Results of a Phase 3 Trial of an Oral CXCR4 Antagonist, Mavorixafor, for Treatment of Patients With WHIM Syndrome

ClinicalTrials.gov Identifier
NCT03995108

4WHIM Study Group

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WHIM Syndrome At-a-Glance

WHIM Syndrome

A rare immunodeficiency disease that can present with chronic neutropenia, lymphopenia, monocytopenia, and/or recurrent infections, including warts, resulting from impaired leukocyte trafficking predominately caused by gain-of-function variants in CXCR4[1,2]

W — **Warts**
may progress to HPV-related cancers[3,4]

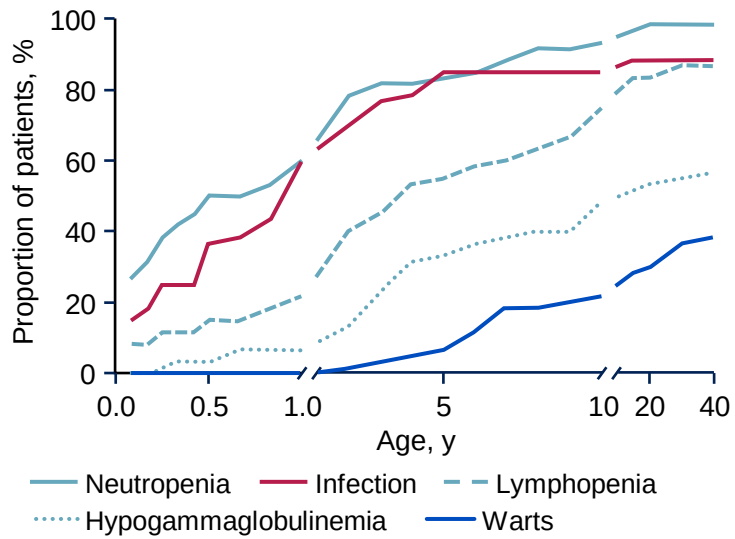
H — **Hypogammaglobulinemia**[3,4]

I — **Infections**[3,4]

M — **Myelokathexis**
retention of mature neutrophils in the bone marrow[3,4]

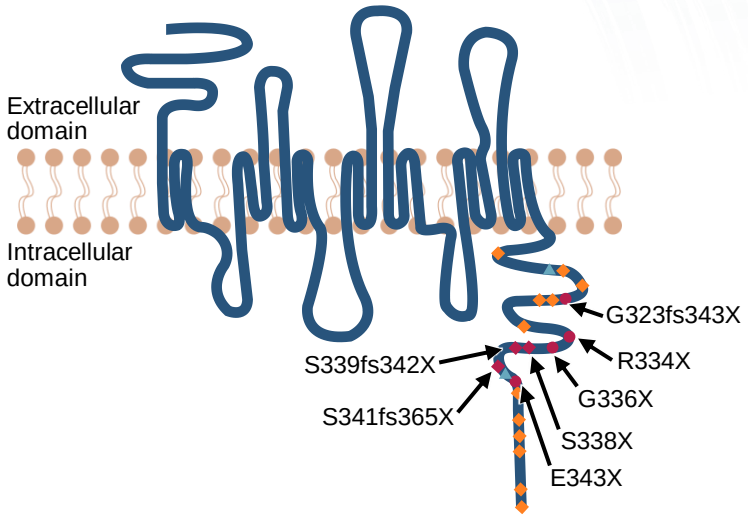
Prevalence of related manifestations[5]

Data From an International Cohort (N=66)



From Geier CB, et al. *J Clin Immunol*. 2022;42(8):1748-1765.

CXCR4 protein[6]



The exact prevalence of WHIM syndrome is unknown

CXCR4, C-X-C chemokine receptor type 4; HPV, human papillomavirus; WHIM, Warts, Hypogammaglobulinemia, Infections, and Myelokathexis.

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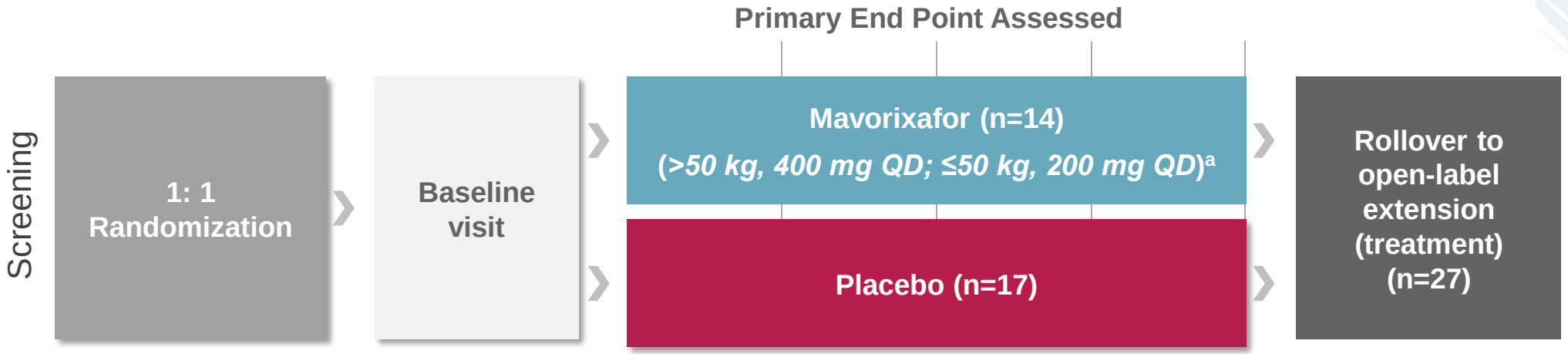
4WHIM Phase 3 Trial Design

