Determination of Phase 3 Dose for X4P-001 in Patients with WHIM Syndrome

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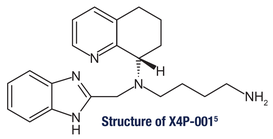
Background

WHIM (Warts, Hypogammaglobulinemia, Infections, Myelokathexis) Syndrome:

- Autosomal dominant, primary immunodeficiency disease caused by mutations in *CXCR4*.
- Gain-of-function *CXCR4* mutations induce leukocyte retention in bone marrow and other extravascular sites, resulting in severe chronic neutropenia and lymphopenia.[1-3]
- Current therapies include immunoglobulins (Ig), granulocyte colony stimulating factor (G-CSF) and antibiotics. However, the efficacy of Ig and G-CSF in WHIM have not been established in the clinical trial setting.[4]
- *CXCR4* antagonists are under investigation as specific, mutation-targeted therapies.[5-7]

X4P-001

- Non-competitive, allosteric, small molecule antagonist of *CXCR4*.
- Orally bioavailable with a mean terminal half-life ($t_{1/2}$) of ~23 hours, allowing once-daily dosing.
- Hypothesis: *X4P-001-mediated inhibition of hyperactive CXCR4 will increase mobilization of neutrophils and lymphocytes into circulation, resulting in improved systemic immune responses and reduced infections.*



Structure of X4P-001[5]

Study Design

This is an interim report on Phase 2 of an open-label, intra-patient, dose-escalation Phase 2/3 study of X4P-001 therapy in WHIM patients ≥18 years of age (X4P-001-MKKA).

Primary Phase 2 Study Objectives:

- Evaluate the safety and tolerability of oral X4P-001 therapy in patients with WHIM syndrome
- Determine the dose required to achieve a consistent increase in absolute neutrophil count (ANC) and absolute lymphocyte count (ALC)

Treatment

- Oral X4P-001 QD was initiated in patients at different starting doses (50, 100, 200, or 300 mg).
- Intra-patient dose escalation is based on 24-hour serial area under the curve (AUC) measurements for ANC and ALC.

Pharmacokinetic and Pharmacodynamic Assessments

- Pharmacokinetic (PK) and Pharmacodynamic (PD) analyses within this interim report were based on a cutoff date of 17 Aug 2018.
- The longest duration of patient exposure for this analysis was 560 days, and the cumulative duration of exposure for all patients was 2227 days.
- Assessment of X4P-001 PK was done using noncompartmental analysis (NCA).
- 24-hour AUC_{ANC} and AUC_{ALC} were calculated using the trapezoidal method (AUC_{last}). For $AUC_{threshold}$ the AUCs were calculated relative to a pre-specified threshold of 600 cells/µL and 1000 cells/µl for ANC and ALC, respectively.
  - The ANC threshold represents a 50% increase over the highest permitted entry ANC, and a transition from Grade 4 to Grade 3 neutropenia. The ALC threshold represents a lymphocyte count within the normal range.
- The correlation between X4P-001 PK parameters and ANC/ALC was explored.

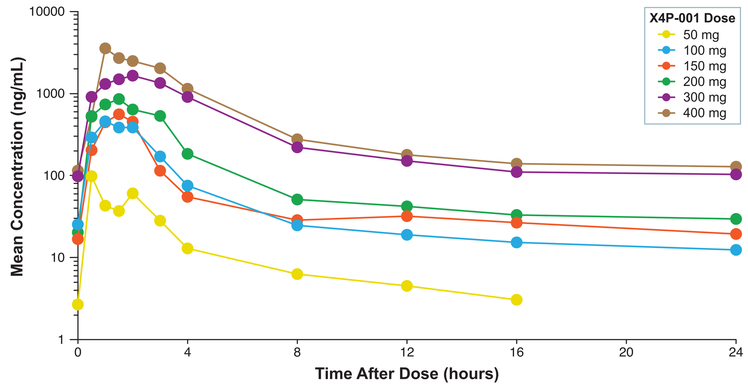
Patient Demographics and Baseline Characteristics

ID	Age (years)	Gender	Race	*CXCR4* Mutation	Time on Study (months) as of 13 Nov 2018	Status
1	37	Male	White	R334X	22.0	Now at 400 mg
2	57	Female	White	R334X	22.0	Now at 400 mg
3	19	Female	White	R334X	8.0	Off study
4	25	Male	White	E343X	5.6	Off study
5	34	Female	White	S365X	0.2	Off study
6	24	Female	White	R334X	12.8	Now at 400 mg
7	41	Female	White	R334X	9.8	Now at 300 mg
8	49	Female	White	R334X	9.6	Now at 300 mg

