Phase 2 Study of X4P-001: A Targeted Oral Therapy for Patients with WHIM Syndrome

PS1056

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Background

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

- Ultra-rare, autosomal dominant, immunodeficiency disease caused by mutations in the *CXCR4* chemokine receptor gene
- CXCR4 mutations cause receptor hyperactivation and leukocyte retention in patient bone marrow, resulting in severe chronic panleukopenia, including neutropenia and lymphopenia[1,2]
- There are no approved therapies for WHIM syndrome; immunoglobulins (Ig) and granulocyte colony stimulating factor (G-CSF) are used to treat clinical symptoms of the disease[3]
- CXCR4 antagonists are being investigated as a treatment for these patients[4-6]

X4P-001

- Selective, allosteric, small molecule antagonist of CXCR4
- Orally bioavailable with a long half-life ($t_{1/2}$ ~ 23 hours), allowing once-daily dosing
- Inhibition of CXCR4 hyperactivation is predicted to increase the mobilization of white blood cells, including neutrophils and lymphocytes, into circulation, resulting in improvement in clinical symptoms

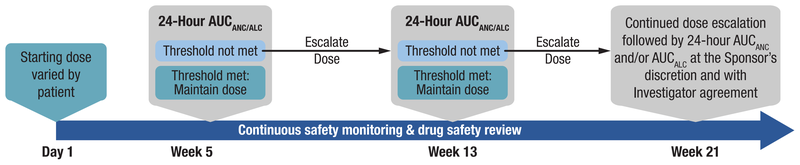
Study Design

X4P-001-MKKA:

- This is an interim report from the Phase 2 part of an ongoing Phase 2/3 study of X4P-001 for treating patients with WHIM syndrome
- As of 20 March 2018, 8 patients have been enrolled

Primary Objectives:

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



- New patients received oral X4P-001 QD at different starting doses
- Intra-patient dose escalation was based on 24-hour serial area-under-the-curve (AUC) measurements of ANC and ALC; the protocol pre-specified thresholds for ANC and ALC are 600/µL and 1000/µL, respectively
- The 24-hour AUC was calculated using the trapezoidal method with area above threshold being positive, and area below threshold, negative. Dose escalation occurred if AUC_{ANC} < 2000 cell*hr/µL or AUC_{ALC} < 5000 cell*hr/µL

Eligibility Criteria

Inclusion:

- ≥ 18 years
- Genetically confirmed *CXCR4* mutation
- Confirmed ANC ≤ 400/µL or ALC ≤ 650/µL (or both)

Exclusion:

- Recent plerixafor treatment (< 2 months)
- Recent G-CSF/GM-CSF or immunoglobulin (< 2 weeks)
- Ongoing HIV, hepatitis B or C virus, or uncontrolled infection

Patient Demographics and Characteristics

ID	Age (years)	Gender	Race	*CXCR4* Mutation	Time on Study	Status
1	37	Male	White	R334X	14+ months	Now at 400 mg
2	57	Female	White	R334X	14+ months	Now at 400 mg
3	19	Female	White	R334X	8 months	Off study
4	25	Male	White	E343X	6 months	Off study
5	34	Female	White	S365X	2 weeks	Off study
6	24	Female	White	R334X	5+ months	Now at 400 mg
7	41	Female	White	R334X	1+ months	Now at 300 mg
8	49	Female	White	R334X	1+ months	Now at 300 mg

