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Assessment of Lymphocyte Subpopulations in Blood: Results of a Phase 3 Trial in WHIM Syndrome

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Introduction

- 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]
- CXCR4 is highly expressed on most leukocytes, including all B and most T lymphocytes and their subsets[1,4-6]
- CXCR4-CXCL12 signaling regulates the balance between retention of immune cells in the bone marrow and mobilization to peripheral blood[7,8]
- In WHIM syndrome, hyperactive CXCR4 signaling due to impaired desensitization leads to increased retention of leukocytes in bone marrow[1,8-10]
- Mavorixafor is an investigational, orally active, selective small-molecule inhibitor of CXCR4 being evaluated for the treatment of WHIM syndrome[11,12]
  - In a phase 2 trial, participants receiving mavorixafor showed increases in peripheral neutrophils, lymphocytes, monocytes, and white blood cells (WBCs)[12,13]
  - In a randomized, placebo-controlled, double-blind, phase 3 trial, participants receiving mavorixafor showed increases in mean time above threshold (TAT) absolute neutrophil count (ANC; TAT_{ANC}) and mean TAT absolute lymphocyte count (ALC; TAT_{ALC})[11,14]

Objectives

- 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 randomized controlled period (RCP) of the phase 3 trial

Methods

Figure 1. 4WHIM Study Design. The phase 3 trial (NCT03995108) included an initial 12-month (52-week) randomized, double-blind, placebo-controlled period followed by an OLE (ongoing).[7,15]
OLE, open-label extension; 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.

- Absolute and fold change from baseline in absolute numbers of T, B, and natural killer lymphocyte subpopulations was assessed
- Blood samples were collected at baseline, before dose, and 4 hours after dose at Weeks 13, 26, 39, and 52, and at end of study for analysis of peripheral mononuclear cell subpopulations
- The significance of the difference between lymphocyte levels in participants receiving mavorixafor and placebo was assessed using 2-way analysis of variance (ANOVA), followed by Fisher's least significant difference test
  - All *P* values are nominal based on hierarchical testing of secondary endpoints as no multiplicity adjustment was performed

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Disclosures

RB is a consultant for X4 Pharmaceuticals, Angelini, and Janssen. **YH, LK, HM, CHN, AGT, SZ, KZ** are current employees and/or have equity ownership in X4 Pharmaceuticals. **JD** is a consultant for X4 Pharmaceuticals.

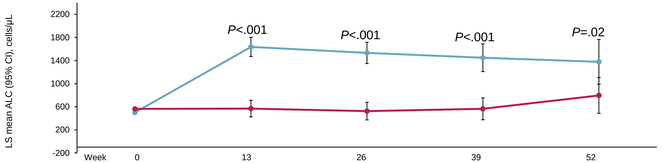
Results

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

	Mavorixafor (n=14)		Placebo (n=17)		Normal range (10^6/μL)[15,16]
	Value	n	Value	n	
Age, median (range), y	18 (12-58)	14	23 (13-72)	17	
12 to <18 y, n (%)	7 (50)		8 (47)		
≥18 y, n (%)	7 (50)		9 (53)		
Sex, female, n (%)	9 (64)	14	9 (53)	17	
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

Table 1. Key Demographics and Baseline Characteristics.
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 Evans syndrome during the trial and was excluded from the analysis.

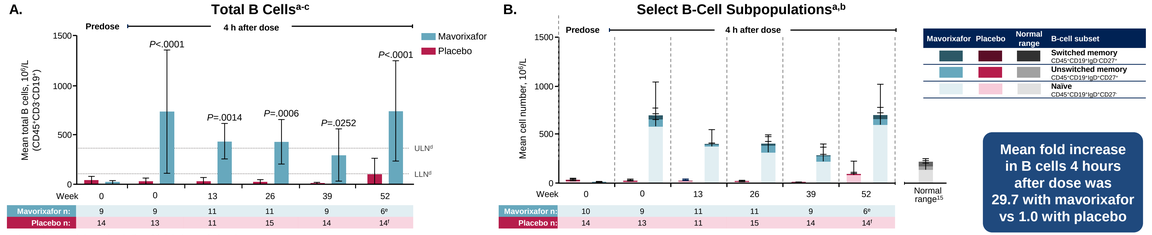
Participants treated with mavorixafor showed increased mean ALC from baseline over 52 weeks (ITT population[a])[14]



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

Figure 2. Mean ALC From Baseline Over 52 Weeks (ITT Population).
ALC, absolute lymphocyte count; ITT, intent to treat; LS, least squares.
[a]The ITT population comprised all participants randomized to treatment, including 1 participant in the placebo arm who received 1 dose of rituximab for Evans syndrome during the trial. [b]One participant in the mavorixafor group did not receive mavorixafor dose at Week 52. [c]Three placebo participants were given mavorixafor at the Week 52 visit.

