Results of a Phase 3 Trial of an Oral CXCR4 Antagonist, Mavorixafor, for the Treatment of Participants With WHIM Syndrome: Investigational Assessment of Lymphocyte Subpopulations in Peripheral Blood

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Disclosures

Teresa K. Tarrant, MD is a principal investigator in the Phase 3 trial of mavorixafor for WHIM syndrome and consultant to X4 Pharmaceuticals

Dr Tarrant has also consulted for the US Department of Justice, has served as an independent grant reviewer for Pfizer, and has received research funding from AbbVie and Viela Bio

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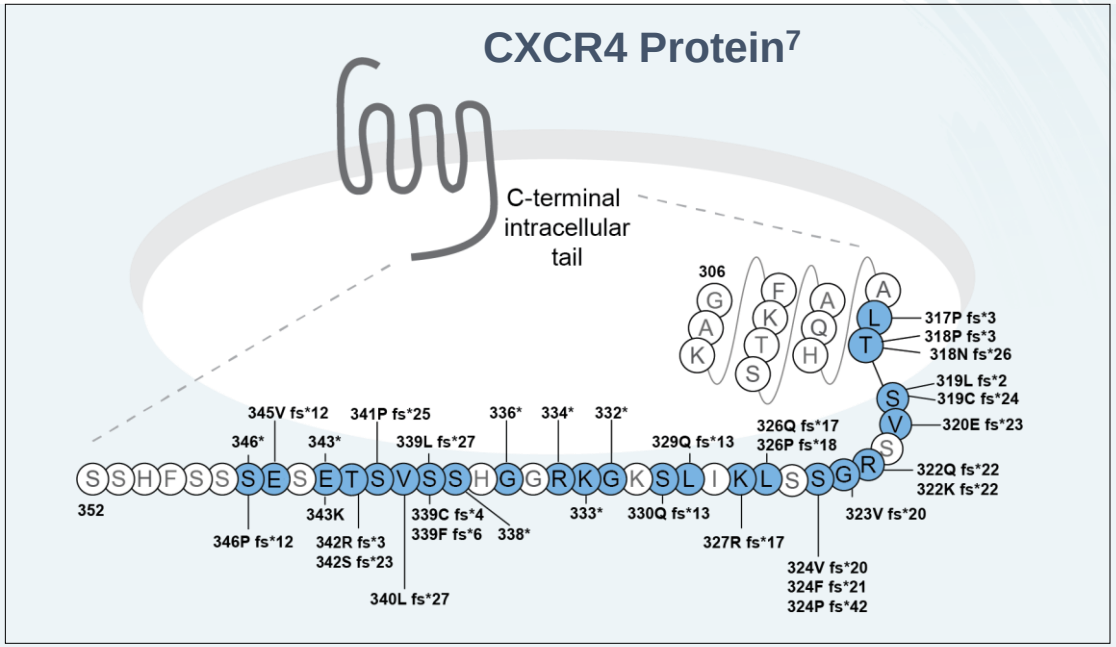
WHIM Syndrome at a Glance

Warts, Hypogammaglobulinemia, Infections, Myelokathexis (WHIM) Syndrome, is a rare combined primary immunodeficiency and chronic neutropenic disorder resulting from impaired leukocyte mobilization from bone marrow to peripheral blood. It is characterized by chronic neutropenia, lymphopenia, recurrent and/or severe infections with variable hypogammaglobulinemia and warts, and is predominantly caused by gain-of-function variants in CXCR4[1-3]

Prevalence of Manifestations in the WHIM Acronym[a]

In the largest cohort study (N=66), only 1 out of 4 patients presented with all 4 manifestations in the WHIM acronym[3]

CXCR4 Protein[7]



>35 pathogenic and likely pathogenic variants in CXCR4 have been identified[3,7-9]

True global prevalence is unknown[1,2]

CXCR4, C-X-C chemokine receptor type 4; fs, frameshift; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; WHIM, Warts, Hypogammaglobulinemia, Infections, and Myelokathexis.

[a]The bar graph reflects the lower percentage range of the prevalence of the manifestation.[b]Includes patients with confirmed myelokathexis and patients without myelokathexis but who had neutropenia.

1. Heusinkveld LE, et al. *J Clin Immunol*. 2019;39(6):532-556. **2.** WHIM syndrome. NORD Rare Disease Database. Accessed December 5, 2023. https://rarediseases.org/rare-diseases/whim-syndrome/. **3.** Geier CB, et al. *J Clin Immunol*. 2022;42(8):1748-1765. **4.** Beaussant Cohen S, et al. *Orphanet J Rare Dis*. 2012;7:71. **5.** Dotta I, et al. *J Allergy Clin Immunol Pract*. 2019;7(5):1568-1577. **6.** Tassone L, et al. *J Allergy Clin Immunol*. 2009;123(5):1170-3, 1173.e1-3. **7.** Zmajkovicova K, et al. Poster presented at: International Primary Immunodeficiencies Congress (IPIC) 2023; November 8-10, 2023; Rotterdam, The Netherlands. **8.** National Library of Medicine, National Center for Biotechnology Research. Search of CXCR4[gene] WHIM. ClinVar. Accessed January 24, 2024. https://www.ncbi.nlm.nih.gov/clinvar/?term=CXCR4%5Bgene%5D&redir=gene **9.** Zmajkovicova K, et al. *Genes Immun*. 2022;23(6):196-204.

