
# A Deeper Dive into Mavorixafor Phase 3 Data and Unmet Patient Needs in WHIM Syndrome

May 16, 2023

X4 PHARMACEUTICALS

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# Today’s Agenda

01 Welcome

02 Overview of Mavorixafor Opportunity

03 The Challenge of Infections in WHIM

04 New Phase 3 Data in WHIM

05 Path Forward: WHIM, CN Disorders, and Beyond

06 Conclusion and Q&A

# Today's Event Participants

**Charlotte Cunningham-Rundles, MD, PhD**
Professor of Pediatric Immunology, Icahn School of Medicine at Mount Sinai

**Jean Donadieu, MD, PhD**
Pediatric Heme-Oncology, Chronic Neutropenia Registry Coordinator Trousseau Hospital, Paris

**Peter Newburger, MD**
Professor of Pediatrics, Molecular, Cell, & Cancer Biology at UMass Chan Medical School

**Akiko Shimamura, MD, PhD**
Professor of Pediatrics at Harvard Medical School, Director Bone Marrow & MDS Program at Boston Children's

**Teresa Tarrant, MD, FAAAAI**
Assoc. Professor at Duke School of Medicine, Vice Chair, Translational Research Rheumatology, Immunology

**Gabrielle**
Diagnosed with WHIM

**Willow**
Diagnosed with WHIM

**Courtney**
Diagnosed with WHIM

**Paula Ragan, PhD**
X4 President & CEO

**Murray Stewart, DM, FRCP**
X4 Interim CMO

# Mavorixafor: Potential Breakthrough for Treating Chronic Neutropenic Disorders

## Only oral candidate in development to treat CN disorders, including WHIM syndrome

- Proven mechanism of action (MOA) / ability to increase white blood cells, including neutrophils
- Demonstrated tolerability in >200 individuals, some for >4 years
- Breakthrough Therapy Designation (BTD) and Orphan Drug Designation in first indication: WHIM syndrome; Priority Review Voucher (PRV) eligible
- Patent protection expected through 2038

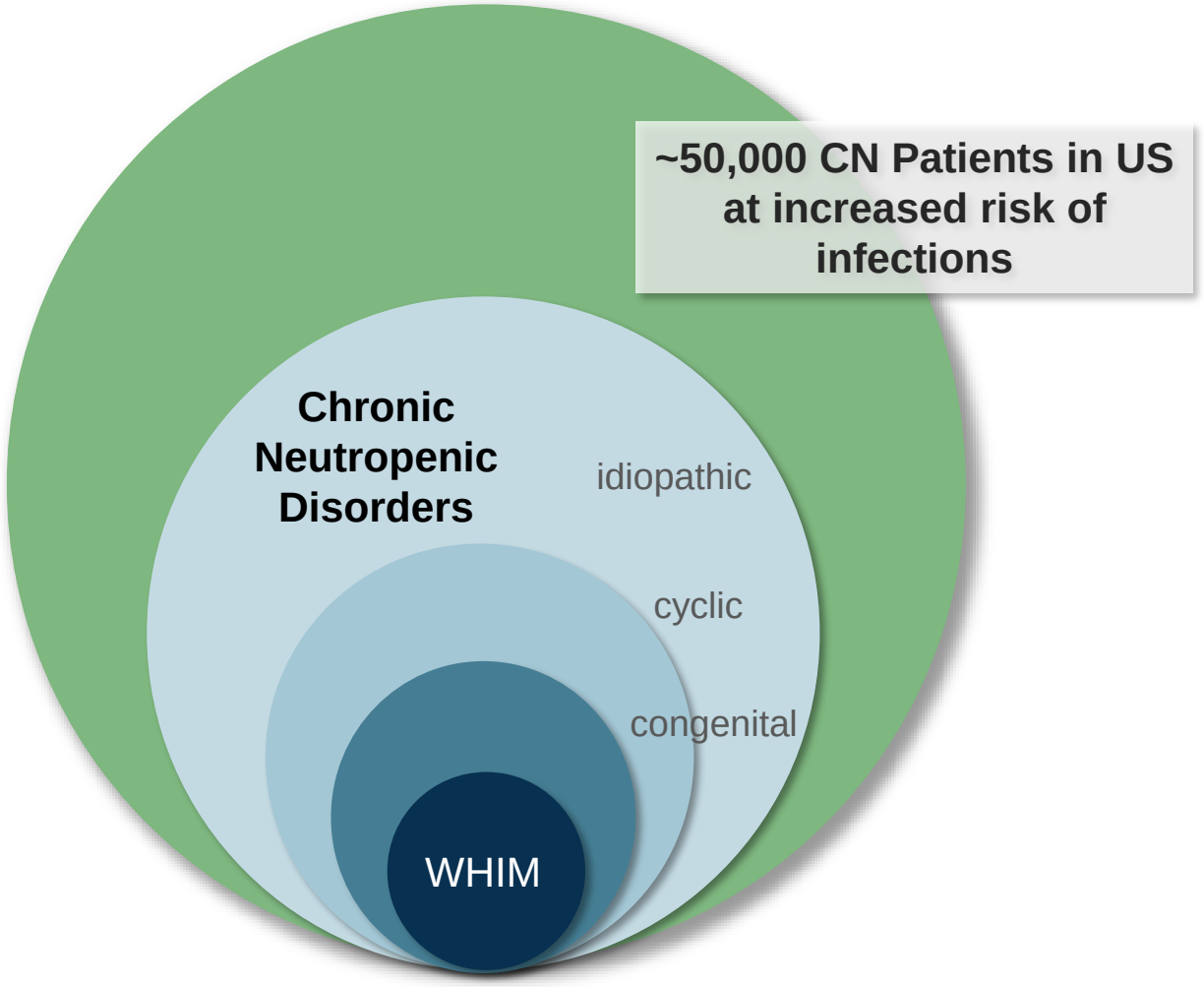
# Mavorixafor's Market Potential: Addressing Infection Risk in CN and Beyond

## Chronic Neutropenic (CN) Disorders

- Increased risk of serious infections
- Neutropenia
- ~50,000 estimated US patients[1]