(NCT03995108)



Primary end point

- Mean TAT_{ANC} – mean of the 13, 26, 39, and 52-week assessments[b]

First key secondary end point[c]

- Mean TAT_{ALC} – mean of the 13, 26, 39, and 52-week assessments[d]

Other secondary end points[e]

- Infection-related end points
- Wart-related end points
- Safety and tolerability across 52 weeks

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; QD, once daily; TAT, time above threshold.
[a]Adults and adolescents (aged 12-17 years) weighing >50 kg received 400 mg mavorixafor QD; adolescents aged 12-17 years weighing ≤50 kg received 200 mg QD. [b]TAT_{ANC} is defined as time (in hours) above threshold ANC ≥500 cells/μL over a 24-hour period, assessed every 3 months for 52 weeks. [c]Secondary end points were analyzed per a hierarchical approach prespecified in the trial protocol; not all key secondary end points included in the hierarchical sequence are shown. [d]TAT_{ALC} is defined as time (in hours) above threshold ALC ≥1000 cells/μL over a 24-hour period, assessed every 3 months for 52 weeks. [e]Not all other secondary end points are shown.

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Time Above Threshold as an End Point
TAT_{ANC} and TAT_{ALC}

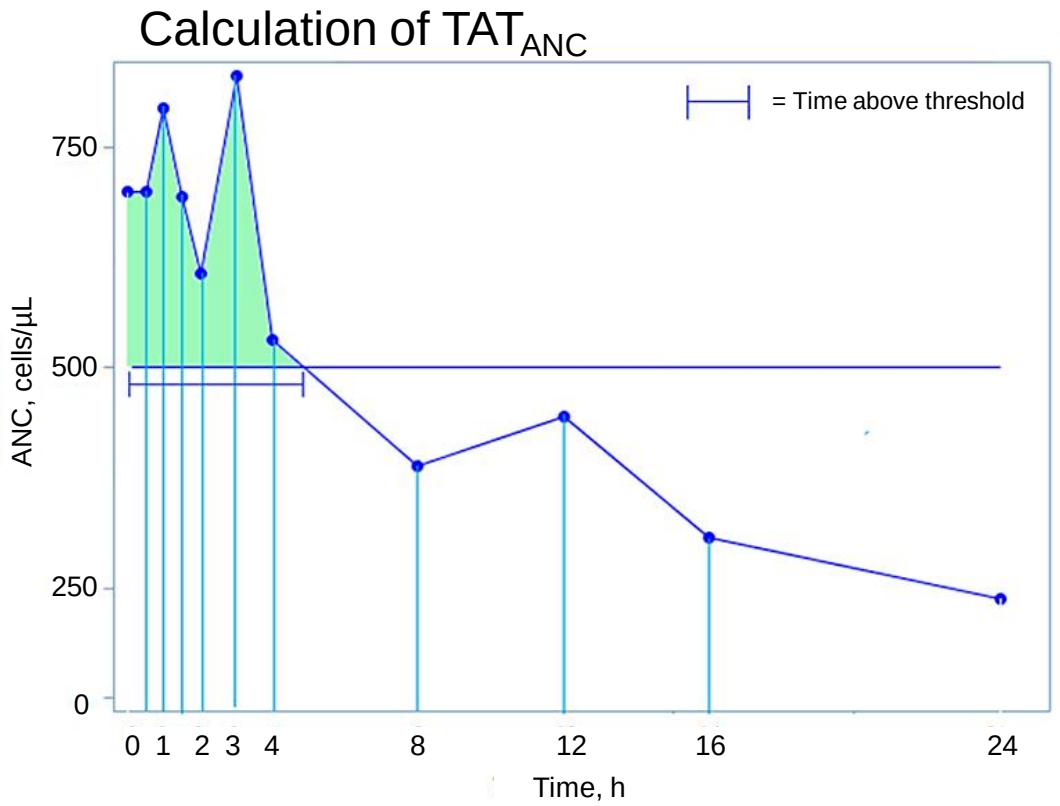
- Clinically relevant end points[7]
- Used to predict the risk of serious bacterial infections in patients with neutropenia and lymphopenia, resulting from disorders of bone marrow production[7]