CXCR4 Antagonism as a Potential Strategy for Treatment of WHIM Syndrome

- **CXCR4** is highly expressed on most leukocytes, including all B and most T lymphocytes and their subsets[1-4]
- **CXCR4-CXCL12** signaling regulates the balance between retention of immune cells in the bone marrow and egress to peripheral blood[5,6]
- In WHIM syndrome, hyperactive **CXCR4** signaling due to impaired desensitization leads to increased retention of leukocytes in bone marrow[4,6-8]

Mavorixafor is an investigational, orally active, selective small molecule inhibitor of CXCR4 being evaluated for the treatment of WHIM syndrome[9,10]

CXCR4, C-X-C chemokine receptor type 4; CXCL12, C-X-C chemokine ligand 12; WHIM, Warts, Hypogammaglobulinemia, Infections, and Myelokathexis; WT, wild-type.

1. García-Cuesta EM, et al. *Front Endocrinol (Lausanne)*. 2019;10:585. **2.** Nie Y, et al. *J Exp Med*. 2004;200(9):1145-56. **3.** Contento RL, et al. *Proc Natl Acad Sci U S A*. 2008;105(29):10101-6. **4.** Heusinkveld LE, et al. *J Clin Immunol*. 2019;39(6):532-556. **5.** Bachelerie F. *Dis Markers*. 2010;29(3-4):189-198. **6.** Badolato R, et al. *Blood*. 2017;130(23):2491-2498. **7.** McDermott DH, Murphy PM. *Immunol Rev*. 2019;287(1):91-102. **8.** Al Ustwani O, et al. *Br J Haematol*. 2014;164(1):15-23. **9.** ClinicalTrials.gov identifier: NCT03995108. Updated October 6, 2023. Accessed February 2, 2024. https://clinicaltrials.gov/study/NCT03995108. **10.** Dale DC, et al. *Blood*. 2020;136(26):2994-3003.

Evaluation of Mavorixafor as a Treatment for WHIM Syndrome

Phase 2 trial (NCT03005327; PMID: 32870250)

Increases in peripheral neutrophils, lymphocytes, monocytes, and WBCs were observed[1,2]

Phase 3 trial (4WHIM; NCT03995108)

Randomized, placebo-controlled, double-blind trial evaluated efficacy and safety of once-daily mavorixafor in participants with WHIM syndrome vs placebo[3,4]

- The trial met its primary end point, mean TAT_{ANC}, and first key secondary end point, mean TAT_{ALC}[a,b]

OBJECTIVE

To report the results of an investigational assessment evaluating changes in lymphocyte subpopulations in participants with WHIM syndrome treated with once-daily mavorixafor vs placebo during the 52-week RCP of the Phase 3 trial

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CXCL12, C-X-C chemokine ligand 12; CXCR4, C-X-C chemokine receptor type 4; NK, natural killer; QD, once daily; RCP, randomized controlled period; TAT, time above threshold; WBC, white blood cell; WHIM, Warts, Hypogammaglobulinemia, Infections, and Myelokathexis.

[a]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.[4] [b]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.[4]

1. ClinicalTrials.gov identifier: NCT03005327. Updated September 9, 2023. Accessed January 4, 2024. https://clinicaltrials.gov/study/NCT03005327. **2.** Dale DC, et al. Blood. 2020 Dec;136(26):2994-3003. **3.** ClinicalTrials.gov identifier: NCT03995108. Updated October 6, 2023. Accessed February 2, 2024. https://clinicaltrials.gov/study/NCT03995108. **4.** Badolato R, Donadieu J. Presented at Clinical Immunology Society (CIS) Annual Meeting 2023; May 18-21, 2023; St. Louis, MO.

Key Baseline Laboratory Characteristics

	Mavorixafor (n=14)		Placebo (n=17)		Normal range (10^6/μL)[1,2]
	Value	n	Value	n	
Blood cell counts, mean (95% CI), 10^6/L[a]					
Lymphocytes	485.8 (268.0-703.5)	9	519.9 (300.4-739.4)	15	959-3644
B cells[b]	17.8 (1.7-33.9)	9	40.4 (2.1-78.8)	14	106.0-364.6
T cells[b]					
$CD4^+$ T cells	243.0 (79.9-406.1)	9	254.6 (131.4-377.9)	14	454.5-1249.0
$CD8^+$ T cells	102.6 (51.5-153.6)	9	109.4 (29.8-189.0)	13	218.1-690.7
NK cells[b]	86.9 (44.6-129.2)	9	101.5 (60.8-142.2)	14	98.1-441.2

