# WHIM Syndrome Management: The First FDA Approval for Patients

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# Resource Information

## About This Resource

These slides are one component of a continuing education program available online at MedEd On The Go titled WHIM Syndrome (A Chronic Neutropenic Disorder): Uncouple the Complex for HCPs and Patients

**Program Learning Objectives:**

- Gain an understanding of WHIM syndrome as a rare PID/ chronic neutropenic disorder with diverse clinical presentations
- Implement strategic measures to improve the early identification of WHIM syndrome patients for prompt assessment and diagnosis to avoid potential complications and long-term sequelae
- Understand the CXCR4 pathway dysregulation and how it relates to the underlying causes of WHIM syndrome
- Garner an understanding of the limitations of current approaches for WHIM syndrome and potential new approaches for patients

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# CXCR4 Antagonists are being evaluated in Clinical Trials for WHIM

| | Plerixafor[22-25, 32] | Mavorixafor[25-31] |
|---|---|---|
| Drug class | Small molecule | Small molecule |
| Target | CXCR4 antagonist | CXCR4 antagonist |
| Route of administration | Subcutaneous injection | Oral |
| Approved indications | Use in combination with G-CSF for autologous transplantation of bone marrow cells in patients with non-Hodgkin lymphoma or multiple myeloma | Approved by the FDA in April 2024 |
| Clinical studies | • WHIM syndrome<br>• HIV infection (discontinued; limited bioavailability) | • WHIM syndrome<br>• Waldenström's macroglobulinemia<br>• Congenital and cyclic neutropenia<br>• Chronic idiopathic neutropenia |

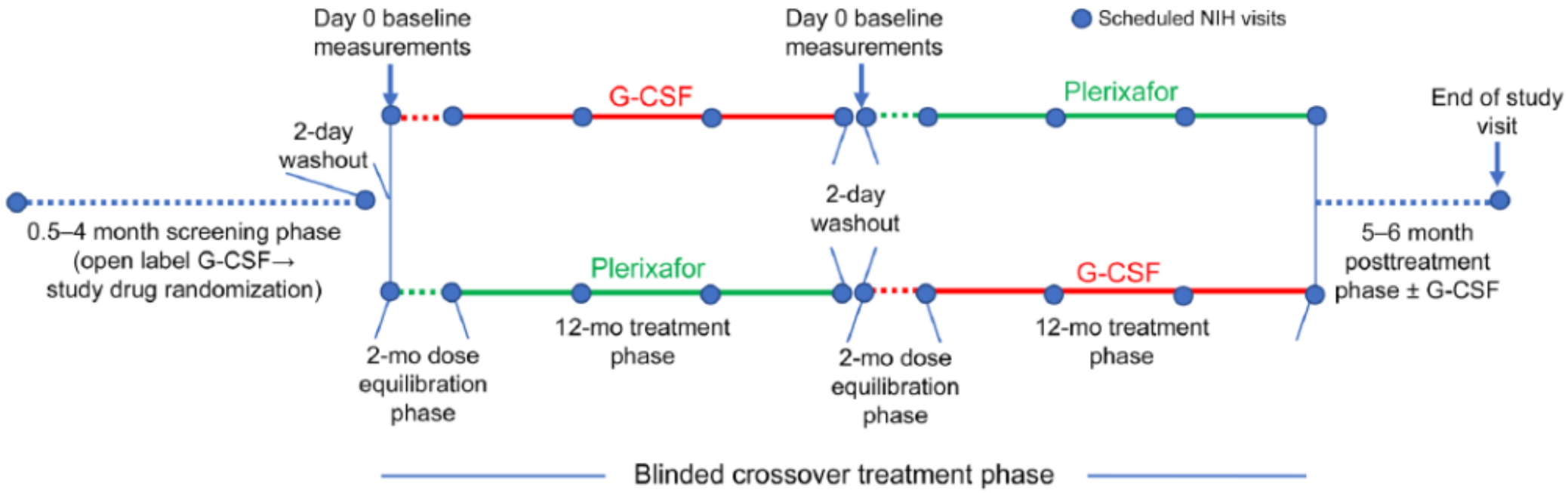
# Phase 3: Randomized, Quadruple-masked, Crossover Trial of CXCR4 antagonist, Plerixafor, vs. G-CSF in WHIM syndrome[32]