## WHIM Syndrome

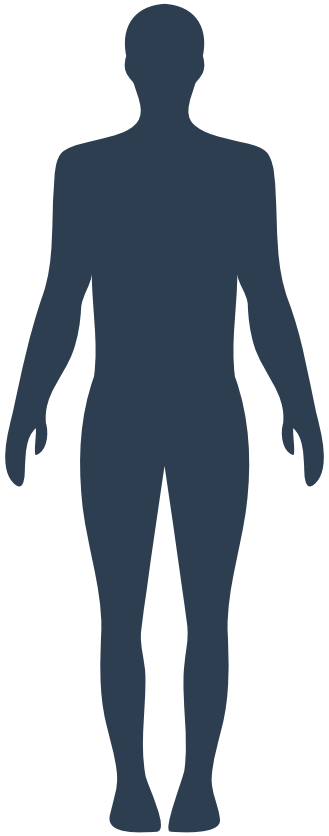
- Increased risk of serious infections
- Neutropenia and lymphopenia
- >1,000 estimated US patients[2]



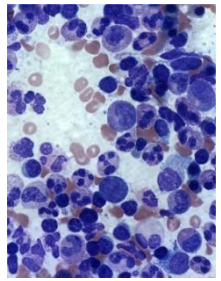

1. U.S. Prevalence Based on ICD-10 Code Research, Average Across 3 Years (2018, 2019, & 2021); >90% greater than 18 years of age, ~2/3 female, mixed G-CSF use. 2. Company market research. Qessential market research, 2019 and IPM.ai artificial intelligence study, 2020.

# WHIM[1] Syndrome: Poorly Functioning Immune System, Starting from Birth

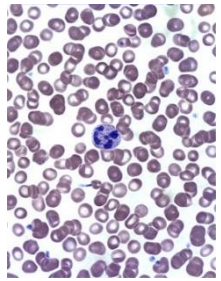
*Clinical diagnosis driven by over-signaling in the CXCL12/CXCR4 pathway*



WHIM Disease Bone Marrow[2]



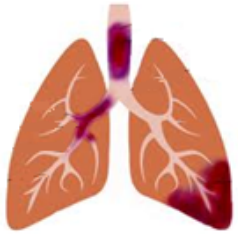
Healthy Bone Marrow[2]



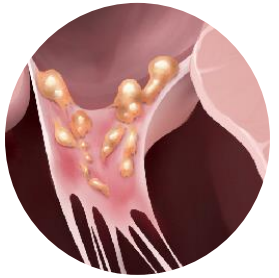
*Decreased white blood cell counts & impaired cell maturation lead to immune system dysfunction and increased risk of infections*

## Increased Risk of Infections

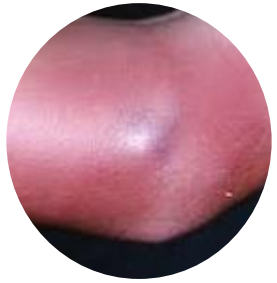
**Ear, Sinus, and Lung:** Upper/Lower Respiratory Tract Infections



**Heart:** Endocarditis



**Skin:** Cellulits



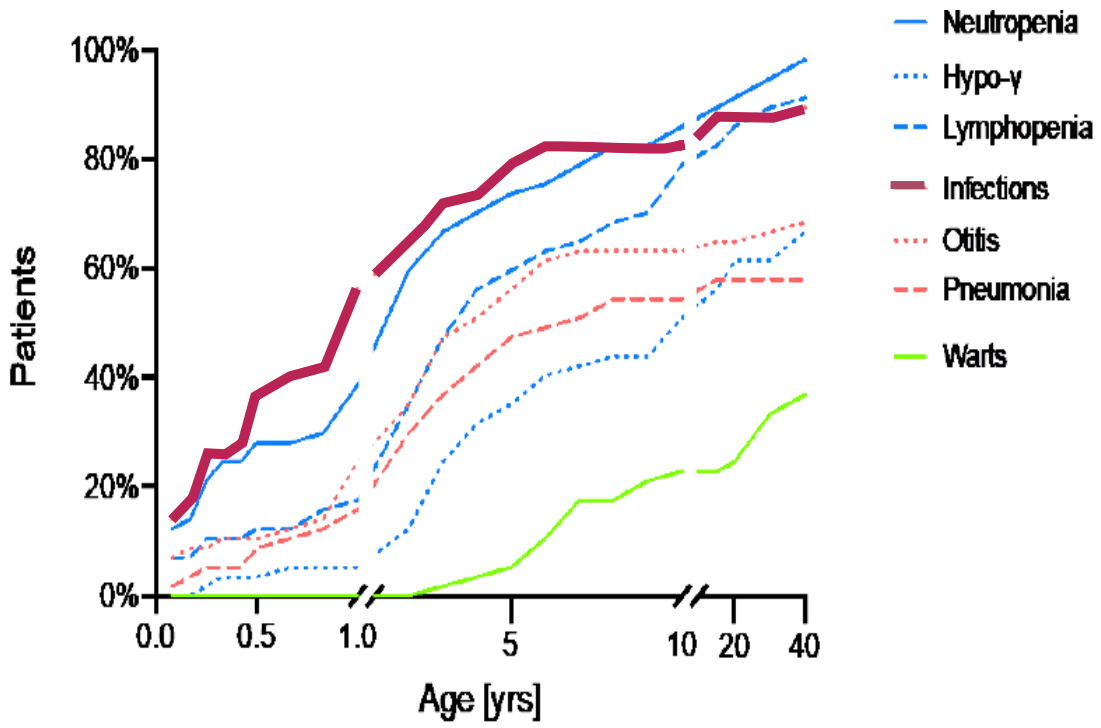
**Genitourinary Areas:** HPV-related Cancers

1. **WHIM = Warts, Hypogammaglobulinemia, Infections and Myelokathexis**
2. McDermott: Stiehm's Immune Deficiencies 2014, Pages 711-719

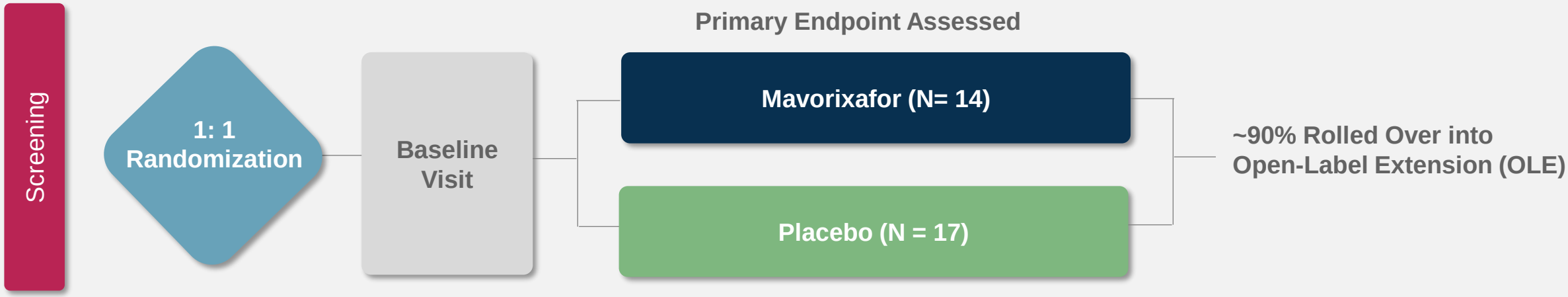
# Infection Risk Tracks with Neutropenia in WHIM Syndrome