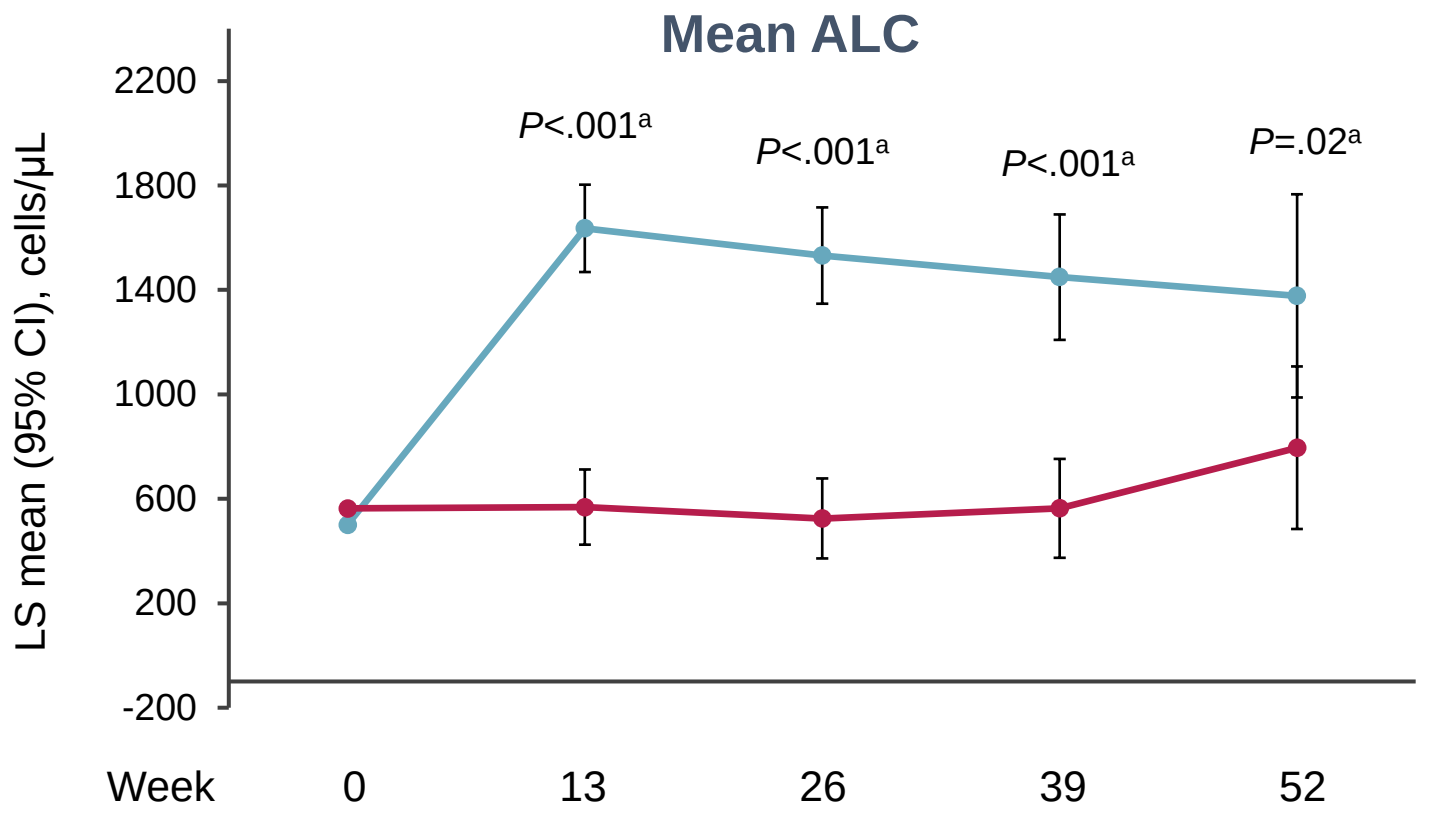
Most participants were lymphopenic at baseline, and the sex and age in treatment groups were well balanced

CD, cluster of differentiation; NK, natural killer; WHIM, Warts, Hypogammaglobulinemia, Infections, and Myelokathexis.

[a]Lymphopenia was observed in 8 of 9 participants receiving mavorixafor and 13 of 15 participants receiving placebo. [b]One participant in the placebo arm received 1 dose of rituximab for Evan Syndrome during the trial and was excluded from the analysis.

1. Apoil PA, et al. *Data Brief*. 2017;12:400-404. **2.** Oras A, et al. *Clin Exp Immunol*. 2020;202(3):363-378.

Patients Treated With Mavorixafor Showed Increases in Mean ALC From Baseline Over 52 Weeks[a] (ITT Population[b])



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

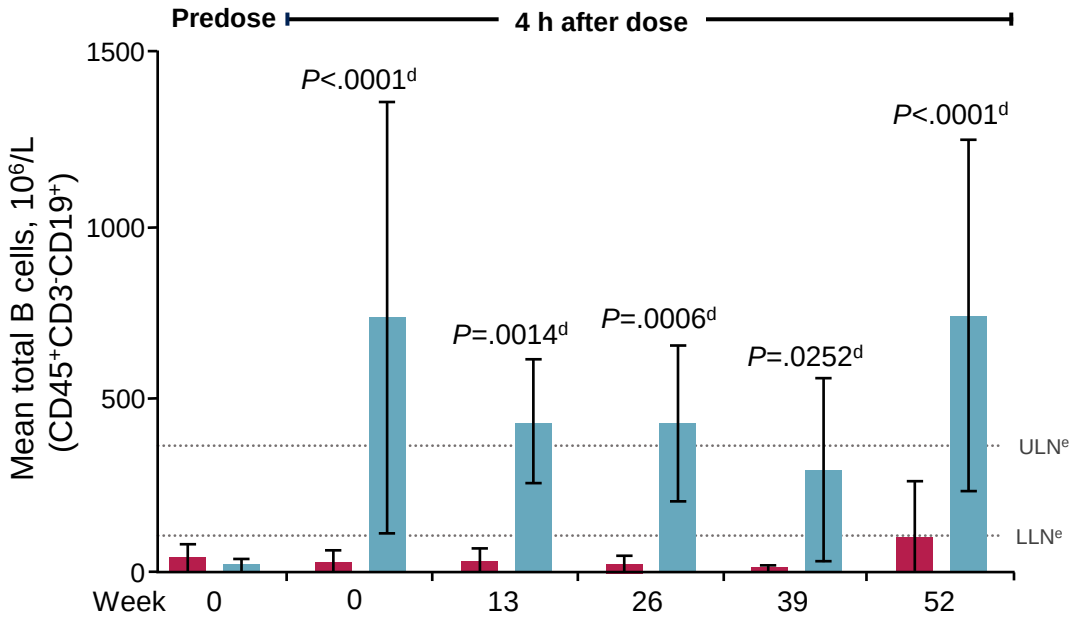
ALC, absolute lymphocyte count; ITT, intent to treat; LS, least squares.