## Demographics and Baseline Characteristics

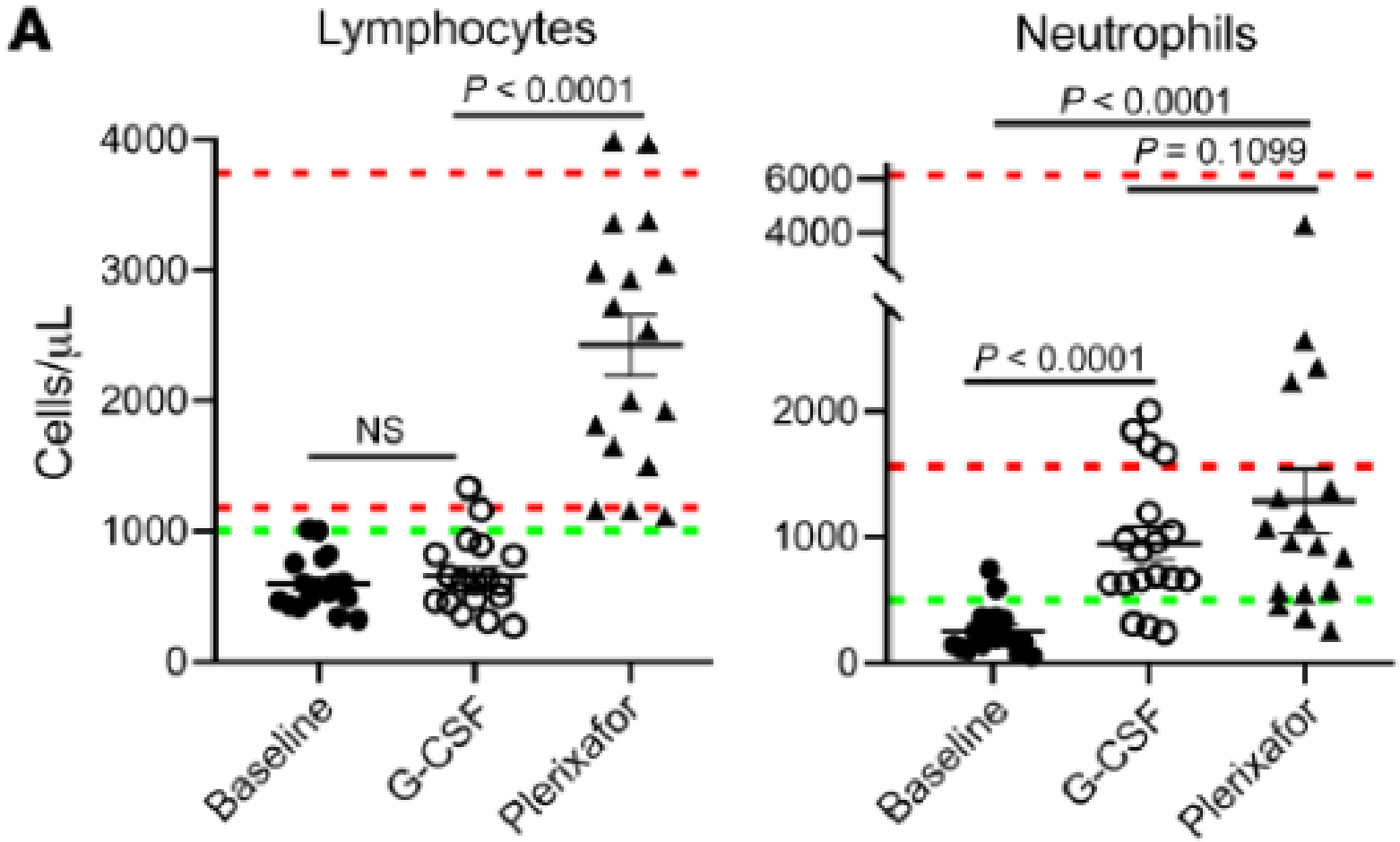
| | Plerixafor vs. GCSF (n=19) |
|---|---|
| **Adolescents 15 to <18 y, n (%)** | 5 (26) |
| **Adults ≥18 y, n (%)** | 14 (74) |
| **Sex, female, n (%)** | 13 (68) |
| **Previous immunoglobulin usage, n (%)** | 8 (42) |
| **Screening ANC (cells/μL)** ± SEM | 246 ± 42 |
| **Screening ALC (cells/μL)** ± SEM | 597 ± 48 |