- Infections start within the first year of life
- Neutropenia tracks with infection risk from birth and continues as patients age
- Most patients have both neutropenia and infections by the second decade of life

## Relationship Between Neutropenia & Infections in WHIM Syndrome Natural History



# 4WHIM Pivotal Phase 3 Clinical Trial Overview




**Baselines:** 100% of patients had severe chronic neutropenia (median ANC ~200 cells/μL) and chronic lymphopenia (median ALC ~500 cells/μL)

**Primary & First Secondary Endpoint**: Time above Threshold (TAT) for ANC and ALC calculated as mean of the 13, 26, 39, and 52-week

**Infection-Related Assessments**: Data reviewed by blinded, centralized, independent adjudication committee for rate, severity, duration

**Safety Assessments:** Throughout the 52-weeks by an independent Data Safety Monitoring Board

**GOAL LABEL**: Indicated for the treatment of people aged 12 and above **diagnosed with WHIM syndrome**

ANC = absolute neutrophil count; ALC = absolute lymphocyte count

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**Phase 3 Clinical Trial**

# Mavorixafor

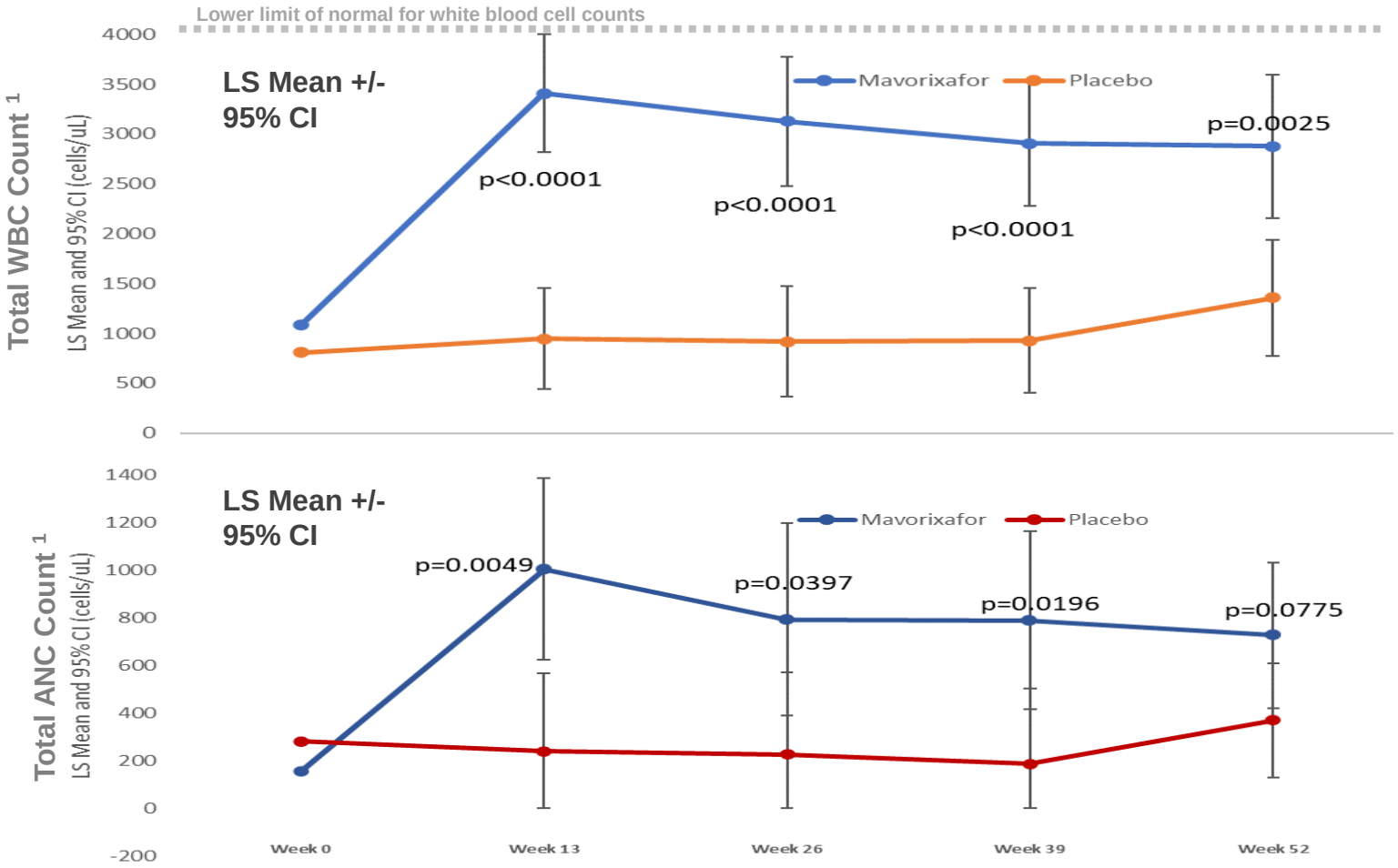
demonstrated significant clinical benefit & favorable safety profile


**4WHIM trial** met primary endpoint of time above threshold for absolute neutrophil counts ($TAT_{ANC}$) and key clinical benefit assessments

**Mavorixafor** achieved statistically significant increases in all white blood cells – neutrophils, lymphocytes, & monocytes – versus placebo

# Mavorixafor MOA Proven

## Statistically Significant Increases in Total White Blood Cell (WBC) and Absolute Neutrophil Counts (ANC) over the 52 Week Study




| | | | | | |
|---|---|---|---|---|---|
| Mavorixafor n: | 13 | 13 | 11 | 9 | 10 |
| Placebo n: | 16 | 16 | 17 | 17 | 17[2] |

## Increased Cell Counts

- Statistically significant, durable increases in WBC and ANC
- Absolute WBCs approach near normal levels
- Statistically significant, durable increases in all WBC subtypes[3]
  - Absolute Neutrophil Count (ANC)
  - Absolute Lymphocyte Count (ALC)
  - Absolute Monocyte Count (AMC)

1. Calculated as the mean of absolute cell counts over the 24-hr assessment period.
2. At week 52, 3 of 17 placebo patients were given mavorixafor in advance of their TAT measurements as they entered the open-label portion of the study. All data are included in ITT analysis.
3. Data on file.