[a]Nominal *P* as no multiplicity adjustment was performed. [b]The ITT population comprised all participants randomized to treatment, including 1 participant in the placebo arm who received 1 dose of rituximab for Evan syndrome during the trial. [c]One participant in mavorixafor group did not receive mavorixafor dose at Week 52. [d]Three placebo participants were given mavorixafor at the Week 52 visit.

1. Badolato R, Donadieu J. Presented at Clinical Immunology Society (CIS) Annual Meeting 2023; May 18-21, 2023; St. Louis, MO. **2.** ClinicalTrials.gov identifier: NCT03995108. Updated October 6, 2023. Accessed February 2, 2024. https://clinicaltrials.gov/study/NCT03995108

Mean Total B Cell and Subpopulation Counts Increased and Were Sustained 4 Hours After Dose With Mavorixafor vs Placebo

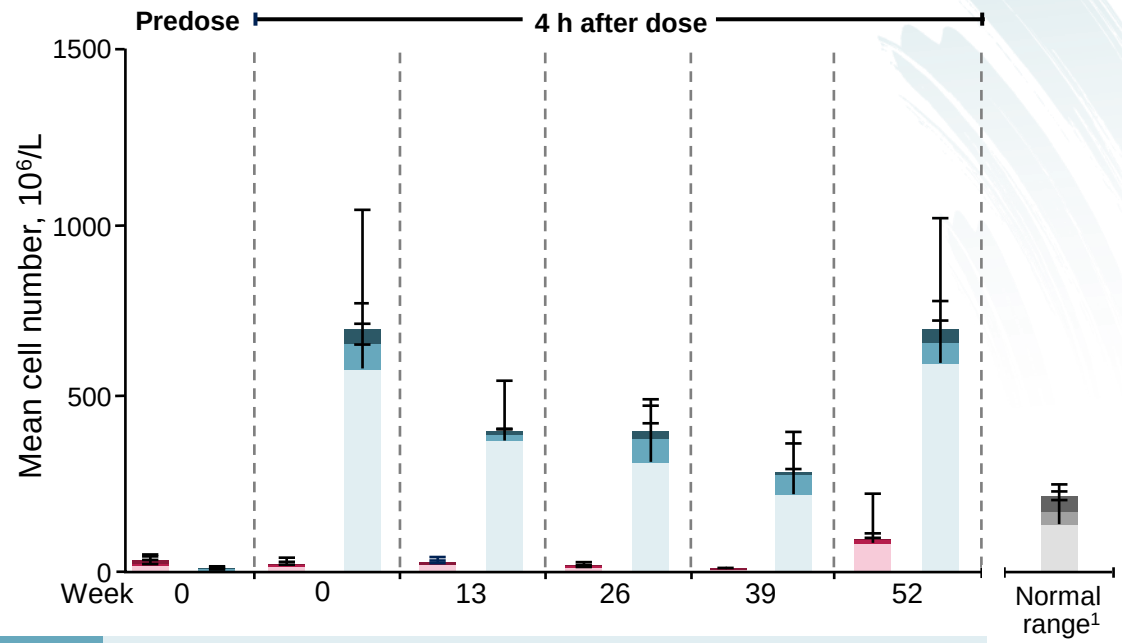
Total B Cells[a-d]



Mavorixafor n:	9	9	11	11	9	6[f]
Placebo n:	14	13	11	15	14	14[g]

Mavorixafor group Placebo group

Select B Cell Subpopulations[a,b]



Mavorixafor n:	10	9	11	11	9	6[f]
Placebo n:	14	13	11	15	14	14[g]

Mavorixafor	Placebo	Normal range	B cell subset
			Switched memory $CD45^+CD19^+IgD^-CD27^+$
			Unswitched memory $CD45^+CD19^+IgD^+CD27^+$
			Naïve $CD45^+CD19^+IgD^+CD27^-$

ANOVA, analysis of variance; CD, cluster of differentiation; LLN, lower limit of normal; ULN, upper limit of normal.

[a]One participant in the placebo arm received 1 dose of rituximab for Evan Syndrome during the trial and was excluded from the analysis. [b]Data represent mean and 95% CI. [c]Significance of differences between 2 groups was determined by 2-way ANOVA test. [d]Nominal *P* as no multiplicity adjustment was performed. [e]Dashed lines represent normal reference range from healthy donors.[1] [f]One participant in mavorixafor group did not receive mavorixafor dose at Week 52. [g]Three placebo participants were given mavorixafor at the Week 52 visit.

