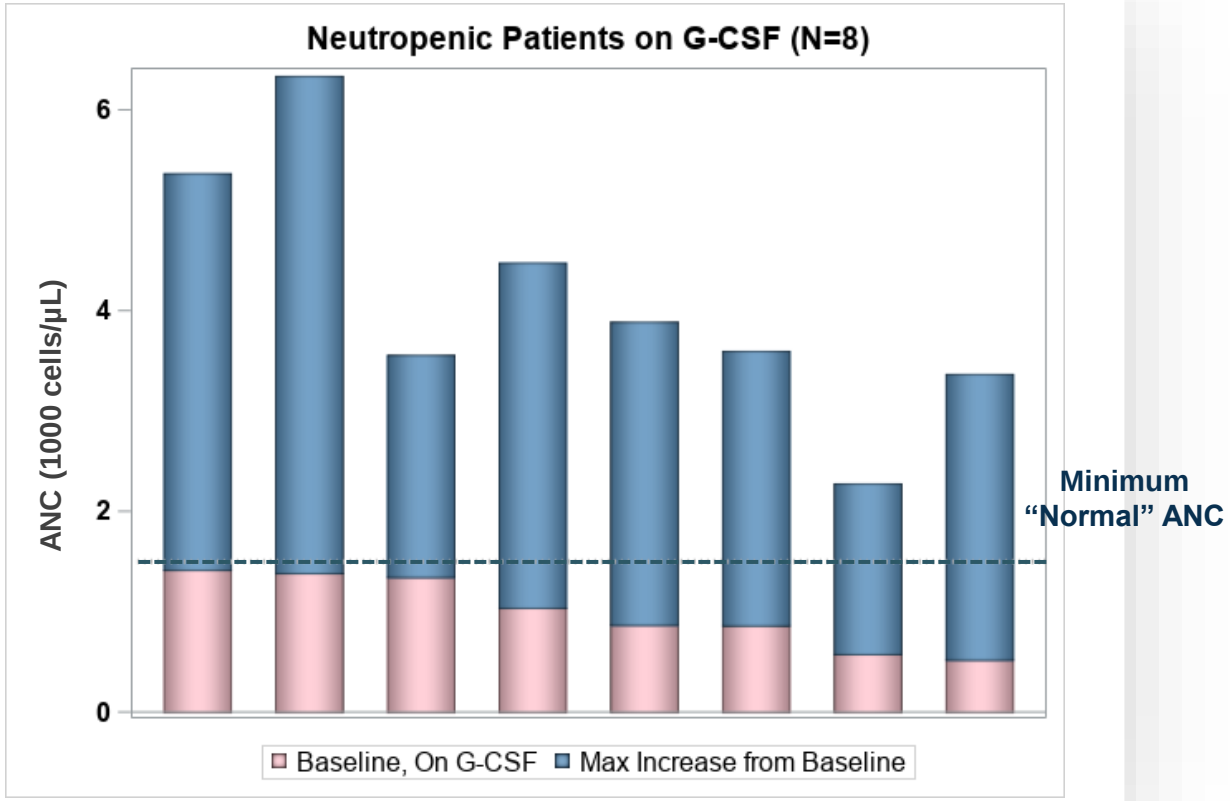
- ANC reached normal levels throughout dosing cycle
- Mean ANC increase of >3,000 cells/µL in neutropenic patients





