Mavorixafor, an Oral CXCR4 Antagonist, for Treatment of Patients With WHIM Syndrome: Results From the Long-Term Extension of the Open-Label Phase 2 Study

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Poster #1121

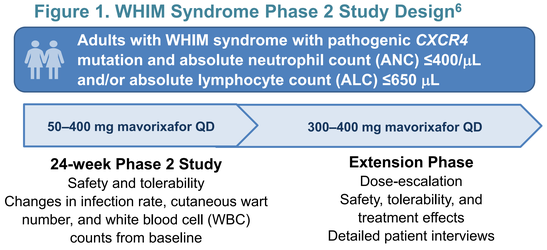
Background

- WHIM (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis) syndrome is a rare primary immunodeficiency classically caused by gain-of-function *CXCR4* mutations[1-5]
- Oral, once-daily (QD) mavorixafor is an investigational, small-molecule, selective CXCR4 antagonist in clinical development for the treatment of WHIM syndrome[6]
- We present updated results from the open-label, prospective, dose-escalation phase 2 study (NCT03005327) including the ongoing long-term extension (LTE) phase evaluating mavorixafor in patients with WHIM syndrome[6]

Methods

- The phase 2 and LTE study design is summarized in Figure 1

Figure 1. WHIM Syndrome Phase 2 Study Design[6]



Results

- Patient disposition and baseline characteristics are shown in Figure 2 and Table 1. Median treatment duration in the LTE was 148.4 weeks

Figure 2. Patient Disposition

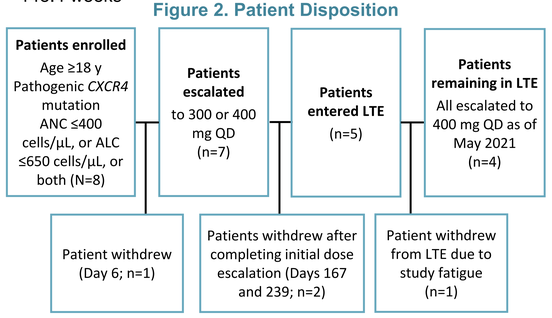


Table 1. Baseline Demographic and Clinical Characteristics

	Age, y	Sex	Race	*CXCR4* mutation	Time on study,[a] mo	Dose
Participant 1	**37**	**Male**	**White**	***R334X***	**40**	**400 mg**
Participant 2	**57**	**Female**	**White**	***R334X***	**40**	**400 mg**
Participant 3	19	Female	White	*R334X*	8	off study
Participant 4	25	Male	White	*p.E343X*	5.6	off study
Participant 5	34	Female	White	*S324fs365X*	0.2	off study
Participant 6	**24**	**Female**	**White**	***R334X***	**36.8**	**400 mg**
Participant 7	**41**	**Female**	**White**	***R334X***	**33.8**	**300 mg**
Participant 8	**49**	**Female**	**White**	***R334X***	**33.6**	**300 mg**

[a]Cutoff date November 2020.

Long-term Mavorixafor Treatment Shows Durable Effectiveness in Increasing Peripheral WBC and WBC SubType Counts and Reducing Infection Rates

Figure 3. Improvements in Peripheral WBC Counts After Mavorixafor (300-400 mg) Treatment

- Total WBC count, ANC, ALC, and absolute monocyte count (AMC) increased after the first dose of mavorixafor and the increases were sustained at 339%, 652%, 239%, and 486% of baseline at 6 months (n=5) (Figure 3)

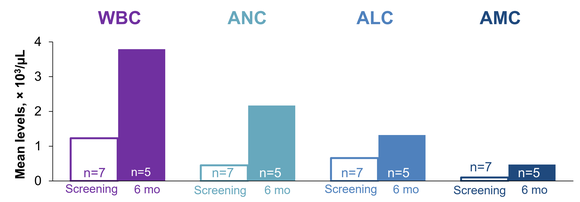


Figure 4. Mean TAT for WBC Subsets

- Mean time above threshold (TAT, hours) for ANC, ALC, and AMC were greater at doses of 300/400 mg QD versus 50 mg QD (Figure 4)

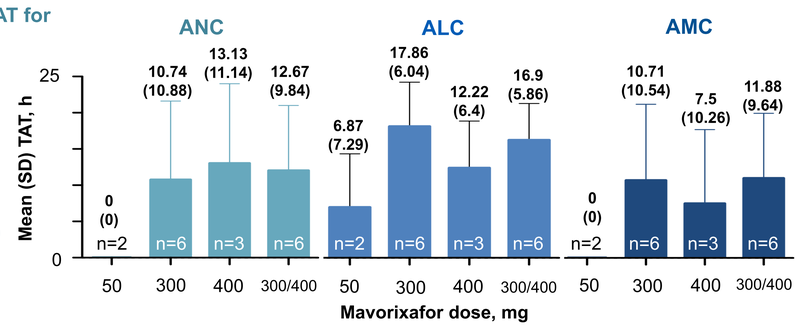
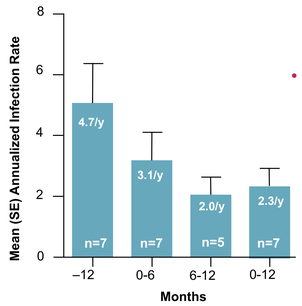
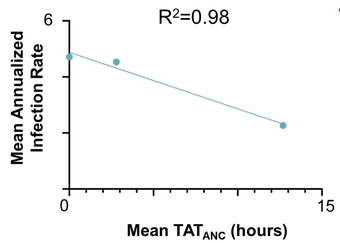