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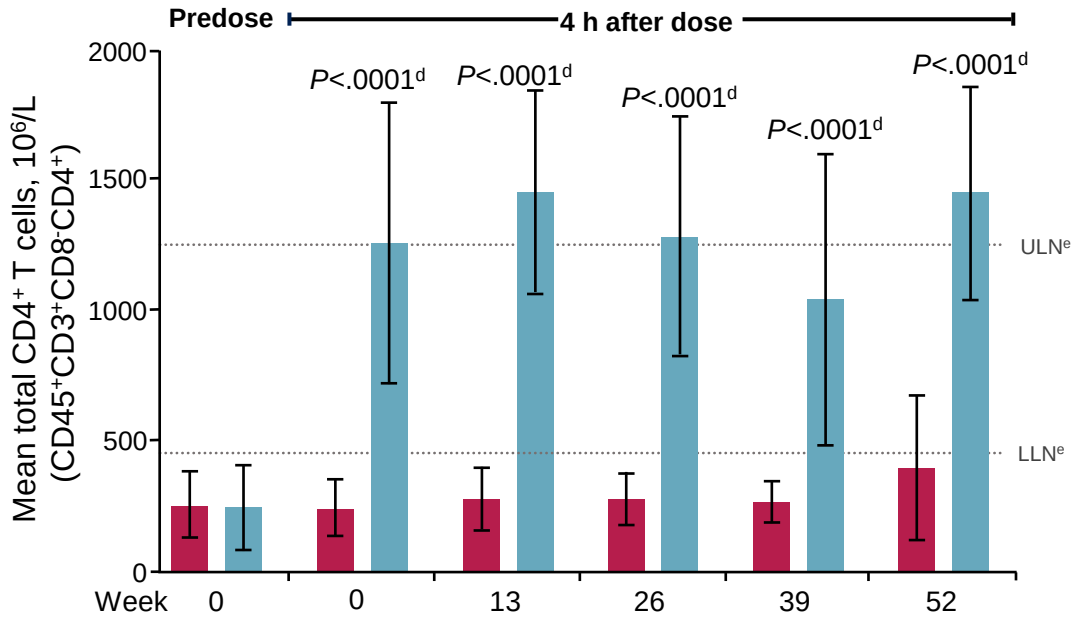
Mean Total CD4+ T Cell and Subpopulation Counts Increased and Were Sustained 4 Hours After Dose With Mavorixafor vs Placebo

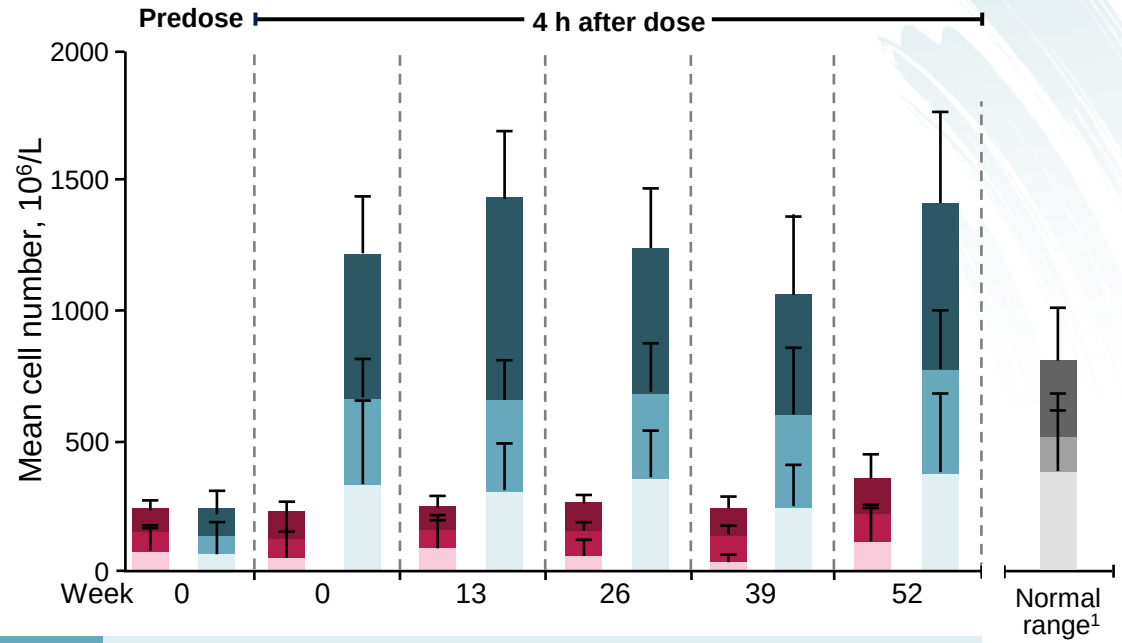
Total CD4+ T Cells[a-d]



Mavorixafor n:	9	8	10	11	9	6[f]
Placebo n:	14	12	11	15	14	14[g]

Mavorixafor group Placebo group

Select CD4+ T Cell Subpopulations[a,b]



Mavorixafor n:	9	8	10	11	8	6[f]
Placebo n:	14	12	10	15	14	14[g]

Mavorixafor	Placebo	Normal range	CD4+ T cell subset
			Central memory $CD3^+CD8^-CD4^+CD45RA^-CCR7^+$
			Effector memory $CD3^+CD8^-CD4^+CD45RA^-CCR7^-$
			Naïve $CD3^+CD8^-CD4^+CD45RA^+CCR7^+$

ANOVA, analysis of variance; CD, cluster of differentiation; LLN, lower limit of normal; ULN, upper limit of normal.