Sub-Analysis 2: Mavorixafor + G-CSF Normalized ANC in Neutropenic Participants

Individual Participant Data



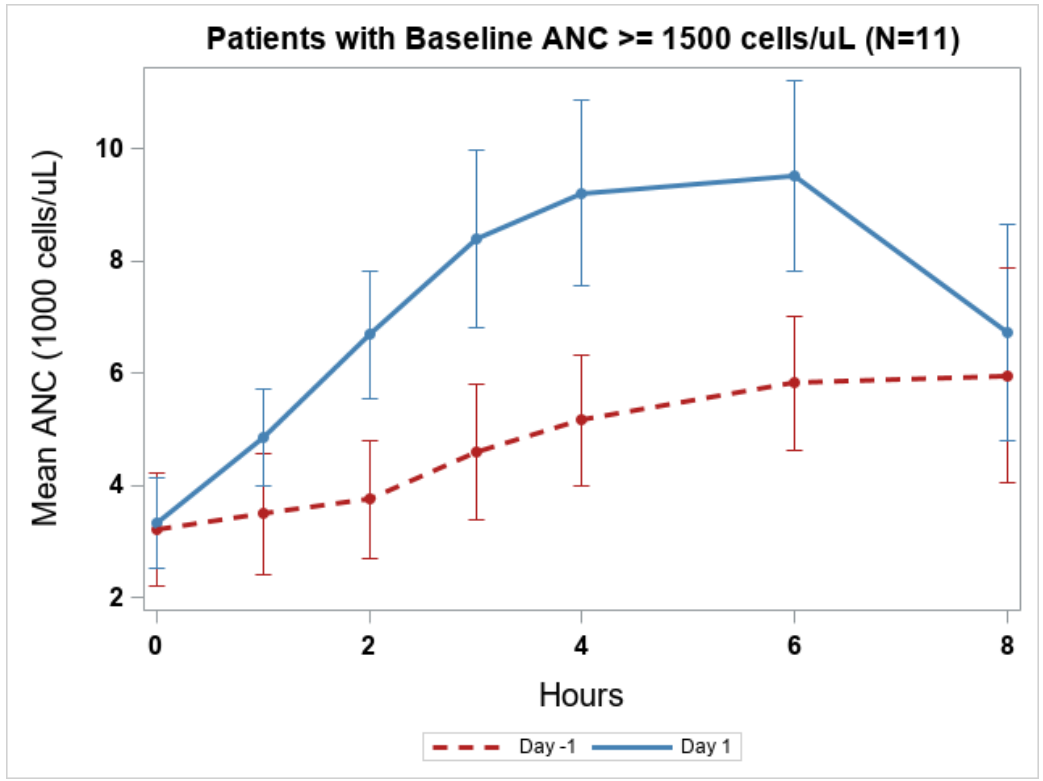
All are neutropenic; 5/8 (~60%) participants ***continued to have moderate or severe neutropenia although on G-CSF***

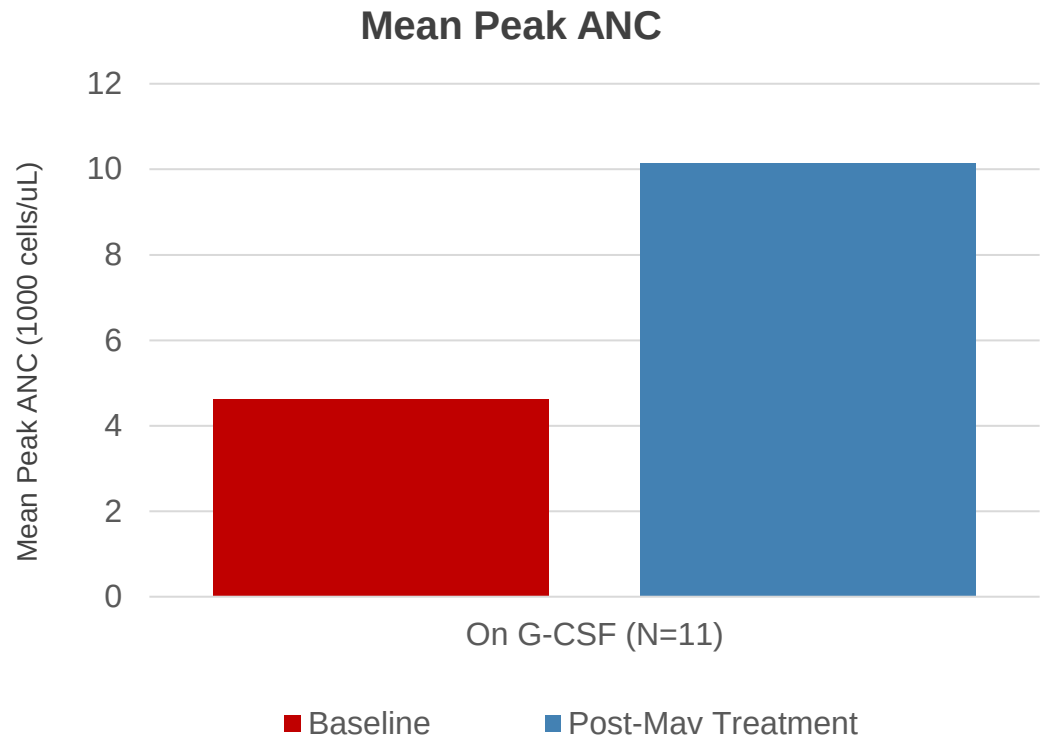
- All (100%) participants responded
- All (100%) achieved normalized ANC levels