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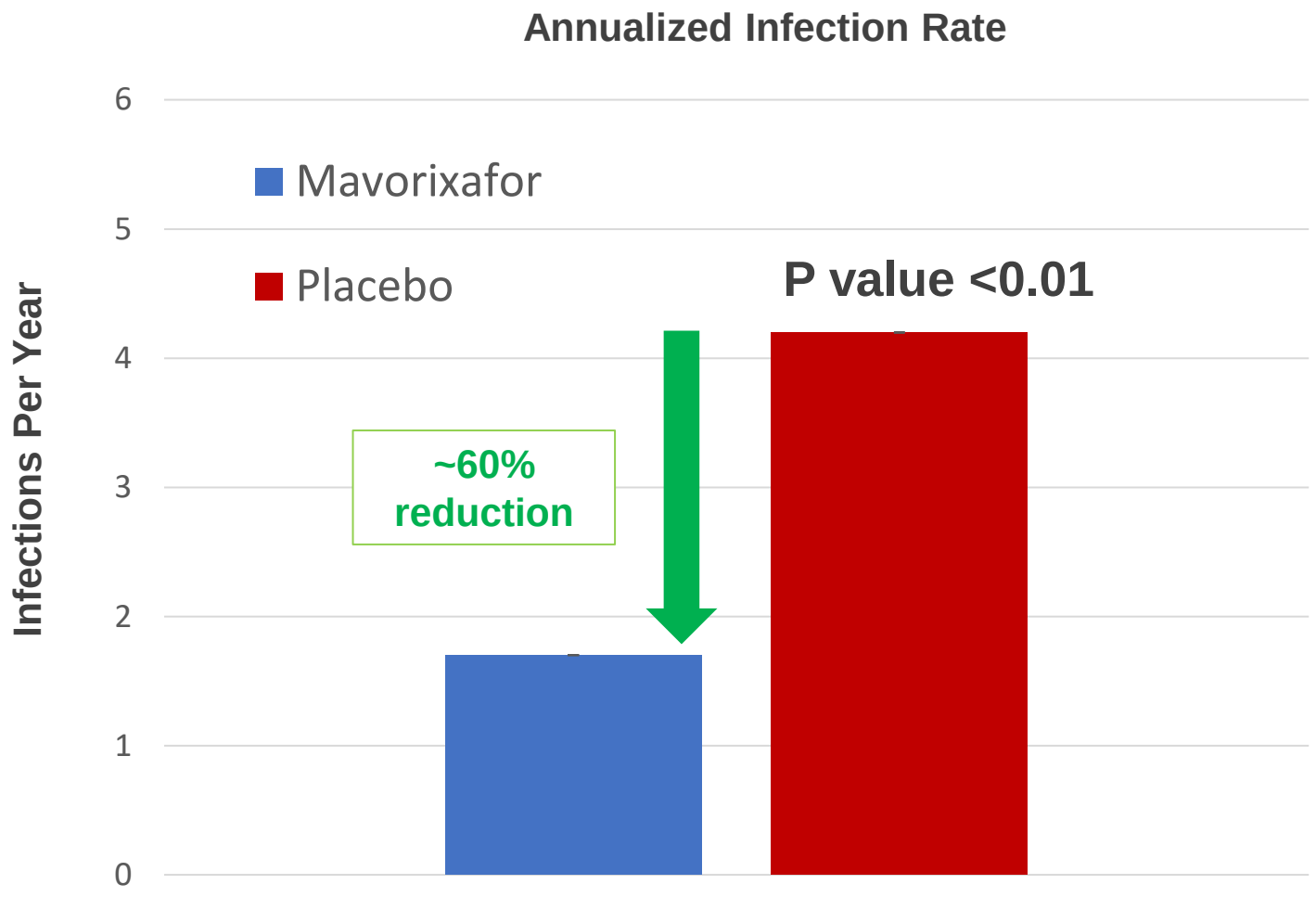
## Phase 3 Clinical Trial


Infections Are The Major Problem in WHIM:
**Mavorixafor Delivered Benefit**

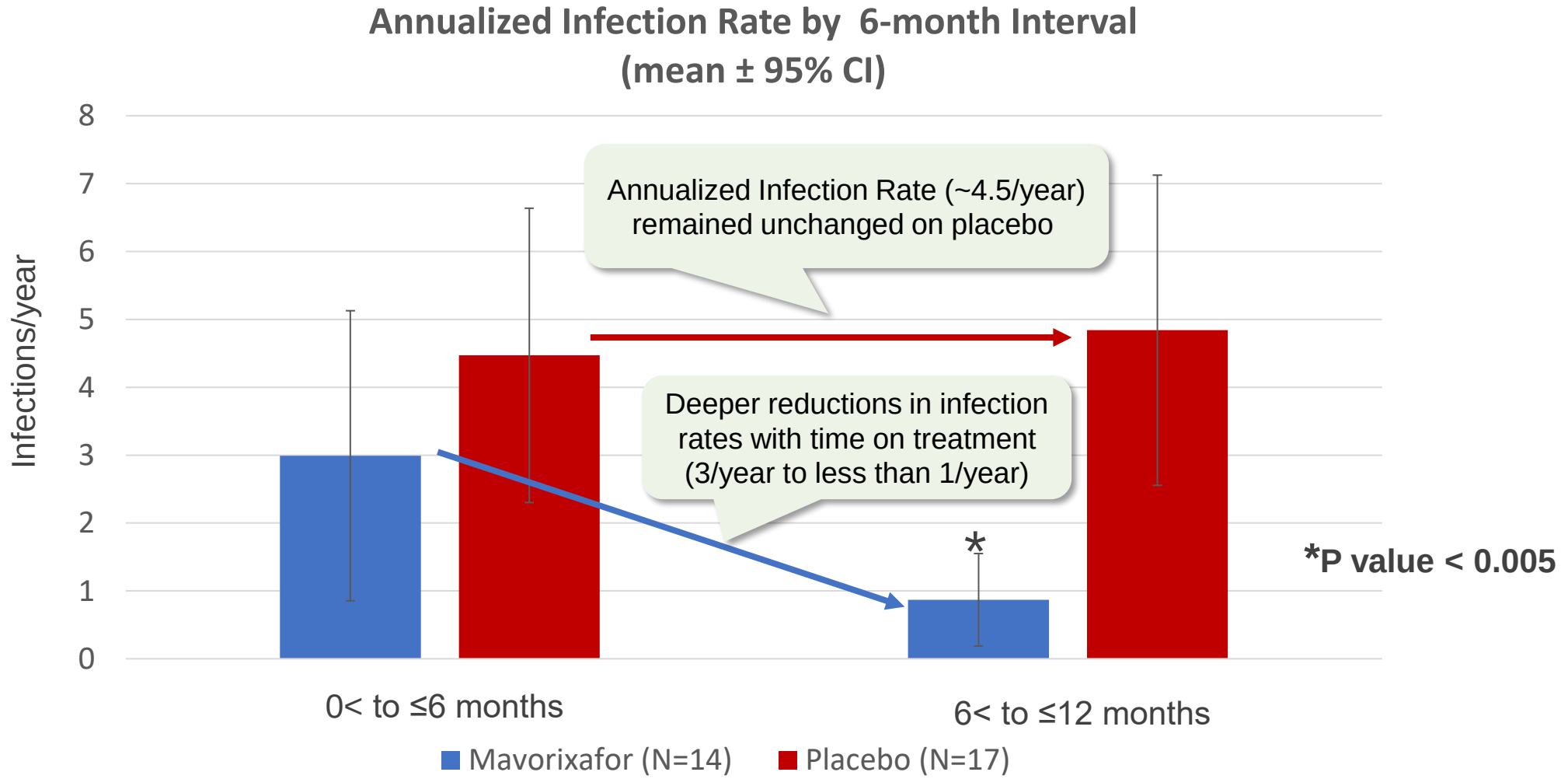
# Statistically Significant 58% Reduction in Annualized Infection Rate