All patients had previously identified CXCR4 pathogenic mutations, G-CSF = Granulocyte Colony Stimulating Factor

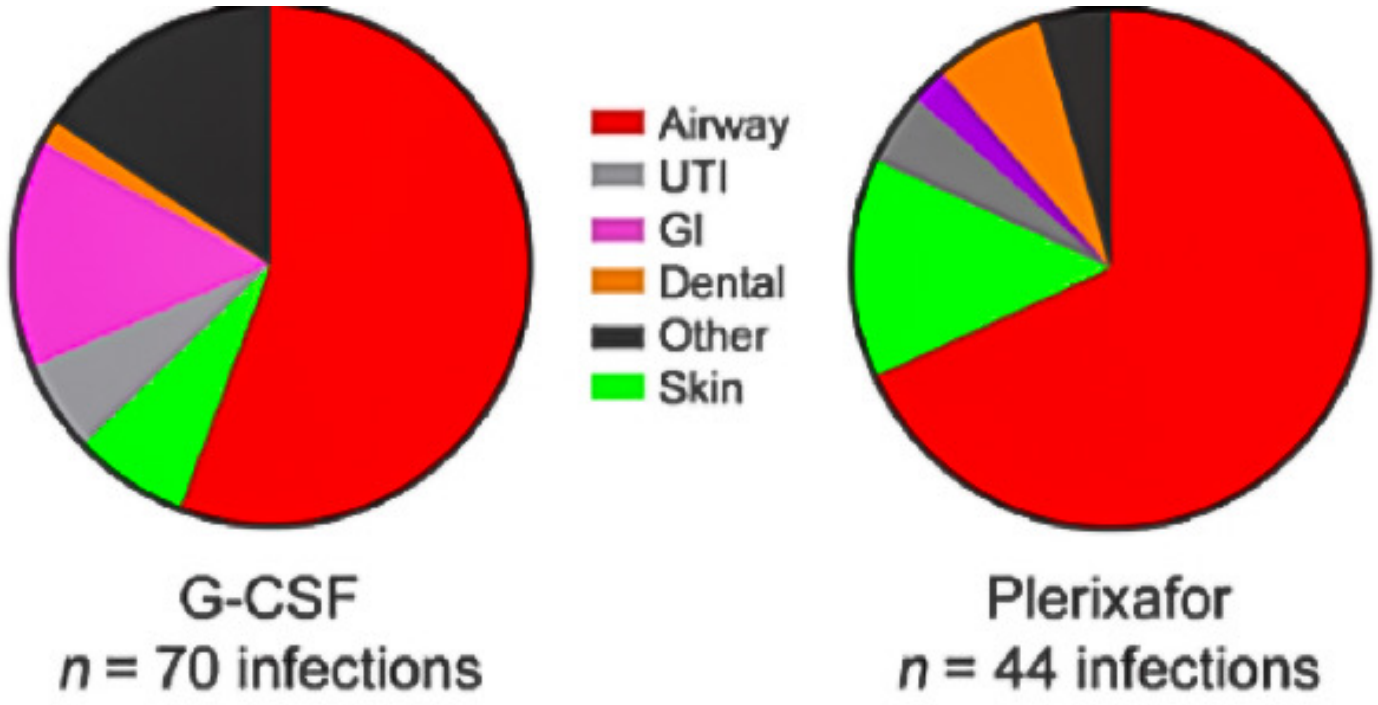
# Phase 3 Plerixafor vs. G-CSF Trial Design[32]