[a]One participant in the placebo arm received 1 dose of rituximab for Evan Syndrome during the trial and was excluded from the analysis. [b]Data represent mean and 95% CI. [c]Significance of differences between 2 groups was determined by 2-way ANOVA test. [d]Nominal *P* as no multiplicity adjustment was performed. [e]Dashed lines represent normal reference range from healthy donors.[1] [f]One participant in mavorixafor group did not receive mavorixafor dose at Week 52. [g]Three placebo participants were given mavorixafor at the Week 52 visit.

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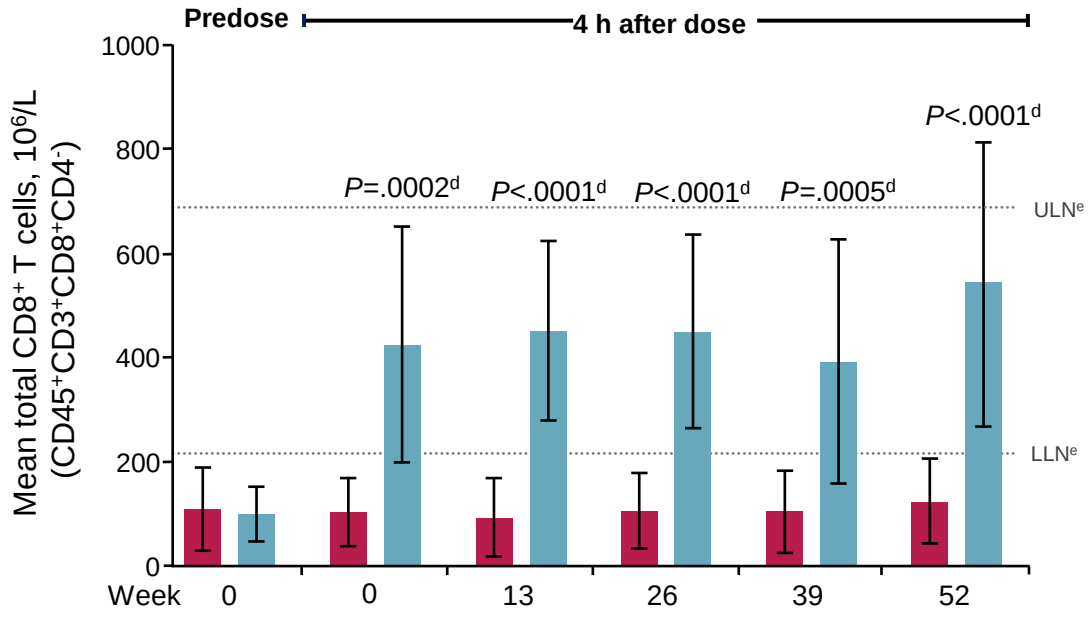
Mean Total CD8+ T Cell and Subpopulation Counts Increased and Were Sustained 4 Hours After Dose With Mavorixafor vs Placebo

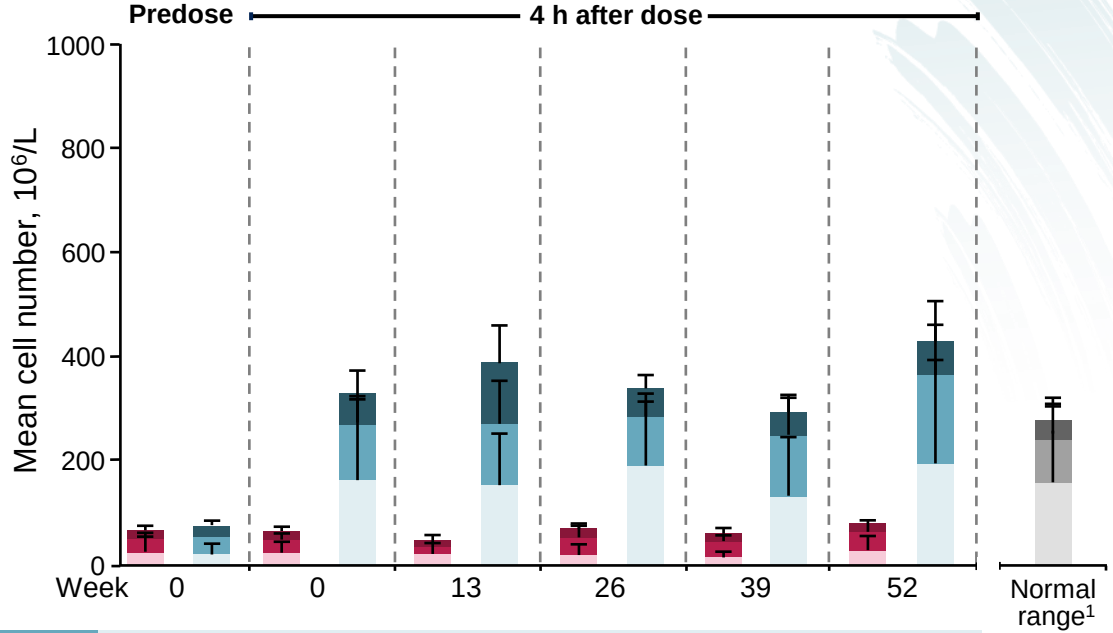
Total CD8+ T Cells[a-d]