*Mavorixafor versus placebo (ITT population)*



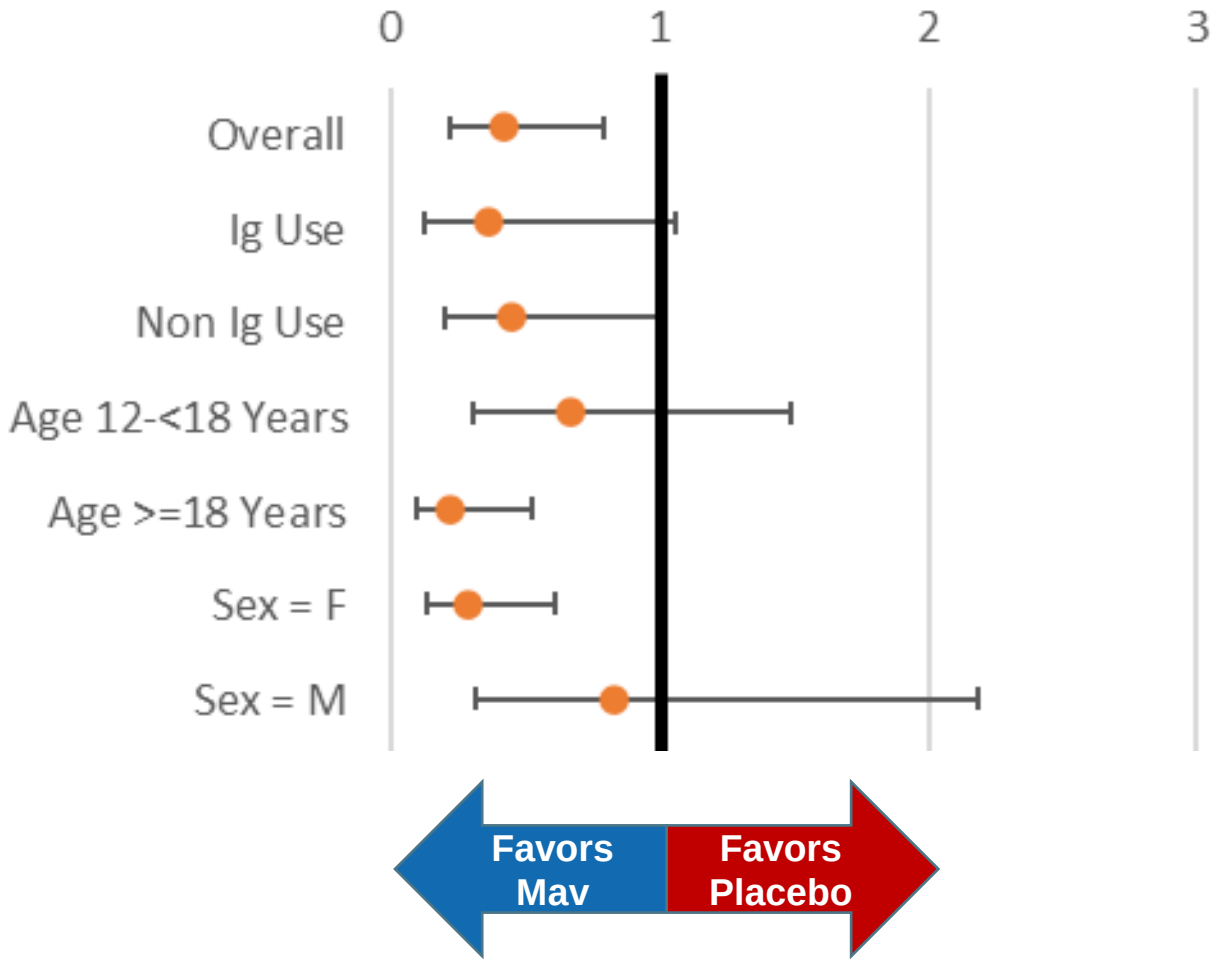
# Deeper Reductions in Infection Rate with Time on Mavorixafor Treatment