Figure 5. Infection Rate Over Time



- Mean annualized infection rate decreased after treatment with mavorixafor 300/400 mg (Figure 5)

Figure 6. Infection Rate Correlation With TAT_{ANC}

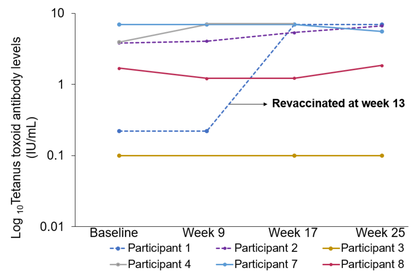


- With increased doses of mavorixafor (0 mg, 50–150 mg, and 300–400 mg, respectively) infection rates decreased; mean annualized infection rate overall inversely correlated with TAT_{ANC} (Figure 6)

Mavorixafor Treatment Resulted in Increased Tetanus Toxoid IgG Antibody Levels

- After mavorixafor treatment, tetanus toxoid IgG antibody levels increased slightly in participants 2 and 4 (Figure 7)
- 1 participant was revaccinated at week 13 and showed a jump in tetanus toxoid IgG antibody levels (Figure 7)

Figure 7. Tetanus Toxoid IgG Antibody Levels[a]



[a]Participant 1 was revaccinated at week 13 of study. All other participants may have been vaccinated before study but were not revaccinated during the study

Long-term Treatment With Mavorixafor Was Well Tolerated

- Safety data review in May 2021, showed that out of a total of 91 adverse events (AE), 12 were treatment-emergent AEs possibly related to study drug (Grade 1) and there were no treatment-related infections of grade 3 or higher. There were 5 serious adverse events (SAEs) unrelated to study drug (Table 2)

Table 2. Cumulative Summary of related TEAEs and all SAEs Since Screening

System Organ Class	Preferred Term	AE Count	CTCAE Grade	Relation to Study Drug
Gastrointestinal disorders	Dry mouth	2	1	Possibly related AE
	Dyspepsia	2	1	Possibly related AE
	Nausea	4	1	Possibly related AE
Infections and infestations	Conjunctivitis	1	1	Possibly related AE
Respiratory, thoracic and mediastinal disorders	Nasal dryness	2	1	Possibly related AE
Skin and subcutaneous tissue disorders	Dermatitis psoriasiform	1	1	Possibly related AE
General disorders	Pyrexia	1	2	Unrelated SAE
Infections & Infestations	Bronchitis	1	2	Unrelated SAE
	Cellulitis	1	3	Unrelated SAE
	Influenza	1	2	Unrelated SAE
Injury, poisoning and procedural complications	Left tibia fracture	1	3	Unrelated SAE

CTCAE, Common Terminology Criteria for Adverse Events.

Patients Reported Significant Improvements in Symptoms While on Long-term Mavorixafor Treatment

- Patient interviews were completed by June 2021. 4/4 patients reported improvement in the severity of infections, and 3 out of 4 participants said that their infections resolved more quickly. Reported changes in warts were variable, and participants reported a range of minor gastrointestinal-related symptoms that they suspected were related to taking the medication while fasting (Table 3)

Table 3. Findings From Patient Global Impression of Change

		Experience after treatment			
Participant	Experience before treatment	Infections	Infection frequency, severity, and duration	Warts	Hospital/ doctor visits
1	Sore gums, sinus infections, sores on knuckles, cellulitis, deep tissue infection on foot, 6-10 urgent care visits/year, minimal warts	A little better	Decreased	No change	Decreased
6	Cold sores, ear infections, cellulitis, staph infections, many warts "all over"	Much better	Decreased	Much better	Decreased
7	Skin infections, kidney infection, osteomyelitis, about 6 urgent care visits/year, warts as a child that decreased with age	Much better	Decreased	No change	Decreased
8	Severe oral infections resulting in loss of all teeth, frequent ear infections, frequent lung infections and bronchiectasis, skin infections, genital warts and precancerous lesions, frequent urgent care visits/year and hospitalization	Much better	Decreased	A little better	Decreased

Conclusions

- Ongoing long-term treatment of adults with WHIM syndrome with mavorixafor 300 to 400 mg shows durable increase in neutrophils, lymphocytes, and monocytes, increased TAT for ANC, ALC, and AMC as well as sustained improvements in infections and warts with decreased annualized rates of infections correlating well with TAT_{ANC}
- Detailed patient interviews for patient Global Impression of Change are consistent with sustained clinical benefit of long-term treatment
- After initiation of mavorixafor treatment, tetanus toxoid IgG antibody levels increased slightly in 2/6 patients and 1 participant displayed a significant increase in tetanus toxoid IgG antibody levels following revaccination with tetanus toxoid at week 13 of the study, indicating improved immune response
- It is important to keep in mind that this study included a small patient population with high variability in the dataset
- Mavorixafor has the potential to be a safe, effective, and long-term therapy targeting the underlying cause of WHIM syndrome. A global phase 3 registrational study has been fully enrolled and is ongoing, with top-line results expected in Q4 2022

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Disclosures

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