# Plerixafor increased both neutrophils and lymphocytes in the blood of WHIM participants

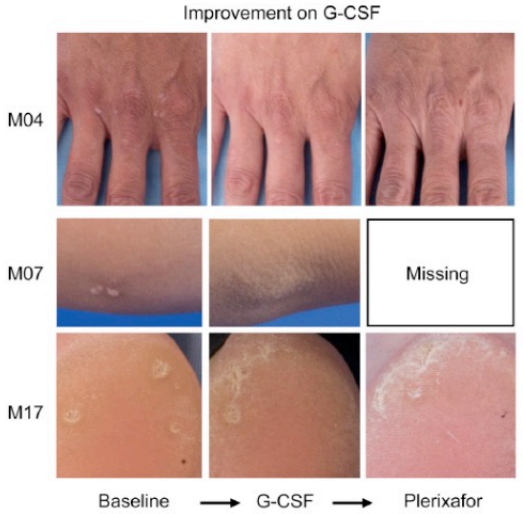


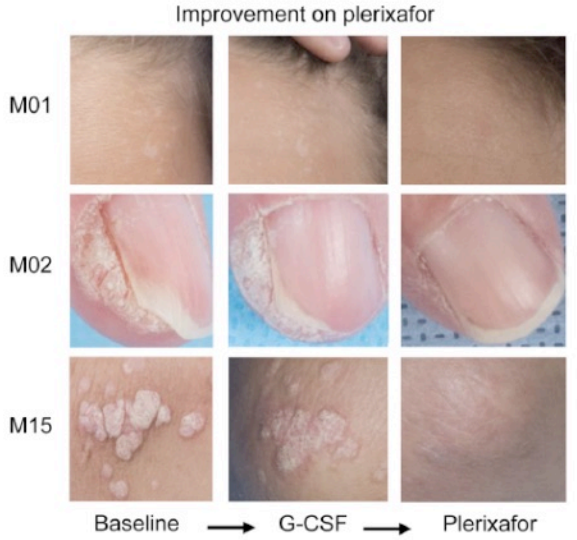
# Distribution of infections over a 12 month treatment period