TAT_{ANC}

Time (in hours) above threshold ANC of ≥500 cells/µL over a 24-hour period, assessed every 3 months for 52 weeks

TAT_{ALC}

Time (in hours) above threshold ALC of ≥1000 cells/µL over a 24-hour period, assessed every 3 months for 52 weeks



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Key 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)		
Mean (SD)	173 (112)	194 (123)
Median (min, max)	150 (40, 390)	200 (0, 400)
Screening ALC (cells/µL)		
Mean (SD)	496 (237)	1015 (1983)
Median (min, max)	420 (260, 1070)	520 (100, 8560)

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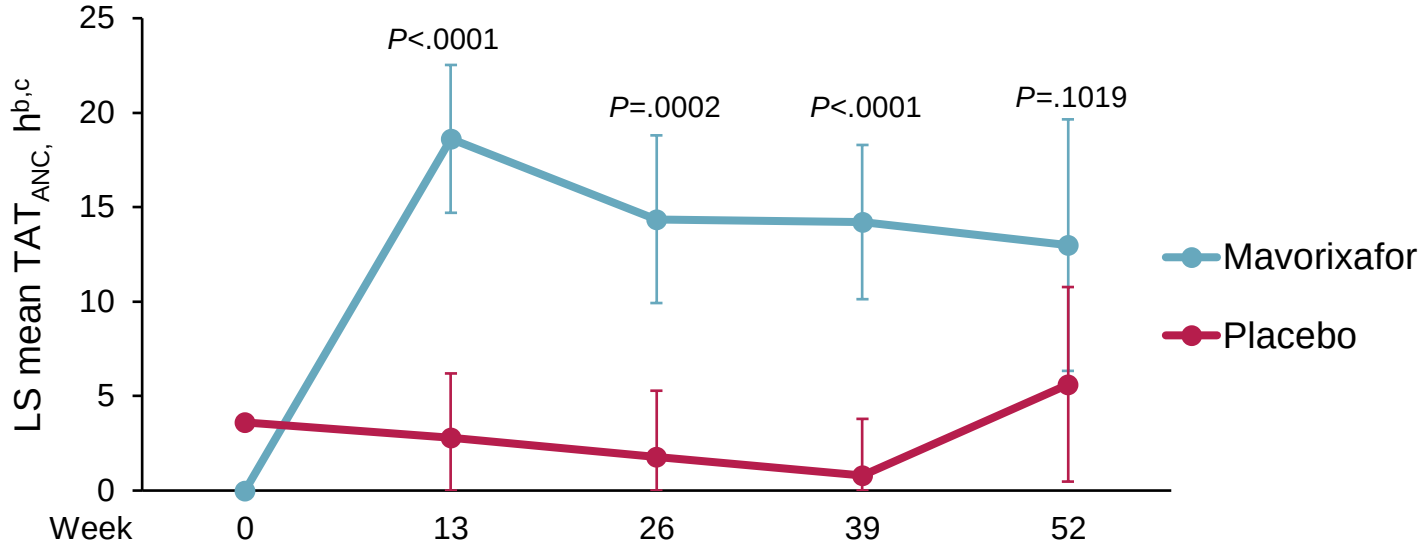
Primary End Point

Trial Met Its Primary End Point

Mean TAT_{ANC} Over 52 Weeks in Intent-to-Treat Population[a]



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

Overall, mean TAT_{ANC} was 15.04 hours for mavorixafor vs 2.75 hours for placebo (*P*<.0001)

ITT, intent to treat; LS, least squares.
[a]The ITT population comprised all participants randomized to treatment who received ≥1 dose of trial treatment. All data are included in ITT analysis. [b]Error bars represent 95% confidence interval. [c]*P* values compare mavorixafor group to placebo group at weeks 13, 26, 39, and 52. [d]At week 52, 3 of 17 placebo participants were given mavorixafor in advance of their TAT measurements as they entered the open-label portion of the trial; 1 mavorixafor patient did not receive mavorixafor.