Supports exploring potential of mavorixafor to reduce use of G-CSF

Sub-Analysis 3: Mavorixafor + G-CSF Increased ANC in Non-Neutropenic Participants

To Assess Potential for G-CSF Taper: *Kinetics and Mean Increase in ANC*





Includes one participant with congenital neutropenia who was not on G-CSF but had baseline ANC > 1,500 cells/µL.

Further supports exploring potential of mavorixafor to reduce use of G-CSF

Study Conclusions: Favorable Results Support Path Forward in CN

Primary Objectives Met
All Participants Responded

- All CN Disorders – Idiopathic, Cyclic and Congenital – responded to mavorixafor
- Increase in ANC of >2,000 cells/µL across all disorders

Potential for Mavorixafor Monotherapy

- Mavorixafor monotherapy increased ANC to normal levels in severe neutropenia
- All (100%) individuals responded and achieved normalized ANC

Data Support Exploration of Mav as G-CSF Replacement

- Mav increased ANCs to normal levels in neutropenic patients on G-CSF
- Mav increased ANCs robustly (2,000–5,000 cells/µL) in all patients treated with G-CSF

Well Tolerated Safety Profile
Consistent with previous studies

- Low-grade treatment-related adverse events were observed
- Safety data from prior studies support chronic dosing over years

Potential New, Oral Treatment for Chronic Neutropenic Disorders, including WHIM

Mavorixafor: potential to become "standard of care" across multiple CN disorders

ANC elevations and corresponding reduction in infection burden being assessed in Phase 3 4WHIM trial – **Q4 readout**

Good tolerability and reduction in treatment burden vs. G-CSF

Previous mavorixafor results suggest high likelihood of success

Oral, once daily treatment with well tolerated safety profile[1]

Durable increase in ANC levels when treated for up to four years[2]

Decreased frequency of infections in chronic studies in WHIM[2] and WM[3]

Significant unmet needs

Larger target market than previously anticipated

~50,000 patients in the U.S. with chronic neutropenia, including idiopathic, cyclical, and congenital

1. Dale, Blood, 2019. 2. Dale, ASH, 2021. 3. X4 WM = Waldenstrom's Macroglobulinemia; Data released in X4 Q3 Earnings Presentation, August 2022.

Significant Near-Term Milestones / Meaningful Growth Potential

Q3 2022

Phase 1b CN Results

Q4 2022

4WHIM Phase 3 Trial Readout

Amended[1] Phase 1b CN Protocol Initiation

1H 2023

CN Regulatory Path Clarity

ANC Durability in CN

G-CSF Taper in CN

Chronic Monotherapy Safety

2H 2023

WHIM NDA Filing

CN Phase 3 Ready

1. Phase 1b protocol amendment near completion: 6-month dosing in up to 50 patients to assess ANC durability, G-CSF taper, tolerability vs. G-CSF and other.

Sharp focus on chronic neutropenic disorders

Unparalleled expertise in immune system dysfunction and CXCR4 biology

Mavorixafor – a late-stage clinical CXCR4 antagonist candidate with broad commercial potential

Key mavorixafor clinical milestones expected over next 3 to 6 months

Strong balance sheet, with cash runway expected to fund operations into 3Q 2023