*First 6-months vs. second 6-months (ITT population)*



# Mavorixafor Reduced Infection Rate Consistently Across Subgroups

**Treatment Difference in Infection Rate**
**(ratio of mavorixafor over placebo)**

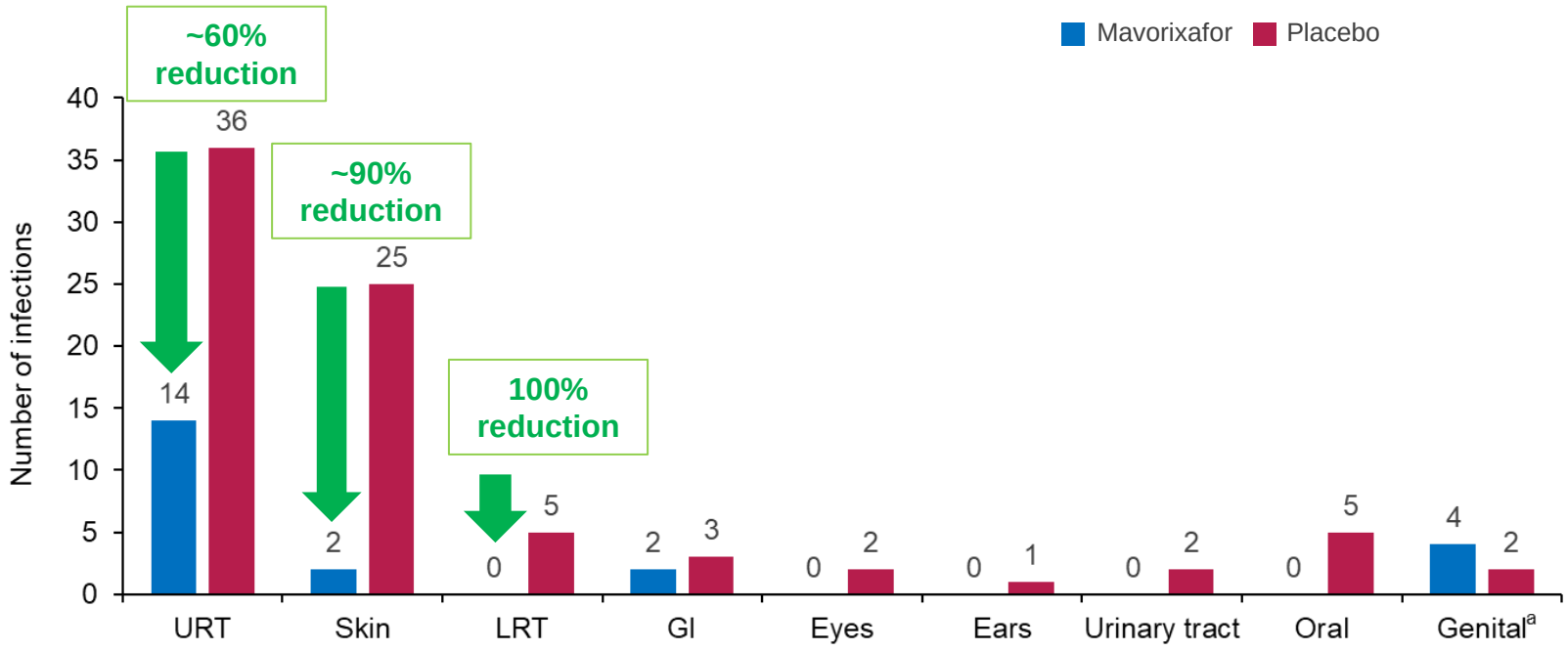



**All Sub-Groups Had Benefit Favoring Mavorixafor Treatment**

- ✓ In those with or without concomitant Ig treatment
- ✓ In both adolescents and adults
- ✓ In both women and men

# Mavorixafor Reduced Infections Across Most Organ Systems

## Reported Benefit Observed in Bacterial, Viral, and Fungal Infections




URT, upper respiratory tract; GI, gastrointestinal; LRT, lower respiratory tract. [a]Excluding warts.

## Assessment of Warts

First placebo-controlled study assessing warts in WHIM

- ~70% of patients had warts
- Warts assessed at wks 0, 26, and 52
- Photographic images captured
- Visual changes scored via central, blinded committee

Results

- No difference between groups in reducing pre-selected, existing warts
- Fewer participants on mavorixafor developed new warts at week 52

## Phase 3 Clinical Trial

Reduced RATE of infections

**Reduced SEVERITY of infections**

Reduced DURATION of infections

Infections are the Major Problem in WHIM:
**Mavorixafor Delivered Benefit**

# **Severity of Infections:** Assessed by Standard CTCAE[1] Criteria

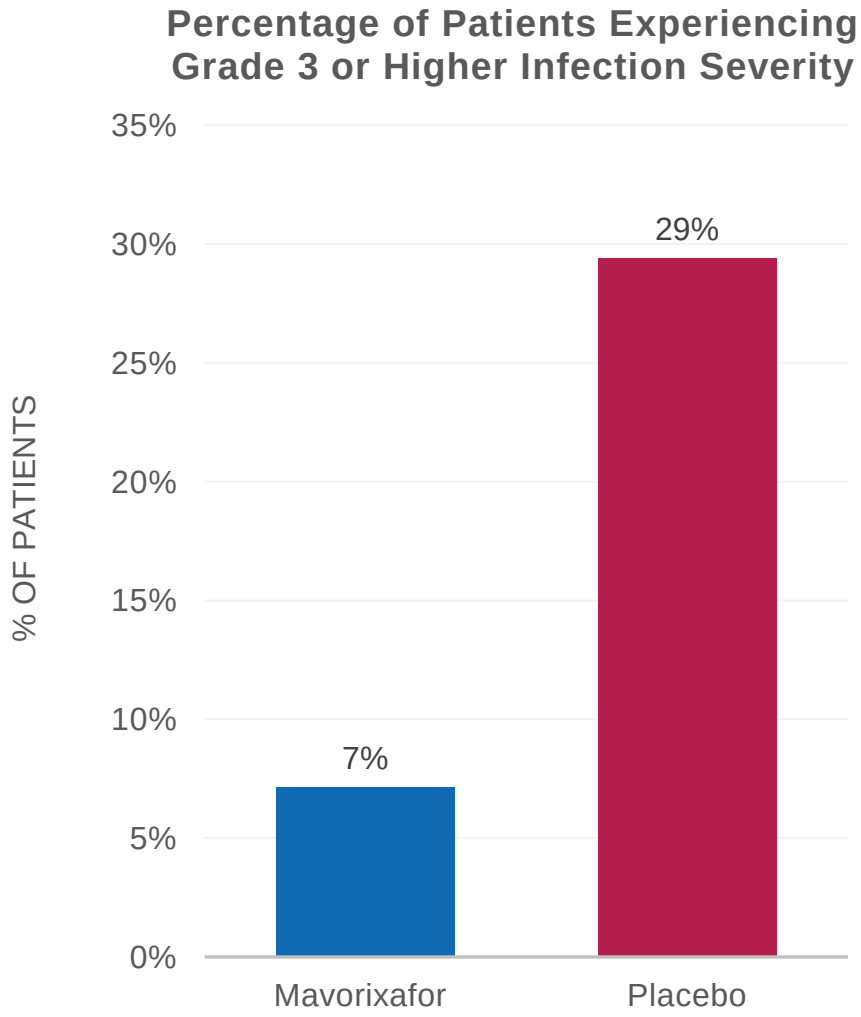
- **Severe Infections: Grade 3 or Higher**
  - Require significant intervention (oral and/or IV antibiotics) and/or hospitalization
  - **Assessed by blinded, centralized, independent, adjudication committee**

| Severity Scale | Description |
|---|---|
| Grade 3 | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living (ADL**) |
| Grade 4 | Life-threatening consequences; urgent intervention indicated. |
| Grade 5 | Death |