Mavorixafor n:	9	9	11	11	9	6[f]
Placebo n:	13	13	11	15	14	14[g]

Mavorixafor group Placebo group

Select CD8+ T Cell Subpopulations[a,b]



Mavorixafor n:	9	9	11	11	8	6[f]
Placebo n:	13	13	10	15	14	14[g]

Mavorixafor	Placebo	Normal range	CD8+ T cell subset
			Central memory $CD3^+CD8^+CD4^-CD45RA^-CCR7^+$
			Effector memory $CD3^+CD8^+CD4^-CD45RA^-CCR7^-$
			Naïve $CD3^+CD8^+CD4^-CD45RA^+CCR7^+$

ANOVA, analysis of variance; CD, cluster of differentiation; LLN, lower limit of normal; ULN, upper limit of normal.

[a]One participant in the placebo arm received 1 dose of rituximab for Evan Syndrome during the trial and was excluded from the analysis. [b]Data represent mean and 95% CI. [c]Significance of differences between 2 groups was determined by 2-way ANOVA test. [d]Nominal *P* as no multiplicity adjustment was performed. [e]Dashed lines represent normal reference range from healthy donors.[1] [f]One participant in mavorixafor group did not receive mavorixafor dose at Week 52. [g]Three placebo participants were given mavorixafor at the Week 52 visit.

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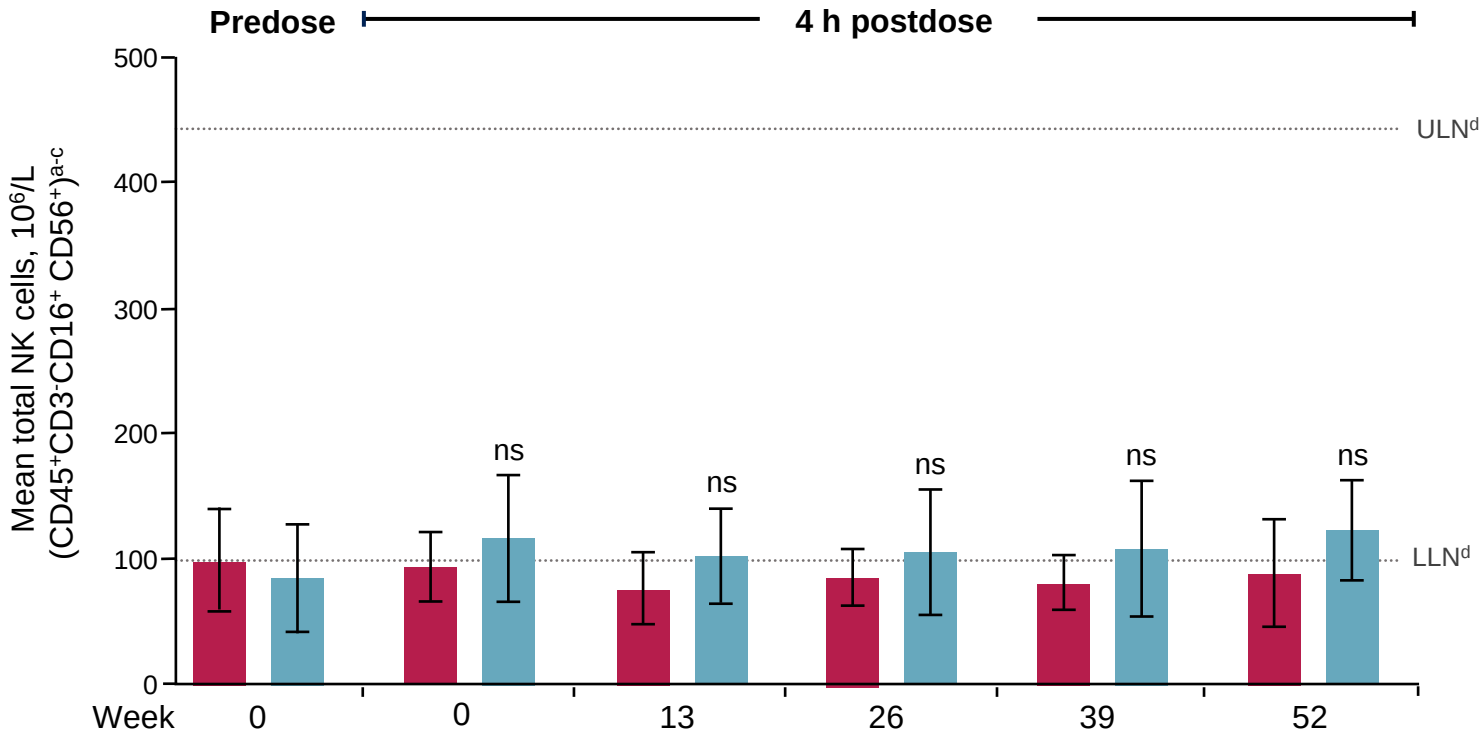
Mean Total NK Cell Counts Were Unchanged With Mavorixafor and Similar to Placebo



Mavorixafor n:	9	9	11	10	9	6[e]
Placebo n:	14	13	11	15	14	14[f]

ANOVA, analysis of variance; CD, cluster of differentiation; LLN, lower limit of normal; NK, natural killer; ns; not significant; ULN, upper limit of normal.