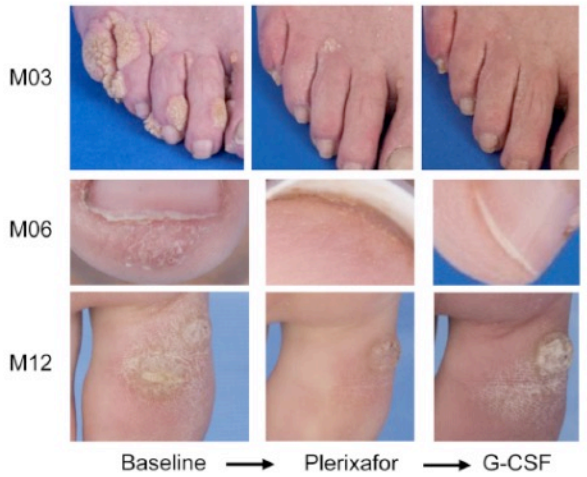


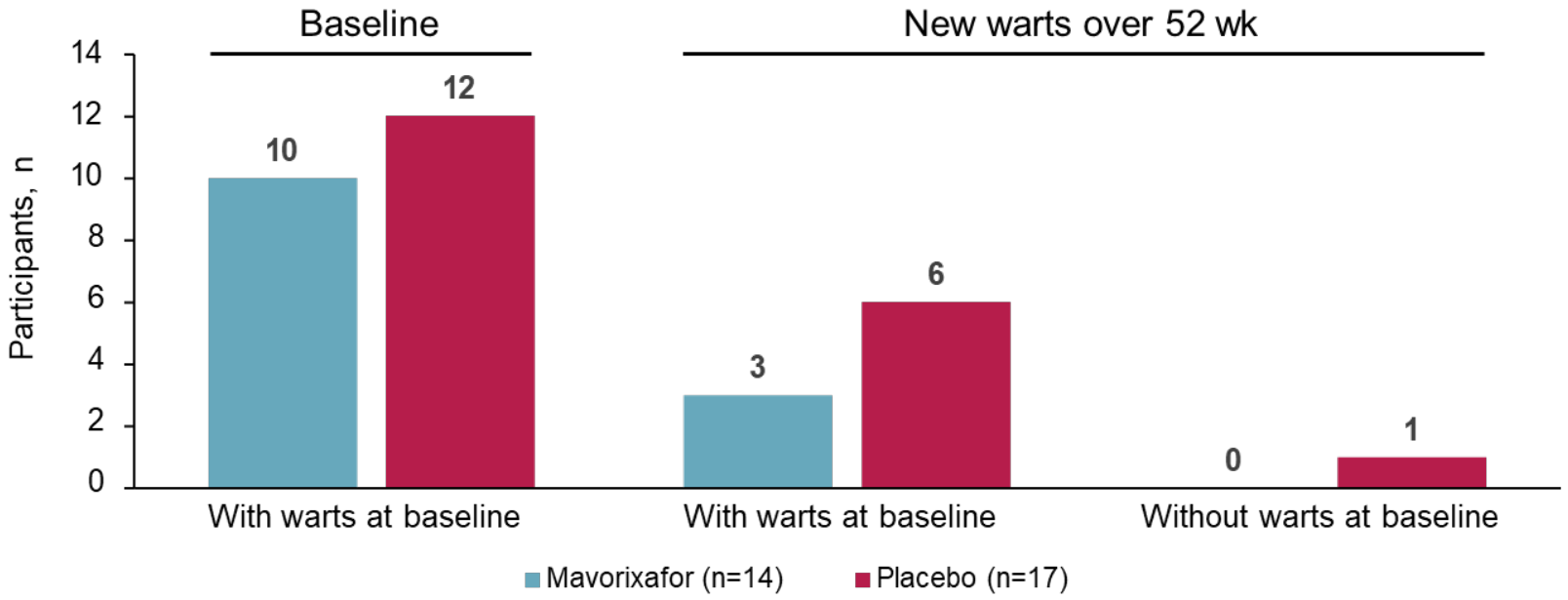

Superiority of plerixafor over G-CSF was not demonstrated

# Wart improvement was variable on plerixafor and mavorixafor



# Plerixafor and G-CSF Safety Data

| | Treatment period during which the adverse event occurred | | | | | |
|---|---|---|---|---|---|---|
| Adverse event | G (*n*) | P (*n*) | G and P (*n*) | Neither (*n*) | *P* value[A] | Relationship of event to drug |
| Bone pain | 8 | 1 | 6 | 4 | 0.039 | Definitely related |
| Arthralgia | 9 | 3 | 2 | 5 | 0.146 | Probably or definitely related |
| Rash | 0 | 6 | 3 | 10 | 0.031 | Probably or definitely related |
| Headache/migraine | 6 | 4 | 1 | 8 | 0.754 | Possibly related |
| Nausea | 6 | 1 | 0 | 12 | 0.125 | Possibly related |
| Hyperuricemia | 2 | 1 | 2 | 14 | 1.000 | Possibly related |
| Weight gain | 0 | 3 | 2 | 14 | 0.250 | Possibly related |
| Hyperglycemia | 2 | 0 | 2 | 15 | 0.500 | Possibly related |
| Injection site reaction | 0 | 4 | 0 | 15 | 0.125 | Probably or definitely related |
| Ovarian cyst | 2 | 0 | 1 | 16 | 0.500 | Possibly related |
| Splenomegaly | 2 | 0 | 0 | 17 | 0.500 | Probably related |
| Anemia | 1 | 1 | 1 | 16 | 1.000 | Possibly related |
| Drug failures | 0 | 3 | 1 | 15 | 0.250 | Definitely related |

[A]We calculated the proportion with each adverse event while assigned to the particular treatment. Then, we calculated the difference in proportions with 95% CIs and provide the 2-sided *P* value from the exact McNemar's test on whether the proportions are equal using the method of Fay and Lumbard (36). Values indicate the number of patients experiencing the indicated adverse event at least once during the indicated treatment phase. G, G-CSF; P, plerixafor.

# Treatment Emergent Severe Adverse Events

| Patient | Study drug | Serious adverse event | Hospitalization duration (d) | Relationship of event to drug |
|---|---|---|---|---|
| M05 | G-CSF | Outpatient intraoperative transient ischemic attack | 1 | Unrelated |
| M07 | G-CSF | Gastroenteritis | 1 | Unrelated |
| M13 | Plerixafor | Axillary abscess | 7 | Unrelated |
| M14 | G-CSF and plerixafor | Reactive arthritis | 0 | Probably related to both drugs |
| M16[A] | G-CSF | Pneumonia | 4 | Unrelated |
| M19 | G-CSF | Appendicitis and then abdominal abscess | 7 and then 10 | Unrelated |
| M19 | G-CSF | Possible urinary tract infection | 1 | Unrelated |

[A]This event occurred after the end-of-study visit but before locking the database. All phases of the study were considered from randomization until the data base was locked for each patient.