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

1. CTCAE is defined as "Common Terminology Criteria for Adverse Events" and established by the US Dept of Health and Human Services: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf

# More Patients on Placebo Experienced Severe[1] Infections Over 52 Weeks




| | Mavorixafor (n=14) | Placebo (n=17) |
|---|---|---|
| **CTCAE Criteria** | N | N |
| Grade 1 / Grade 2 | 10 | 11 |
| **Grade 3** | **1*** | **4** |
| **Grade 4** | 0 | **1** |
| **Grade 5** | 0 | 0 |

***Grade 3 infection on mavorixafor treatment occurred during first 3 months of treatment; rate of severe infections on placebo unchanged over 52-week period**

**Zero Grade 3 infections on mavorixafor after the first three months of treatment**

1. Severe infections are those Grade 3 or higher by CTCAE criteria.

# Patients on Placebo More Heavily Treated with Anti-bacterials

*Consistent with higher rate and severity of infections*

- **10/17 (59%) on placebo were administered anti-bacterials/penicillins vs. 3/14 (21%) on mavorixafor**
  - Amoxicillin or amoxicillin+other combination were most commonly prescribed anti-bacterial treatments

| Anti-Bacterial Medications Used in Study | Placebo (n=17) | Mavorixafor (n=14) | Total (n=31) |
|---|---|---|---|
| | N (%) | N (%) | N (%) |
| Beta-lactam anti-bacterials, penicillins | 10 (59) | 3 (21) | 13 (42) |

**Mavorixafor-treated participants experienced fewer infections and needed less treatment**

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## Phase 3 Clinical Trial

Reduced RATE of infections

Reduced SEVERITY of infections

**Reduced DURATION of infections**

Infections are the Major Problem in WHIM:
**Mavorixafor Delivered Benefit**

# Total Time with Infection Reduced by >70% with Mavorixafor vs. Placebo

- Mean total time with infection: **~2 weeks on mavorixafor vs. ~7 weeks on placebo**
- Median total time with infection also **showed (~75%) reduction**

**Total Time with Infection**
(in days)

| | Mavorixafor (n=14) | Placebo (n=17) |
|---|---|---|
| | | |
| Mean (SD) | 14.1 (2 weeks) | 49.1 (7 weeks) |
| Median | 8.5 | 32.0 |
| Min, Max | 0, 43 | 8, 134 |

# Oral Mavorixafor was Well Tolerated in the Trial

*Top-line safety data summary for randomization period*

## Overall

- No treatment-related Serious Adverse Events (SAEs)
- No treatment-limiting toxicities
- No discontinuations due to safety events
- ~90% of patients continued into the Open Label Extension study

## Other Adverse Events

- Most related to background disease (infections and low platelets)

# Safety Assessment: Supports Chronic Dosing for Mavorixafor

- Placebo arm had increased (3x to 4x) infections/infestations and respiratory disorders
- Mavorixafor arm had increased skin & GI disorders
  - No discontinuations - all were mild, all resolved
- Other safety assessments showed balance between two arms and/or deemed non-drug related

| | Placebo (n=17) | | Mavorixafor (n=14) | | Total (n=31) | |
|---|---|---|---|---|---|---|
| **System Organ Class** | Subjects N (%) | Events | Subjects N (%) | Events | Subjects N (%) | Events |
| | | | | | | |
| Any TEAE | 17 (100) | 143 | 14 (100) | 88 | 31 (100) | 231 |
| Infections and infestations | 17 (100) | 96 | 11 (79) | 28 | 28 (90) | 124 |
| Respiratory, thoracic and mediastinal disorders | 6 (35) | 9 | 2 (14) | 3 | 8 (26) | 12 |
| Skin disorders | 3 (18) | 6 | 8 (57) | 11 | 11 (36) | 17 |
| GI disorders | 2 (12) | 2 | 5 (36) | 6 | 7 (23) | 8 |

## Path Forward: Preparing for our First NDA Regulatory Submission

- ✓ Pre-NDA meeting with FDA completed in early Q2
  - WHIM Phase 3 clinical and other data discussed
- ✓ Overall favorable commentary and guidance

**US NDA submission for mavorixafor in the treatment of WHIM syndrome remains on track for early 2H 2023**

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**X4 Eligible for Priority Review Voucher (PRV)**

# Preparation Underway for Potential 1H 2024 US Launch in WHIM Syndrome

## 1 Building the WHIM Syndrome Community

- Establish X4 as a trusted partner with key stakeholders
- Educate on WHIM syndrome, highlighting unmet need and enabling better patient identification
- Support earlier diagnoses leading to better patient outcomes

## 2 Ensuring Broad Patient Access

- Communicate the mavorixafor value proposition
- Implement distribution and supply chain
- Engage with Payers to ensure rapid reimbursement