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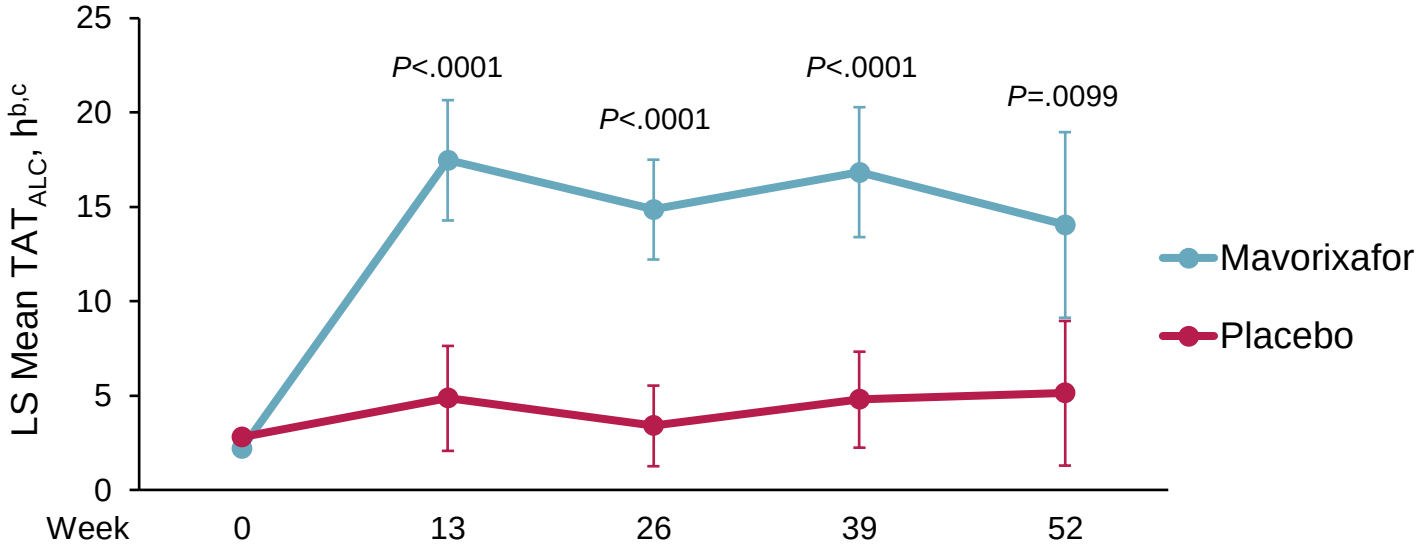
First Key Secondary End Point

Trial Met Its First Key Secondary End Point

Mean TAT_{ALC} Over 52 Weeks in Intent-to-Treat Population[a]



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

Overall, mean TAT_{ALC} was 15.80 hours for mavorixafor vs 4.55 hours for placebo (*P*<.0001)

[a]The ITT population comprised all participants randomized to treatment who received ≥1 dose of trial treatment. All data are included in ITT analysis. [b]Error bars represent 95% confidence interval. [c]*P* values compare mavorixafor group to placebo group at weeks 13, 26, 39, and 52. [d]At week 52, 3 of 17 placebo participants were given mavorixafor in advance of their TAT measurements as they entered the open-label portion of the trial; 1 mavorixafor patient did not take mavorixafor.

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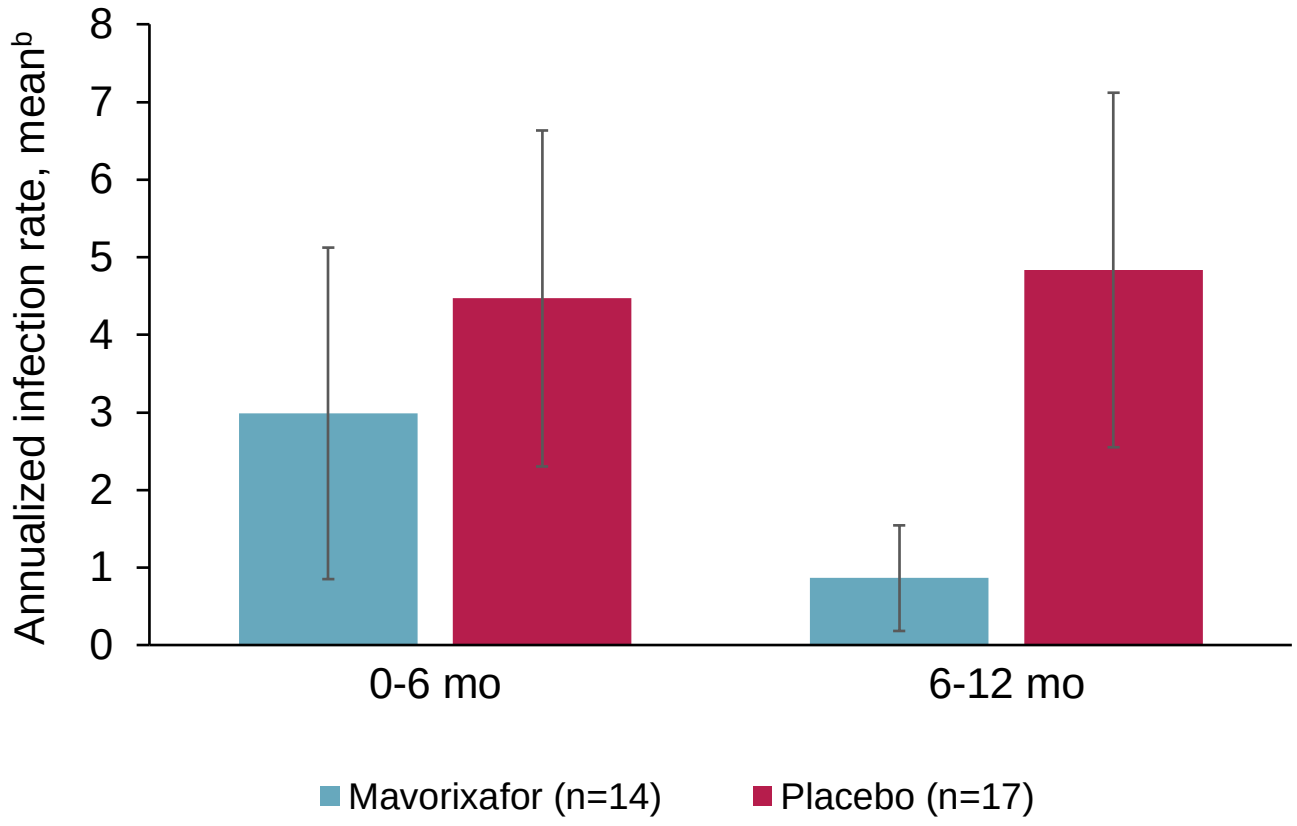
Other Secondary End Point

