Mavorixafor in Adolescents With WHIM Syndrome: A Prespecified Subgroup Analysis From Phase 3 Trial

ClinicalTrials.gov Identifier NCT03995108

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Background

- Warts, Hypogammaglobulinemia, Infections, and Myelokathexis (WHIM) syndrome is a rare combined primary immunodeficiency and chronic neutropenic disorder resulting from impaired leukocyte mobilization from bone marrow to peripheral blood, predominantly caused by gain-of-function variants in CXCR4[1,2]
- Clinical manifestations of WHIM syndrome include chronic neutropenia, lymphopenia, and recurrent and/or severe infections with variable hypogammaglobulinemia. WHIM syndrome typically manifests in early childhood but diagnosis is often delayed[1,2]
- Mavorixafor is an investigational, orally active, selective antagonist of CXCR4 that leads to egress of leukocytes from the bone marrow to peripheral blood
- Mavorixafor was evaluated in a phase 3 trial for the treatment of patients (aged ≥12 years) with WHIM syndrome (NCT03995108)[3,4]
- Results from the randomized placebo-controlled period of this phase 3 trial (previously presented) showed that mavorixafor-treated participants experienced significant increases in mean time above threshold (TAT) absolute neutrophil count (ANC; TAT_{ANC}) and mean TAT absolute lymphocyte count (ALC; TAT_{ALC}) compared with placebo. Additionally, mavorixafor was generally well tolerated[4]
- The open-label extension period is ongoing

Objective

- To evaluate the efficacy and safety of mavorixafor vs placebo in the adolescent cohort (aged 12 to <18 years) with WHIM syndrome enrolled in the 52-week randomized period of the phase 3 trial

Methods

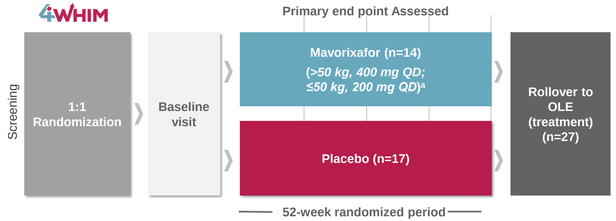


Figure 1. 4WHIM Study Design. The phase 3 trial (NCT03995108) included a 12-month (52-week) randomized, double-blind, placebo-controlled period followed by an OLE (ongoing). TAT_{ANC} is defined as time (in hours) above threshold ANC ≥500 cells/μL over a 24-hour period, assessed every 3 months for 52 weeks. TAT_{ALC} is defined similarly to TAT_{ANC} but with ALC threshold ≥1000 cells/μL. OLE, open-label extension; QD, once daily; TAT, time above threshold.
[a]Adults and adolescents (aged 12 to <18 years) weighing >50 kg received 400 mg mavorixafor QD; adolescents aged 12 to <18 years weighing ≤50 kg received 200 mg QD.

- Analysis of the prespecified subgroup of participants included the following assessments: time (hours) above ANC threshold (≥500 cells/μL) over 24 hours (TAT_{ANC}), TAT_{ALC} over 24 hours (ALC threshold ≥1000 cells/μL), infection rate, and safety
- Results presented are from the 52-week randomized, placebo-controlled period only

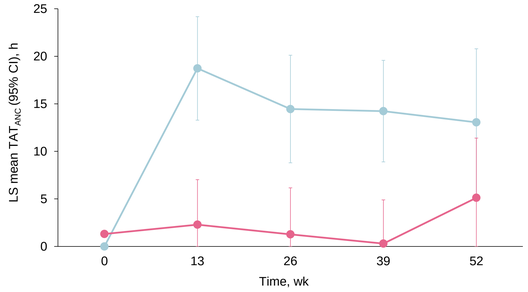
Results

- Of 31 participants who were randomized, 15 were adolescents distributed 1:1 into mavorixafor and placebo groups. At baseline, all adolescents had neutropenia and lymphopenia