References: **1)** Hernandez PA, Gorlin RJ, Lukens JN, et al. Mutations in the chemokine receptor gene CXCR4 are associated with WHIM syndrome, a combined immunodeficiency disease. Nature Genetics 2003;34(1):70-74. **2)** Gulino AV, Moratto D, Sozzani S, et al. Altered leukocyte response to CXCL12 in patients with Warts Hypogammaglobulinemia, Infections, Myelokathexis (WHIM) syndrome. Blood 2004;104(2):444-452. **3)** Biajoux, et al. Efficient Plasma Cell Differentiation and Trafficking Require CXCR4 Desensitization. Cell Rep. 2016 Sep 27;17(1):193-205. **4)** Badolato R Donadieu J; WHIM Research Group. How I treat warts, hypogammaglobulinemia, infections, and myelokathexis syndrome. Blood. 2017;130(23):2491-2498. **5)** Dale DC, Bolyard AA, Kelley ML, et al. The CXCR4 antagonist plerixafor is a potential therapy for myelokathexis, WHIM syndrome. Blood 2011;118(18):4963-4966. **6)** McDermott DH, Liu Q, Velez D, et al. A phase 1 clinical trial of long-term, low-dose treatment of WHIM syndrome with the CXCR4 antagonist plerixafor. Blood. 2014;123(15):2308-16. **7)** Heusinkveld LE, Yim E, Yang A, et al. Pathogenesis, diagnosis and therapeutic strategies in WHIM syndrome immunodeficiency. Expert Opin Orphan Drugs. 2017;5(10):813-825.

X4P-001 Pharmacokinetics and Pharmacodynamics

X4P-001 Plasma Concentrations Over Time



- Maximum X4P-001 plasma concentrations were reached 1.5 hours after oral administration.
- X4P-001 displays bi-phasic elimination, with a rapid initial decline, followed by a longer terminal phase.
- Exposures appear to increase in a supra-proportional manner.

ANC AUC Above Threshold by Dose Level

Dashed line: ANC $AUC_{threshold}$, calculated based on 600 cells/µL x 24 hr dosing interval. Dotted line: baseline threshold, calculated as geometric mean baseline ANC across subjects x 24 hr dosing interval. N = number of patients at each dose level.

ALC AUC Above Threshold by Dose Level

Dashed line: ALC $AUC_{threshold}$, calculated based on 1000 cells/µL x 24 hr dosing interval. Dotted line: baseline threshold, calculated as geometric mean baseline ALC across subjects x 24 hr dosing interval. N = number of patients at each dose level.

ANC AUC PK/PD Correlations

ALC AUC PK/PD Correlations

- X4P-001 exposure appears to correlate with ANC and ALC AUC.
- ALC response to X4P-001 appears to be maximal by the 100 mg dose, whereas a dose of ≥ 300 mg is required to achieve clinically relevant ANC in any patient.
- Patient 8 (outlier, marked with arrows) met the inclusion criteria and has a history of splenectomy. None of the other patients have had splenectomy. During study period patient had persistent high neutrophils, greater than 1100 cells/µL.

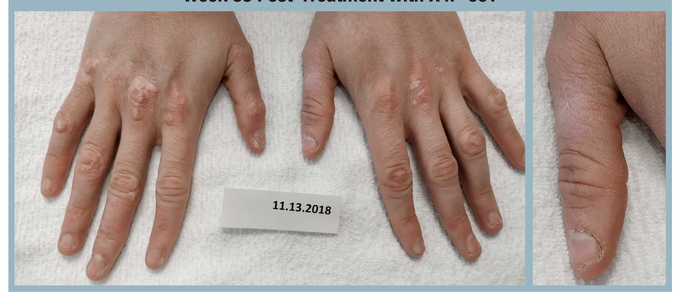
Safety

- X4P-001 was well-tolerated with no serious adverse events (AEs) reported at the doses tested.
- Treatment-emergent AEs occurring in more than one patient included: dry mouth (2), nasopharyngitis (2), nausea (3), sinusitis (2) and upper respiratory tract infection (2).
- All X4P-001-related AEs were grade 1.
- In 9+ months at the 400 mg dose level, 2 infections reported in 3 patients dosed (27+ months of combined X4P-001 exposure):
  - Patient 1 had 1 infection event - pharyngitis
  - Patient 2 had no infection events
  - Patient 6 had 1 infection event - sinusitis

Reductions in Warts Following X4P-001 Therapy

Pre-Treatment

Week 55 Post-Treatment with X4P-001



X4P-001 Exposure: WHIM patient #6 after 55 weeks of investigational X4P-001 therapy (200 mg QD for 6 weeks, 300 mg QD for 6 weeks, and 400 mg QD for 43 weeks). Patient did not use topical medications during the treatment period. Improvement in wart lesions was reported by the investigator as a probable drug effect. Photos courtesy of Dr. Dale.

Conclusions

- X4P-001 is safe and well tolerated at doses up to 400 mg QD for durations up to 22 months.
- X4P-001 drug exposure following doses of 50 to 400 mg appears to correlate with ANC and ALC AUCs.
- An X4P-001 dose of 400 mg is required to achieve consistent clinically relevant ANC levels.
- Based on these data, the Data Review Committee concluded that X4P-001 at 400 mg/day is the recommended dose to be used in a randomized clinical trial to assess the correlation between increases in ANC and ALC levels achieved and the clinical manifestation of WHIM syndrome.

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