- No deaths
- Only reactive arthritis was a TESEA deemed possibly drug related
- No hospitalizations while on either G-CSF or plerixafor

# Plerixafor: Summary

- Dermatitis and arthritis led to discontinuation of plerixafor in 3 patients.
- Plerixafor was not superior to G-CSF in patients with WHIM for TISS, the primary endpoint.
- Together with wart regression and hematologic improvement, the infection severity results support continued study of plerixafor as a potential treatment for WHIM syndrome.
- Plerixafor was noninferior to G-CSF for maintaining neutrophil counts of more than 500 cells/μL ($P = 0.023$) and was superior to G-CSF for maintaining lymphocyte counts above 1,000 cells/μL ($P < 0.0001$).
- Complete regression of a subset of large wart areas occurred on plerixafor in 5 of 7 patients with major wart burdens at baseline.

# Phase 3: Randomized, Placebo-Controlled Trial of an Oral, Selective CXCR4 antagonist, Mavorixafor, in WHIM syndrome

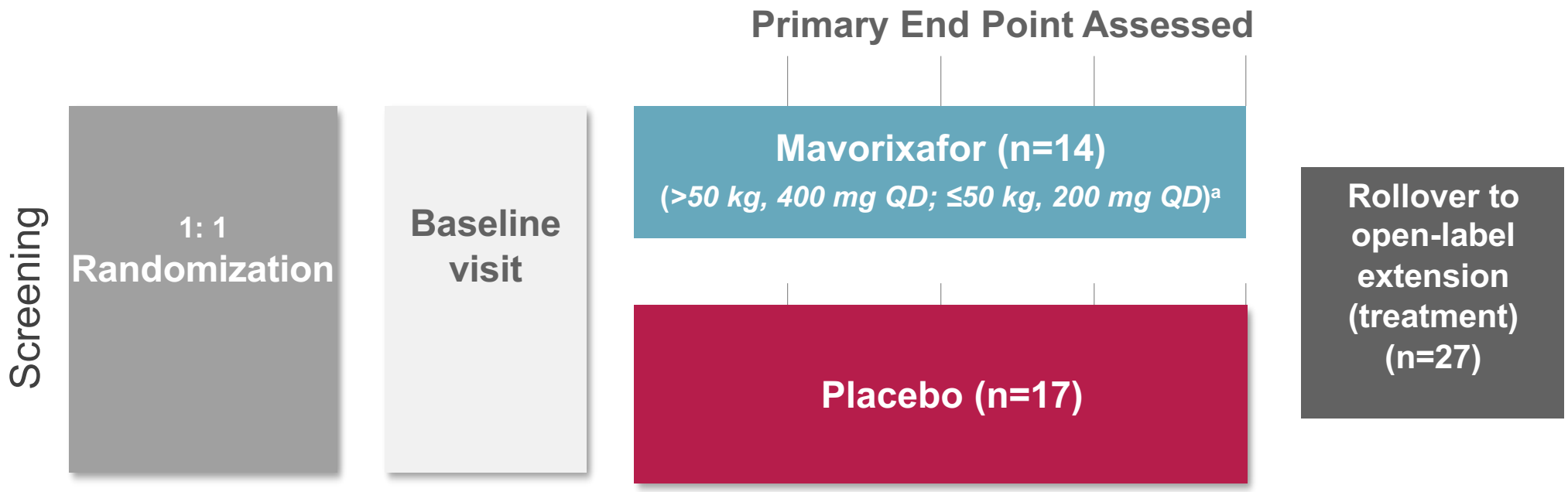
## Demographics and Baseline Characteristics

| | Mavorixafor (n=14) | Placebo (n=17) |
|---|---|---|
| **Adolescents 12 to <18 y, n (%)** | 7 (50) | 8 (47) |
| **Adults ≥18 y, n (%)** | 7 (50) | 9 (53) |
| **Sex, female, n (%)** | 9 (64) | 9 (53) |
| **Previous immunoglobulin usage, n (%)** | 6 (43) | 8 (47) |
| **Screening ANC (cells/µL)** | | |
| Median (min, max) | 150 (40, 390) | 200 (0, 400) |
| **Screening ALC (cells/µL)** | | |
| Median (min, max) | 420 (260, 1070) | 520 (100, 8560) |