Reduction in Annualized Infection Rate

Mavorixafor vs Placebo (ITT Population)

- 60% reduction in annualized infection rate (*P*<.01)[a]
- >80% reduction in infection rate with mavorixafor vs placebo during 6-12 months (*P*<.005)[a]



[a]*P* values are nominal; [b]Error bars represent 95% confidence interval.

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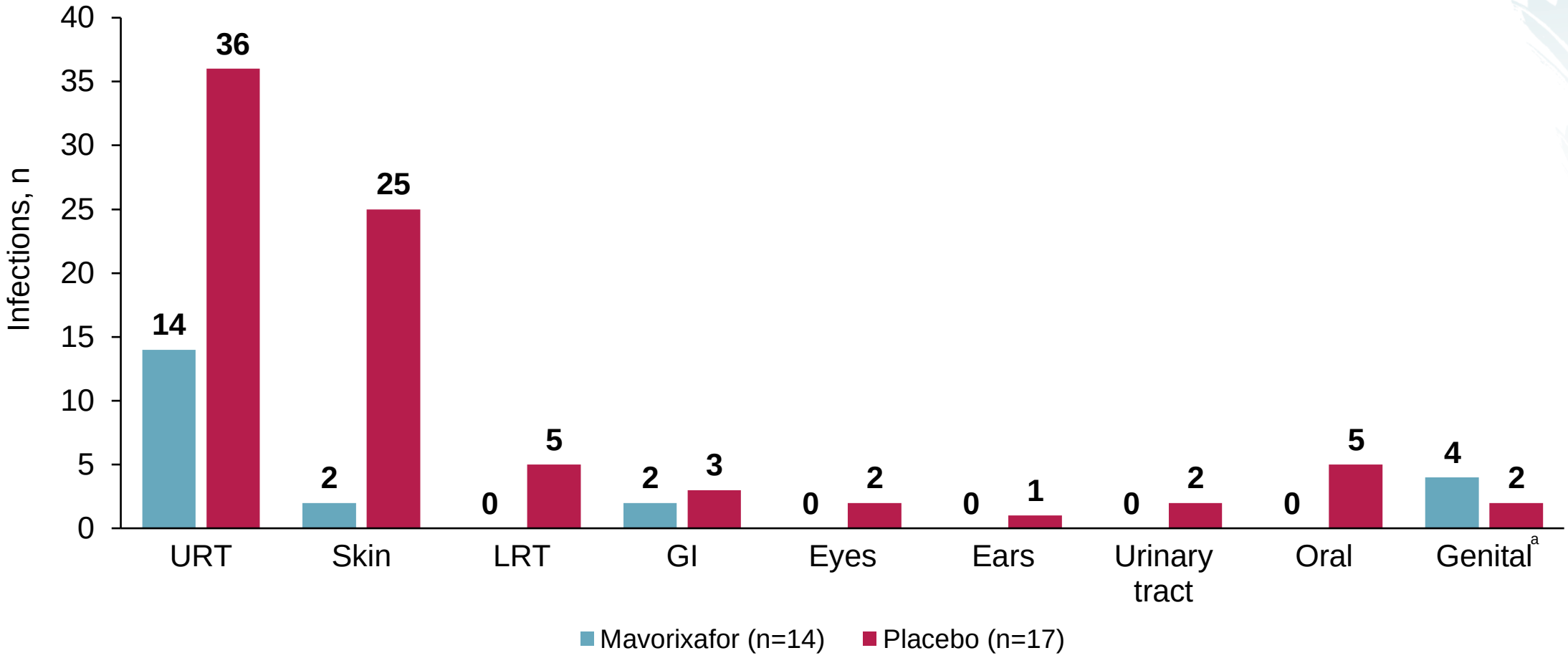
Types of Infections