Baseline characteristics	Mavorixafor		Placebo	
	Adolescents (12 to <18 y) (n=7)	Overall ITT population (N=14)	Adolescents (12 to <18 y) (n=8)	Overall ITT population (N=17)
Sex, female, n (%)	3 (42.9)	9 (64.3)	5 (62.5)	9 (52.9)
Screening ANC (cells/μL) Median (min, max)	118 (40, 330)	150 (40, 390)	160 (80, 330)	200 (0, 400)
Screening ALC (cells/μL) Median (min, max)	386 (280, 670)	420 (260, 1070)	419 (250, 660)	520 (100, 8560)
Screening AMC (cells/μL) Median (min, max)	85 (40, 100)	70 (30, 390)	93 (60, 150)	100 (0, 420)
Screening WBC count (cells/μL) Median (min, max)	718 (500, 1610)	600 (300, 1800)	794 (540, 2740)	800 (200, 9300)

Table 1. Key Demographics and baseline characteristics. ALC, absolute lymphocyte count; AMC, absolute monocyte count; ANC, absolute neutrophil count; ITT, intent-to-treat; WBC, white blood cell; y, year.

Adolescent participants receiving mavorixafor showed improvements in TAT_{ANC} compared with placebo over 52 weeks

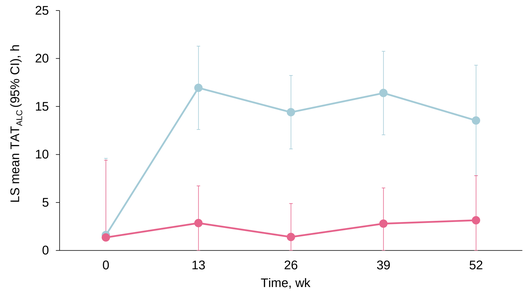


Mavorixafor, <18 y n:	6	7	7	6	6
Placebo, <18 y n:	7	8	8	8	8

Figure 2. TAT_{ANC} versus time on treatment with mavorixafor vs placebo over 52 weeks in adolescents. 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. ANC, absolute neutrophil count; h, hour; LS, least squares; TAT, time above threshold; wk, week; y, year.

- In the adolescent subgroup, the overall least squares (LS) mean TAT_{ANC} was 15.11 hours (95% CI, 9.99–20.24) for the mavorixafor group vs 2.25 hours (95% CI, 0.00–6.74) for the placebo group through week 52

Adolescent participants receiving mavorixafor showed improvements in TAT_{ALC} compared with placebo over 52 weeks



Mavorixafor, <18 y n:	6	7	7	6	6
Placebo, <18 y n:	7	8	8	8	8

Figure 3. TAT_{ALC} versus time on treatment with mavorixafor vs placebo over 52 weeks in adolescents. 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. ALC, absolute lymphocyte count; h, hour; LS, least squares; TAT, time above threshold; wk, week; y, year.

- In the adolescent subgroup, the overall LS mean TAT_{ALC} was 15.32 hours (95% CI, 11.44–19.21) for the mavorixafor group vs 2.54 hours (95% CI, 0.00–6.05) for the placebo group through week 52

Adolescent participants receiving mavorixafor showed reduction in annualized infection rate compared with placebo

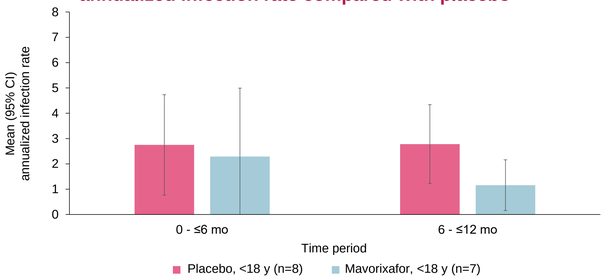


Figure 4. Mean annualized infection rate by 6-month interval with mavorixafor vs placebo in adolescents. mo, month; y, year.