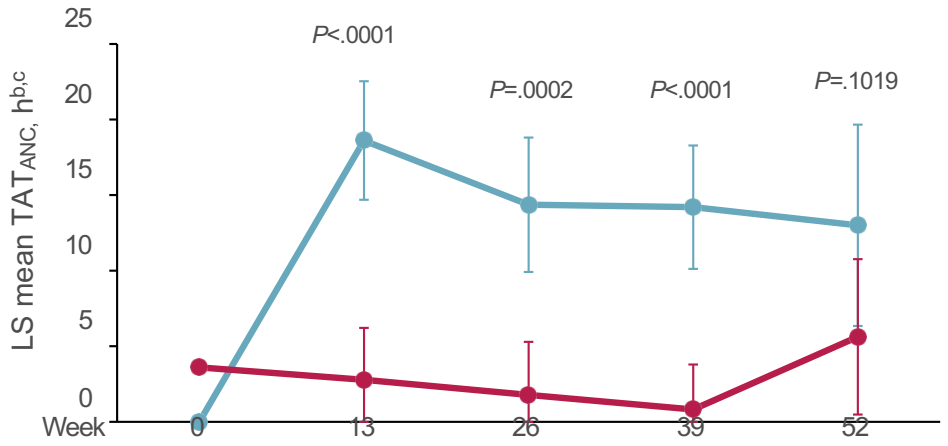
All patients had previously identified *CXCR4* pathogenic mutations