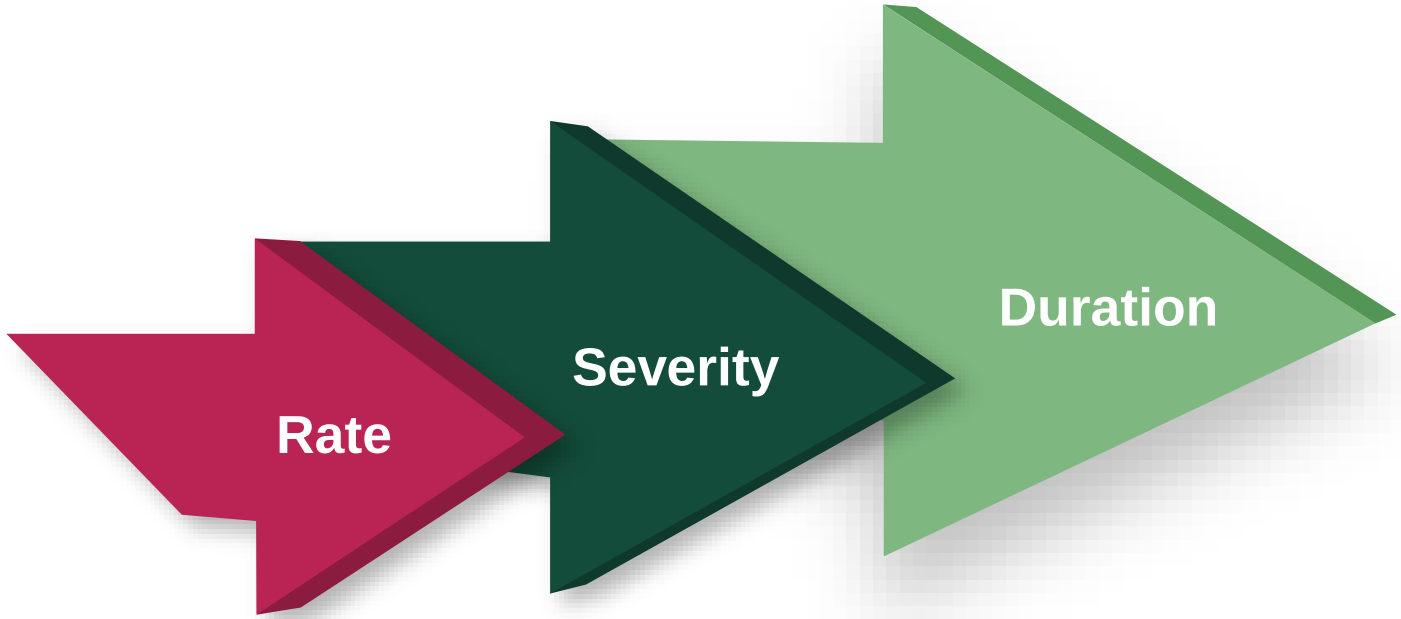
## 3 Evolving X4 to a Fully Integrated Biotech

- Build a rare disease commercial organization
- Establish infrastructure and capabilities
- Coordinate cross-functional launch readiness

# Leveraging Our Success in WHIM into Chronic Neutropenic Disorders

## WHIM Phase 3: Provides Proof of Concept Supporting CN

***Increased Absolute Neutrophil Counts (ANC) and Clinical Benefit in Reducing Infection Burden***




**Mavorixafor**

Potential oral, well tolerated, once-daily option for CN

- Exploring use in idiopathic, cyclic, and congenital chronic neutropenic
- Phase 2 Study ongoing
- Potential Phase 3 trial in 2024

# Maximizing Mavorixafor Potential to Address Infection Risk in CN and Beyond

**WHIM Disease**
>1,000 est. US Patients

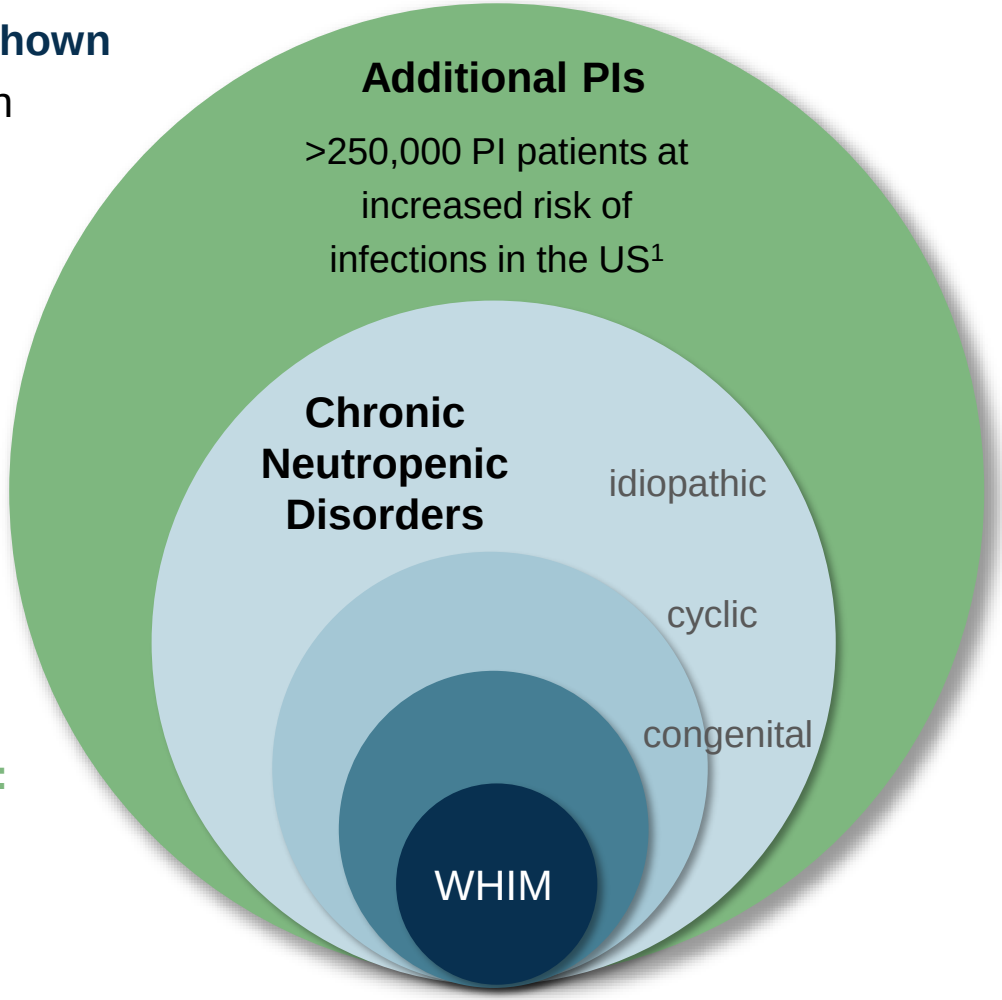
**Significant Infection Benefit Shown**
On track for US NDA submission early 2H 2023

**Chronic Neutropenic Disorders**
~50,000 est. US Patients

**Phase 2 CN trial data and registration path clarity**
Expected 2Q/3Q 2023

**Primary Immunodeficiencies (PIs)**
>250,000[1] est. US Patients
(potential subset for further study)

**Additional WHIM Phase 3 Data: Innate & adaptive immunity**
Data anticipated 1H 2024




1. Boyle JM, Buckley RH. Population prevalence of diagnosed primary immunodeficiency diseases in the United States. *J Clin Immunol*. 2007 Sep;27(5):497-502

# Thank You!