Lower Frequency of Skin, Oral, and Upper and Lower Respiratory Tract Infections Were Observed in the Mavorixafor Group

Other Secondary End Point



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

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Other Secondary End Point

Duration of Infection

Total Time With Infection Was >70% Lower With Mavorixafor vs Placebo

- Mean total time with infection: ≈2 weeks on mavorixafor vs ≈7 weeks on placebo
- Median total time with infection showed ≈75% reduction with mavorixafor

Total time with infection, d	Mavorixafor (n=14)	Placebo (n=17)
Mean	14.1 (2 wk)	49.1 (7 wk)
Median	8.5	32.0
Min, Max	0, 43	8, 134

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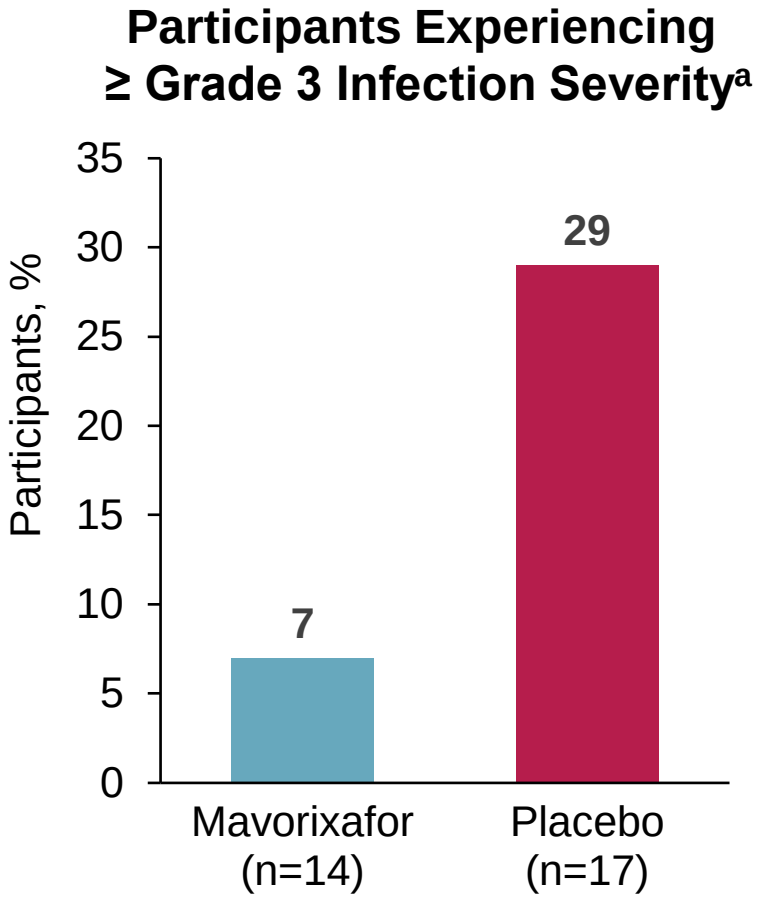
Severity of Infections

Less Severe Infections With Mavorixafor Compared With Placebo Over 52 Weeks

Other Secondary End Point



CTCAE Criteria, n	Mavorixafor (n=14)	Placebo (n=17)
Grade 1 / Grade 2	10	11
Grade 3	1[b]	4
Grade 4	0	1
Grade 5	0	0

CTCAE, Common Terminology Criteria for Adverse Events.
[a]Severe infections are those grade 3 or higher by CTCAE criteria.
[b]Grade 3 infection on mavorixafor treatment occurred during first 3 months of treatment; rate of severe infections on placebo unchanged over 52-week period.

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Participants on Placebo More Often Required Treatment With Antibacterials

Consistent With Higher Rate and Severity of Infections

Other Secondary End Point

- 10/17 (59%) on placebo were administered antibacterials/penicillins vs 3/14 (21%) on mavorixafor
  - Amoxicillin or amoxicillin with another antibiotic were most prescribed antibacterial treatment

Antibacterial Medications Used in Study	Mavorixafor (n=14)	Placebo (n=17)	Total (N=31)
Beta-lactam antibacterials, penicillins, n (%)	3 (21)	10 (59)	13 (42)