# Phase 3 Mavorixafor Trial Design

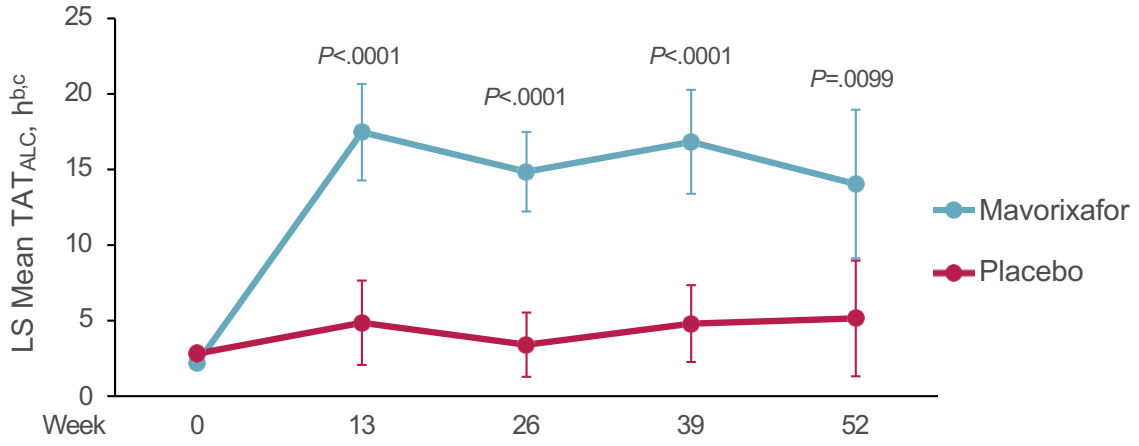
*(NCT03995108)*



# Mavorixafor Trial met Primary End Point (*Mean $TAT_{ANC}$*) and Key Secondary End Point (*Mean $TAT_{ALC}$*)




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

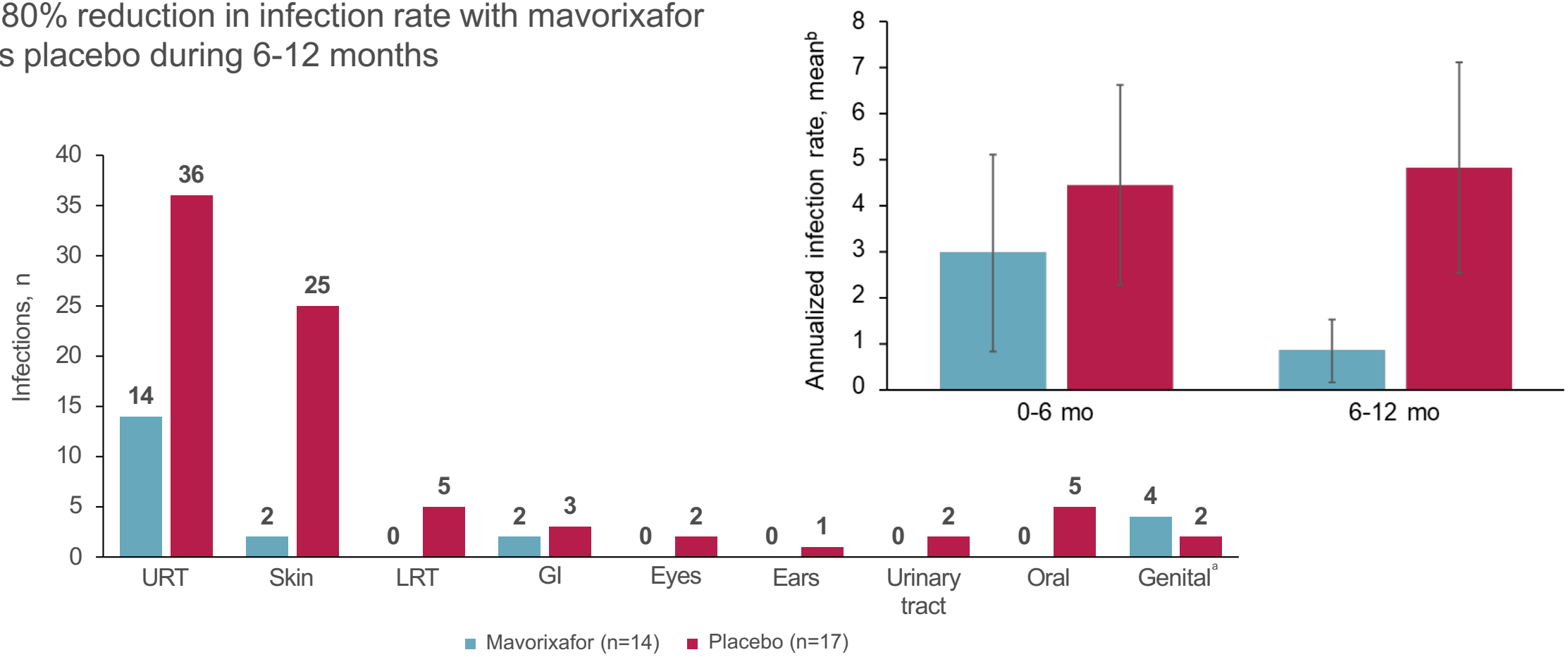



| | | | | | |
|---|---|---|---|---|---|
| Mavorixafor n: | 13 | 13 | 11 | 9 | 10 |
| Placebo n: | 16 | 16 | 17 | 17 | 17[d] |

Intention to Treat analysis was statistically significant over 52 weeks

# Mavorixafor Reduction in Annualized Infection Rate

>80% reduction in infection rate with mavorixafor vs placebo during 6-12 months



# Mavorixafor Trial Safety Data

| | Mavorixafor (n=14) | | Placebo (n=17) | | Total (N=31) | |
|---|---|---|---|---|---|---|
| **System Organ Class** | Participants, n (%) | Events | Participants, n (%) | Events | Participants, n (%) | Events |
| **Any TEAE** | 14 (100) | 88 | 17 (100) | 143 | 31 (100) | 231 |
| **TEAEs occurring in ≥20% of the total cohort** | | | | | | |
| **Infections and infestations** | 11 (79) | 28 | 17 (100) | 96 | 28 (90) | 124 |
| **Skin and subcutaneous tissue disorders** | 8 (57) | 11 | 3 (18) | 6 | 11 (36) | 17 |
| **Nervous system disorders** | 4 (29) | 7 | 5 (29) | 7 | 9 (29) | 14 |
| **Respiratory, thoracic and mediastinal disorders** | 2 (14) | 3 | 6 (35) | 9 | 8 (26) | 12 |
| **GI disorders** | 5 (36) | 6 | 2 (12) | 2 | 7 (23) | 8 |

- No deaths
- No TESAEs were deemed drug related
  - infections, glioma, thrombocytopenia
- No discontinuations due to safety events

# Mavorixafor: Summary

- Treatment with mavorixafor reduced infection frequency, severity, duration, and antibiotic use.
- Mavorixafor showed improvement in infections in WHIM syndrome over a 12 month period.
- Mavorixafor had a well-tolerated safety profile in WHIM participants who were taking the medication chronically for 12 months.
- No discontinuations occurred due to treatment-emergent adverse events (TEAEs); no related serious TEAEs were observed.
- Overall, mavorixafor-treated participants showed significant increases in LS mean TATANC and TATALC, reduced infection frequency, severity/duration.
- Mavorixafor has been approved by the FDA for the treatment of WHIM.

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