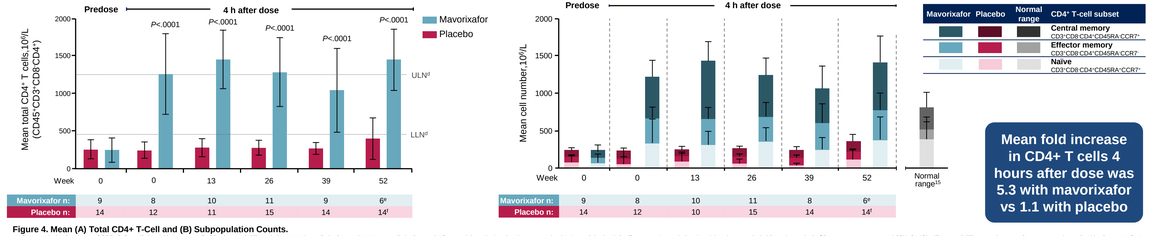
Mean total B-cell and subpopulation counts increased and were sustained 4 hours after dose with mavorixafor vs placebo



Mean fold increase in B cells 4 hours after dose was 29.7 with mavorixafor vs 1.0 with placebo

Figure 3. Mean (A) Total B Cell and (B) Subpopulation Counts.
ANOVA, analysis of variance; CD, cluster of differentiation; IgD, immunoglobulin D; LLN, lower limit of normal; ULN, upper limit of normal. [a]One participant in the placebo arm received 1 dose of rituximab for Evans 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.[15] [e]One participant in the mavorixafor group did not receive mavorixafor dose at Week 52. [f]Three placebo participants were given mavorixafor at the Week 52 visit.

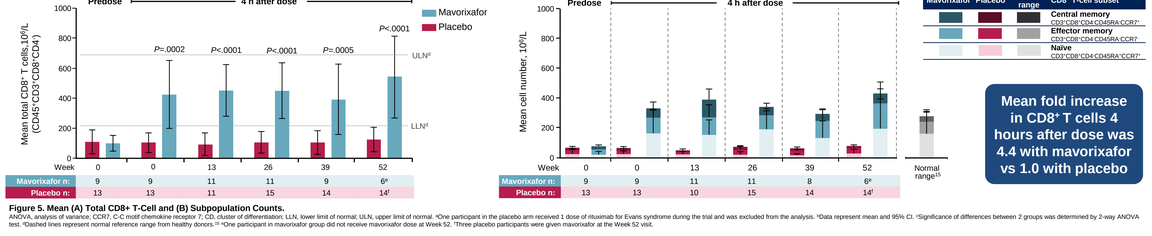
Mean total $CD4^+$ T-cell and subpopulation counts increased and were sustained 4 hours after dose with mavorixafor vs placebo



Mean fold increase in CD4+ T cells 4 hours after dose was 5.3 with mavorixafor vs 1.1 with placebo

Figure 4. Mean (A) Total CD4+ T-Cell and (B) Subpopulation Counts.
ANOVA, analysis of variance; CCR7, C-C motif chemokine receptor 7; 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 Evans 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.[15] [e]One participant in the mavorixafor group did not receive mavorixafor dose at Week 52. [f]Three placebo participants were given mavorixafor at the Week 52 visit.

Mean total $CD8^+$ T-cell and subpopulation counts increased and were sustained 4 hours after dose with mavorixafor vs placebo



Mean fold increase in CD8⁺ T cells 4 hours after dose was 4.4 with mavorixafor vs 1.0 with placebo

Figure 5. Mean (A) Total CD8+ T-Cell and (B) Subpopulation Counts.
ANOVA, analysis of variance; CCR7, C-C motif chemokine receptor 7; 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 Evans 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.[15] [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.

Conclusions

- Increases in peripheral blood lymphocyte counts were observed in mavorixafor-treated participants compared with placebo:
  - Increased B cells including subsets (switched memory, unswitched memory, and naïve)
  - Increased $CD4^+$ and $CD8^+$ T cells including subsets (central memory, effector memory, and naïve)
- B-, $CD4^+$ T-, and $CD8^+$ T-cell counts increased to or above the normal reference range and were 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
- $CD4^+/CD8^+$ T-cell ratio did not change substantially from baseline and was not significantly different between the groups
- Mean total natural killer (NK) cell counts were unchanged with mavorixafor and were similar to placebo. The mean fold increase 4 hours after dose was 1.3 with mavorixafor vs 0.9 with placebo
- Mavorixafor normalized absolute B-, $CD4^+$ and $CD8^+$ T-, and NK-cell counts without prolonged elevation at trough

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