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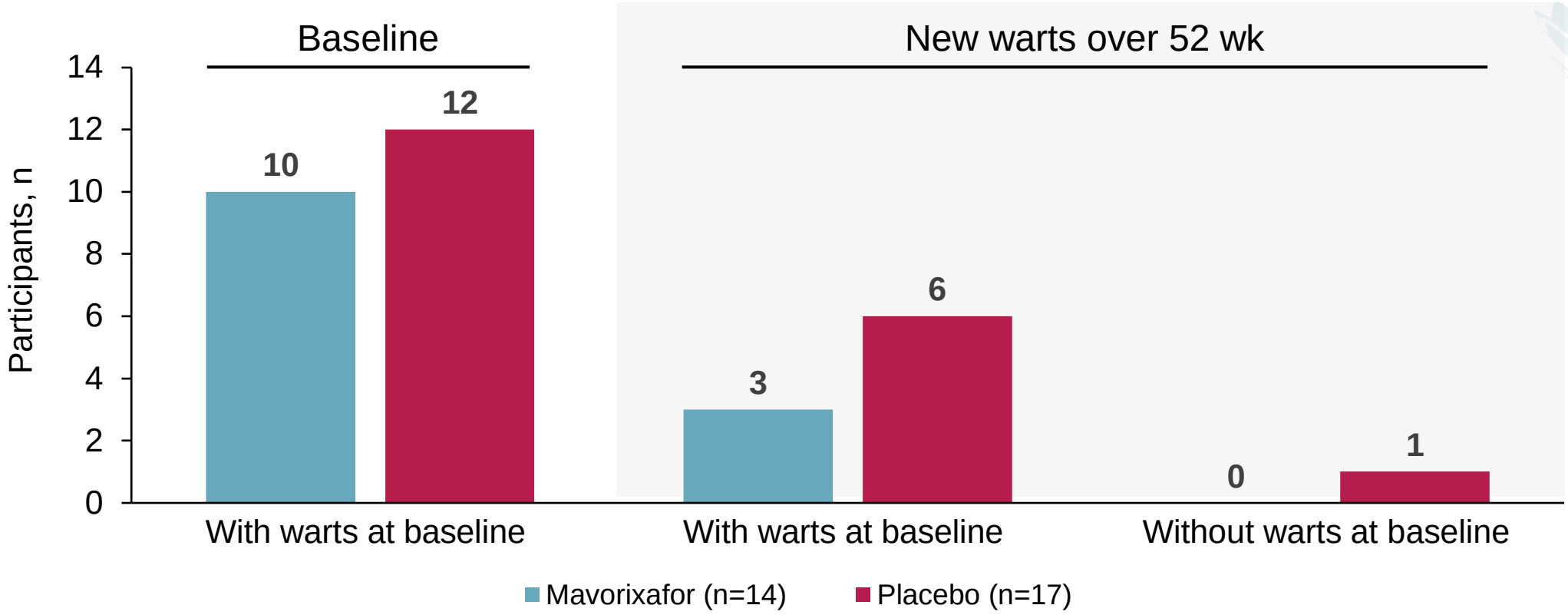
Evaluation of Warts

No New Warts Were Observed in Mavorixafor Group for Participants Without Warts at Baseline

Other Secondary End Point



Minor reduction in wart score in both mavorixafor and placebo groups[a]

[a]No statistical significance between the 2 groups.

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Safety Assessment

	Mavorixafor (n=14)		Placebo (n=17)		Total (N=31)	
System Organ Class	Subjects, n (%)	Events	Subjects, n (%)	Events	Subjects, 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 were reported
- No TESAEs were deemed drug related: TESAEs included infections, glioma, thrombocytopenia
- No discontinuations due to safety events
- Placebo arm had increased infections/infestations and respiratory disorders
- Mavorixafor arm had increased skin and GI disorders: no discontinuations

GI, gastrointestinal; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

Summary

- The trial met its primary and first key secondary end points
  - Mean TAT_{ANC} for mavorixafor vs placebo was 15.04 vs 2.75 hours (*P*<.0001), respectively
  - Mean TAT_{ALC} for mavorixafor vs placebo was 15.80 vs 4.55 hours (*P*<.0001), respectively
- Compared with the placebo group, mavorixafor group showed:
  - Increases in WBC, ANC, ALC, and AMC
  - 60% reduced annualized infection rate
  - 71% less time with infection
  - Lower rate of antibiotic usage
  - Less severe and fewer number of infections
- No drug-related TESAEs or safety-related discontinuations were observed with mavorixafor
- Overall, these data support the filing of a new drug application

ALC, absolute lymphocyte count; AMC, absolute monocyte count; ANC, absolute neutrophil count; TAT, time above threshold; TESAE, treatment-emergent serious adverse event; WBC, white blood cell.