Clinical cut-off date: 20 March 2018

Baseline Blood Count and Immunoglobin Parameters

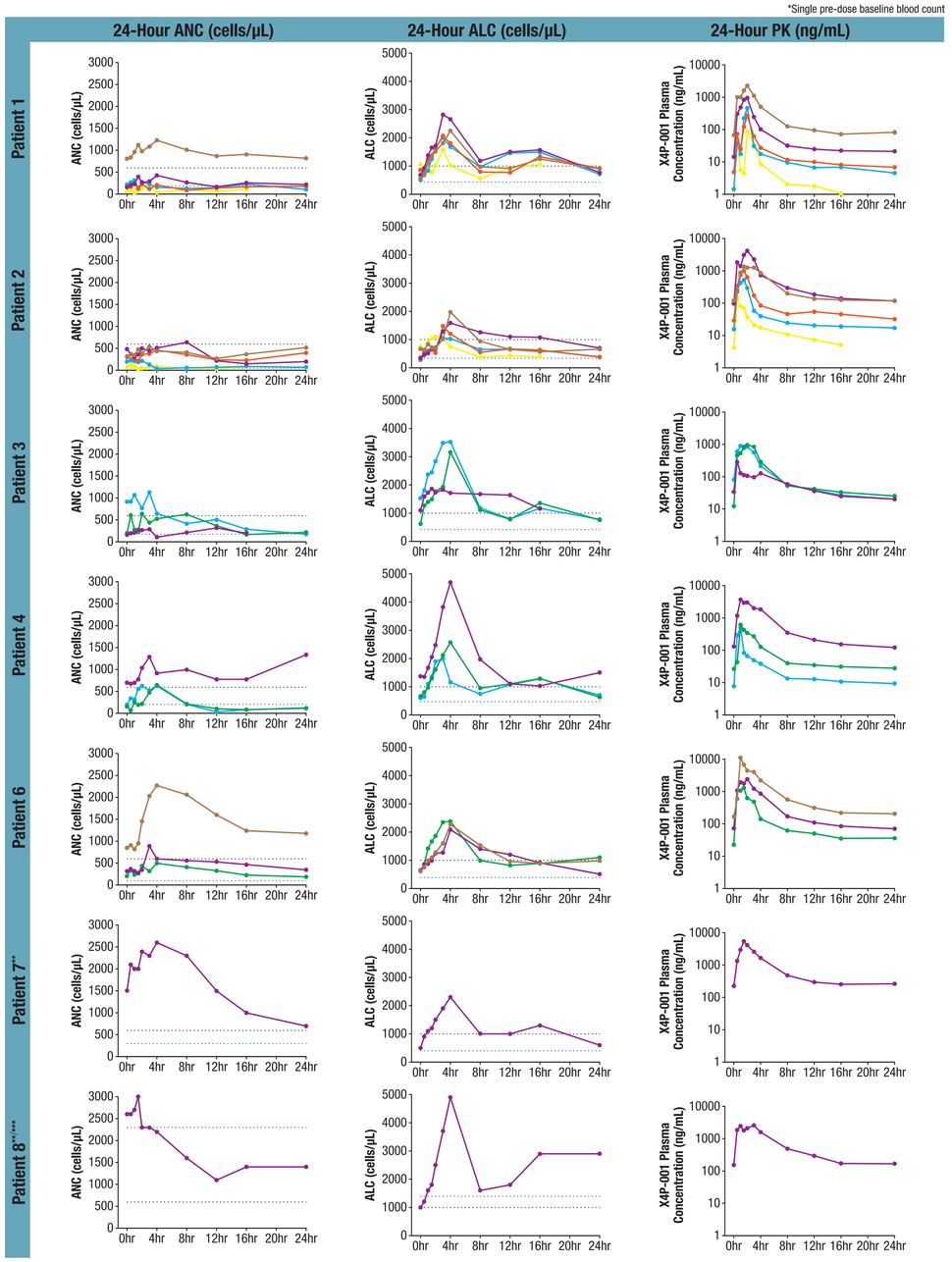
ID	Hemoglobin (g/dL)	Hematocrit (%)	Platelets ($x10^3$/µL)	WBCs ($x10^3$/µL)	ANC ($x10^3$/µL)	ALC ($x10^3$/µL)	AMC ($x10^3$/µL)	IgA** (mg/dL)	IgG** (mg/dL)	IgM** (mg/dL)
1	13.6	NA*	187	0.70	0.19	0.43	0.06	< 5	1047	74
2	11.4	NA*	122	0.44	0.06	0.35	0.01	52	597	70
3	13.2	43	164	0.75	0.14	0.53	0.07	57	498	108
4	14.6	49	174	1.21	0.11	1.04	0.05	85	923	45
5**	12.0	37	176	1.38	0.69	0.58	0.10	173	704	104
6	13.6	40	203	0.54	0.06	0.35	0.11	135	623	32
7	13.7	41	188	0.90	0.30	0.50	0.10	267	1000	120
8	15.1	46	500	4.1	2.3	1.40	0.30	28	1230	42