- Overall annualized infection rate was reduced in the mavorixafor vs placebo group (LS mean 1.6 and 2.4, respectively)

Safety profile for the adolescent population (safety population)[a]

	Mavorixafor (n=7)	Placebo (n=8)
Participants with any TEAE, n (%)	7 (100)	8 (100)
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
TEAEs by SOC ≥2, n (%)		
Infections and infestations	5 (71.4)	8 (100)
Skin and subcutaneous tissue disorders	4 (57.1)	2 (25.0)
GI disorders	3 (42.9)	1 (12.5)
Nervous system disorders	2 (28.6)	3 (37.5)
Blood and lymphatic disorders	2 (28.6)	0
Respiratory, thoracic, and mediastinal disorders	2 (28.6)	3 (37.5)
General disorders and administration site conditions	2 (28.6)	1 (12.5)
Injury, poisoning, and procedural complications	0	3 (37.5)
Investigations	2 (28.6)	1 (12.5)
Participants with any TESAE,[b] n (%)	2 (18.6)	1 (12.5)
Thrombocytopenia	0	0
Febrile neutropenia	0	0
Platelet count decreased	1	0
COVID-19	1 (14.3)[c]	0
Campylobacter gastroenteritis	0	0
Endocarditis	0	0
Sepsis	0	0
Cellulitis	0	0
Sepsis	0	0
Lipase increased	1 (14.3)[c]	0
Malignant glioma	0	0
Pneumonitis	0	1 (12.5)

Table 2. Summary of AEs (safety population). AE, adverse event; GI, gastrointestinal; SOC, system organ class; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.
[a]The safety population included all participants randomly assigned to treatment who received ≥1 dose of study medication. [b]Participants may have experienced ≥2 different categories of AEs. [c]TESAEs reported in the same participant (aged <18 y) receiving mavorixafor.

- Treatment-emergent adverse events (TEAEs) were reported in both mavorixafor and placebo groups
  - Types of TEAEs were similar across adolescent participants and the overall study population
- No treatment-emergent serious adverse events were deemed related to treatment by investigators

Conclusions

- Adolescent participants with WHIM syndrome receiving oral mavorixafor experienced:
  - Improvements in both LS mean TAT_{ANC} and TAT_{ALC} compared with placebo
  - Reduction in annualized infection rates compared with placebo
- Overall, the efficacy and safety profile of mavorixafor in adolescents were comparable to those of the overall treated population in the phase 3 trial,[4] supporting the potential clinical benefit of mavorixafor in adolescents with WHIM syndrome

Acknowledgments

The authors would like to thank the trial participants and their families and caregivers, investigators, and investigational site staff. The authors also would like to acknowledge Diego Cadavid, MD, and Sarah Cohen, MD, formerly of X4 Pharmaceuticals, Inc.; Paula Ragan, PhD, Lori Neri, Eloisa Chapa, Joanna Haas, Ken Gorelick, Candida Fratazzi, Hal Hoffman, MD, Anjali Shartharukumar, MD, Atil Bisgin, MD, Istvan Varkonyi, MD, Felipe Suarez, MD, Weihua Tang, PhD, Peter Olbrich, MD, PhD, Elisa Cordero, MD, PhD, the LLX Solutions Team, Syneos Health, and Valerie Tjon-a-Koy for their contributions; members of the data monitoring committee, including Eric Gershwin, MD, John Levine, MD, and Charles Davis, PhD; and members of the independent adjudication committee, including Craig Platt, MD, PhD, Kathryn Edwards, MD, and Ester de Vries, MD. Medical writing assistance was provided by PRECISIONscientia in Yardley, Pennsylvania, with financial support from X4 Pharmaceuticals, Inc., and in compliance with international Good Publication Practice guidelines.

Disclosures

KED is an advisor for Agios related to the pediatric trials for mitapivat and PK deficiency. **AA** is a consultant for Grifols, argenx, Takeda, Adma, and Octapharma and has received grants from mX4, Grifols, and argenx. **RB** is a consultant for X4 Pharmaceuticals. **JD** is a consultant for X4 Pharmaceuticals. **HJ** is a former employee of X4 Pharmaceuticals and/or has equity ownership in X4 Pharmaceuticals. **SD, YH, HJ, SL, DJS,** and **CAE** are current employees and/or have equity ownership in X4 Pharmaceuticals.

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Presented at the 2024 American Society of Pediatric Hematology/Oncology (ASPHO) Conference; April 3-6, 2024; Seattle, Washington