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Backup slides

Genetic Variants in the Trial Population

Genetic variant, n (%)	Mavorixafor (n=14)	Placebo (n=17)
c.1000C>T p.Arg334*	10 (71.4)	12 (70.6)
c.1013C>G p.Ser338*3	1 (7.1)	2 (11.8)
c.950_953del p.Leu317Profs*3	1 (7.1)	1 (5.9)
c.959_960del p.Val320Glufs*23	1 (7.1)	1 (5.9)
c.976dup p.Leu326Profs*18	1 (7.1)	0
c.077_977del p.Leu326Glnfs*17	0	1 (5.9)

Summary of AEs

	Mavorixafor (n=14)	Placebo (n=17)
Any TEAE, n (%)	14 (100.0)	17 (100)
Treatment-related TEAEs, no. (%)	7 (50.0)	3 (17.6)
Any TESAE[a,b], n. (%)	5 (35.7)	2 (11.8)
COVID-19	1 (7.1)	0
Campylobacter gastroenteritis	1 (7.1)	0
Cellulitis	0	1 (5.9)
Endocarditis	1 (7.1)	0
Sepsis	1 (7.1)	0
Thrombocytopenia	2 (14.3)	0
Febrile neutropenia	1 (7.1)	0
Lipase increased	1 (7.1)	0
Platelet count decreased	1 (7.1)	0
Malignant glioma	1 (7.1)	0
Pneumonitis	0	1 (5.9)
Treatment-related TESAE, n (%)	0	0
TEAE or treatment-related TEAE leading to discontinuation, n (%)	0	0
TEAE or treatment-related TEAE leading to death, n (%)	0	0
Treatment-limiting toxicity, n (%)	0	0

COVID-19, coronavirus disease 2019.
[a]Participants may have experienced ≥2 different categories of AEs.
[b]Preferred term.

	Mavorixafor (n=14)		Placebo (n=17)	
TEAEs reported in ≥2 participants in either group[b], n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
COVID-19	4 (28.6)	–	5 (29.4)	–
Upper respiratory tract infection	3 (21.4)	1 (7.1)	6 (35.3)	0
Thrombocytopenia	3 (21.4)	0	0	1 (7.1)
Dizziness	2 (14.3)	–	1 (5.9)	–
Epistaxis	2 (14.3)	–	1 (5.9)	–
Pityriasis	2 (14.3)	–	0	–
Rhinitis	2 (14.3)	–	0	–
Rash	2 (14.3)	–	0	–
Vomiting	2 (14.3)	–	0	–
Bronchitis	1 (7.1)	–	4 (23.5)	–
Cellulitis	1 (7.1)	0	3 (17.6)	2 (11.8)
Headache	1 (7.1)	–	2 (11.8)	–
Nasopharyngitis	1 (7.1)	0	7 (41.2)	1 (5.9)
Urinary tract infection	1 (7.1)	–	2 (11.8)	–
Conjunctivitis	0	–	3 (17.6)	–
Ear infection	0	0	2 (11.8)	1 (5.9)
Ear pain	0	–	2 (11.8)	–
Lower respiratory tract infection	0	0	3 (17.6)	1 (5.9)
Sinusitis	0	0	2 (11.8)	1 (5.9)
Skin infection	0	0	2 (11.8)	1 (5.9)
Skin laceration	0	–	2 (11.8)	–
Tinea versicolor	0	–	2 (11.8)	–

	Mavorixafor (n=14)		Placebo (n=17)	
Treatment-related TEAEs[a], n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Acute kidney injury	1 (7.1)	–	0	–
Dermatitis psoriasiform	1 (7.1)	–	0	–
Dizziness	1 (7.1)	–	0	–
Dry eye	1 (7.1)	–	0	–
Dry skin	1 (7.1)	–	0	–
Dysgeusia	1 (7.1)	–	0	–
Dyspepsia	1 (7.1)	–	0	–
Nausea	1 (7.1)	–	0	–
Product after taste	1 (7.1)	–	0	–
Pruritus	1 (7.1)	–	0	–
Rash	1 (7.1)	–	0	–
Syncope	1 (7.1)	1 (7.1)	0	0
Vomiting	1 (7.1)	–	0	–
Cellulitis	0	–	1 (5.9)	–
Conjunctivitis	0	–	1 (5.9)	–
Headache	0	–	1 (5.9)	–
Localized infection	0	–	1 (5.9)	–
Lower respiratory tract infection	0	–	1 (5.9)	–
Skin infection	0	–	1 (5.9)	–
Subcutaneous abscess	0	–	1 (5.9)	–
Tonsillitis	0	–	1 (5.9)	–
Upper respiratory tract infection	0	–	1 (5.9)	–

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Other Secondary End Point

WHIM Syndrome Biomarker Summary

- Considerable increases in WBC, ANC, ALC, and AMC levels were observed in the mavorixafor group compared with placebo group
- When compared to baseline:
  - ALC and AMC levels increased into the normal range in the mavorixafor group
  - WBC and ANC levels approached the normal range in the mavorixafor group

ALC, absolute lymphocyte count; AMC, absolute monocyte count; ANC, absolute neutrophil count; WBC, white blood cell.

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