[a]One participant in the placebo arm received 1 dose of rituximab for Evan Syndrome during the trial and was excluded from the analysis. [b]Data represent mean and 95% CI. [c]Significance of differences between 2 groups was determined by 2-way ANOVA test. [d]Dashed lines represent normal reference range from healthy donors.[1] [e]One participant in mavorixafor group did not receive mavorixafor dose at Week 52. [f]Three placebo participants were given mavorixafor at the Week 52 visit.

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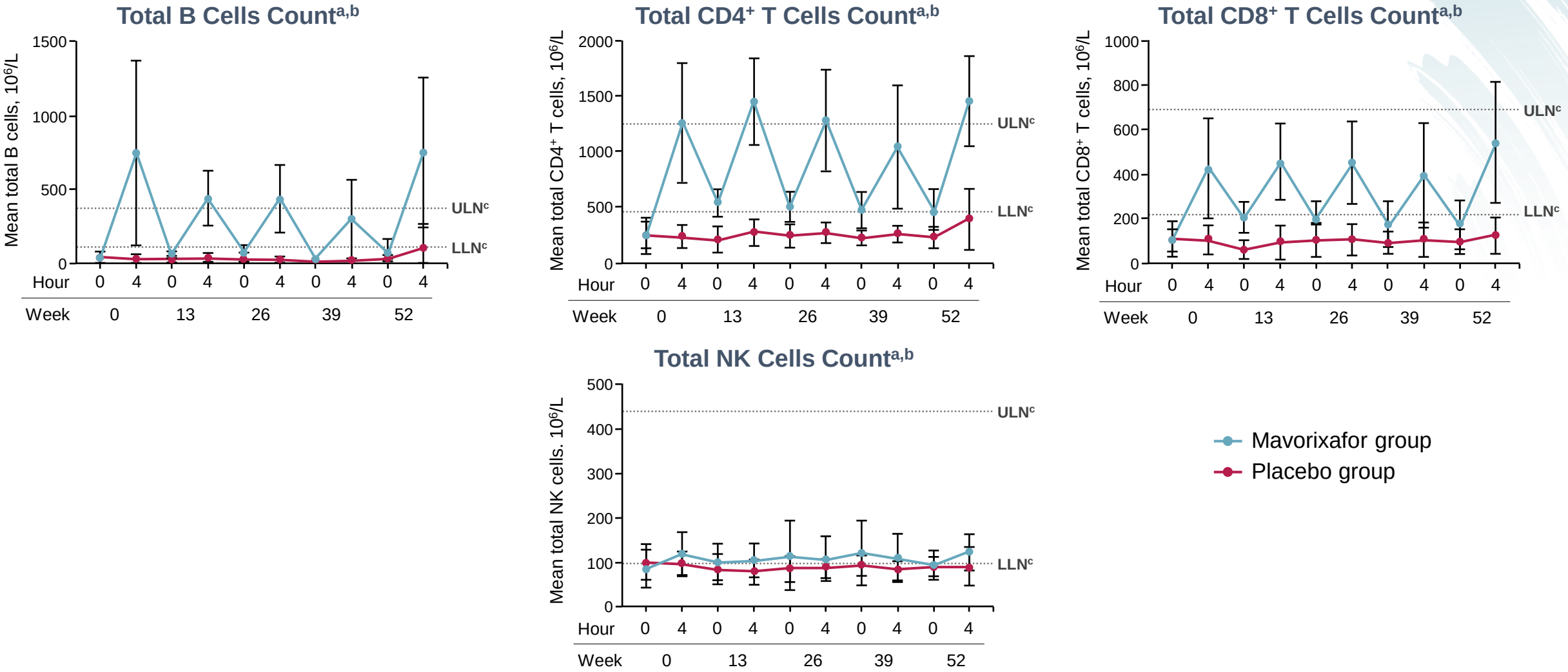
Mavorixafor Normalizes Absolute B- and T-Cell Counts Without Prolonging Elevation at Trough



CD, cluster of differentiation; LLN, lower limit of normal; NK, natural killer; ULN, upper limit of normal.

[a]One participant in the placebo arm received 1 dose of rituximab for Evan Syndrome during the trial and was excluded from the analysis. [b]Data represent mean and 95% CI. [c]Dashed lines represent normal reference range from healthy donors.[1]

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Conclusions

- Statistically significant increases in peripheral blood lymphocyte counts were observed in mavorixafor-treated participants compared with placebo:

↑ B cells

↑ Switched memory, ↑ unswitched memory, and ↑ naïve

↑ $CD4^+$ T cells and ↑ $CD8^+$ T cells

↑ Central memory, ↑ effector memory, and ↑ naïve

- B cell, $CD4^+$ T cell, and $CD8^+$ T cell counts increased to or above the normal reference range and was sustained at all timepoints assessed 4 hours after dose in the mavorixafor-treated group
- Higher levels of B and T lymphocytes and previously observed improved ANC potentially contributed to decreased infection rate, severity, and duration reported during RCP in mavorixafor-treated participants with WHIM syndrome

ANC, absolute neutrophil count; CD, cluster of differentiation; RCP, randomized controlled period; WHIM, Warts, Hypogammaglobulinemia, Infections, and Myelokathexis.

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