Clinical cut-off date: 20 March 2018; *NA: Not Available; **Day 1 values

X4P-001 Induces Dose-dependent Increases in ANC/ALC and Serum Drug Concentration

- No changes in Ig levels or vaccine titers have been observed up to 24 weeks on treatment

*Single pre-dose baseline blood count

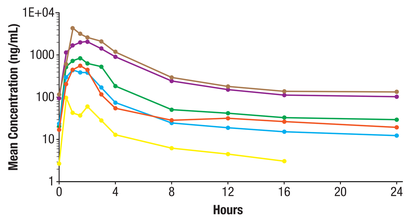


**Patients 7 and 8 also received prophylactic inhaler and systemic antibiotic therapies at times while receiving X4P-001; their AUCs will be reassessed at the 300 mg dose level

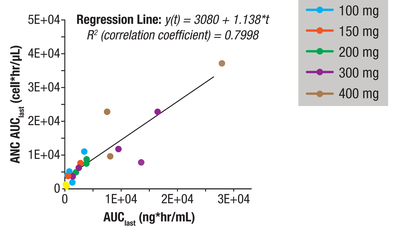
***Patient 8 met the inclusion criteria and has a history of splenectomy, which may lead to greater increases in blood counts with X4P-001 treatment; none of the other patients have had splenectomy. Patient 8 was also receiving antibiotic therapy for a presumed infection while receiving X4P-001.

Pharmacokinetics and PK/PD Relationship

X4P-001 Mean Concentration-Time Profile*



PK-PD Correlation*



*Patients 7 and 8 were not included in the pharmacokinetic analysis; their AUCs will be reassessed at the 300 mg dose level.

Safety

- X4P-001 was well-tolerated with no serious adverse events (AEs) reported at the doses tested
- Treatment emergent AEs (events that began or worsened after administration of the first dose of X4P-001) that occurred in more than 1 patient were sinusitis, dry mouth, and nausea (2 each)
- X4P-001-related AEs were nausea (2 each), dry eye, dry mouth, nasal dryness, dyspepsia, conjunctivitis, and rash (1 each); all related AEs were grade 1

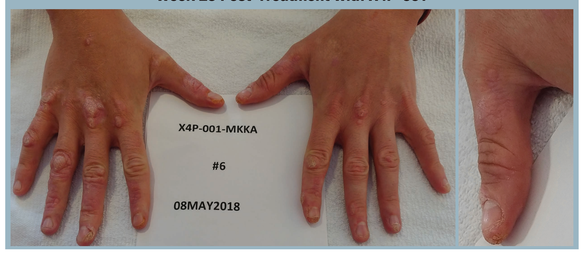
Clinical Events on Study

- At week 16 examination, Patient 2 had developed one small new wart on thumb; patient had been dosed up to 150 mg QD
- Patient 3 developed acute cholecystitis at week 17 of treatment requiring cholecystectomy in an out-patient setting; patient was maintained on X4P-001 at 300 mg and received G-CSF during the peri-operative period and tolerated the procedure well with no sequelae; the event was considered to be unrelated to X4P-001
- Patient 5 developed a rash at Day 5 following 200 mg X4P-001 treatment and was discontinued from the study

Clinical Effects: Reductions in Warts Following X4P-001 Therapy

Pre-Treatment

Week 26 Post-Treatment with X4P-001



X4P-001 Exposure: WHIM patient #6 after 26 weeks of investigational X4P-001 therapy (200 mg QD for 6 weeks, 300 mg QD for 5 weeks, and 400 mg QD for 15 weeks). This patient had received an approved HPV vaccine over 10 years prior to starting X4P-001 treatment. The patient was subsequently re-immunized with the initial HPV vaccine series in January and February 2018 while receiving X4P-001. 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 400 days
- X4P-001 drug exposure shows a dose-dependent increase which is correlated with AUC_{24h} of absolute neutrophil counts
- In the absence of any safety issues, the recommended dose for future studies is the highest dose tested; the recommended Phase 3 dose of X4P-001 is therefore 400 mg QD
- Preliminary evidence of clinical activity observed at doses ≥ 300 mg QD will be confirmed in the Phase 3 portion of the study

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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)** Badolato R Donadieu J; WHIM Research Group. How I treat warts, hypogammaglobulinemia, infections, and myelokathexis syndrome. *Blood.* 2017;130(23):2491-2498. **4)** 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. **5)** 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. **6)** 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.

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