X4P-001: A Novel Molecularly-Targeted Oral Therapy for WHIM Syndrome

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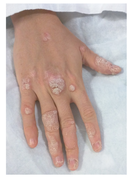
Background

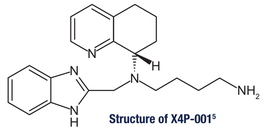
WHIM (Warts, Hypogammaglobulinemia, Infections, Myelokathexis) Syndrome:



- Rare immunodeficiency disease caused by gain-of-function mutations in the chemokine receptor gene *CXCR4*
- Mutations in *CXCR4* result in aberrant retention of leukocytes in patient bone marrow[1,2]
- WHIM syndrome is characterized by severe neutropenia (reduced ANC), lymphocytopenia (reduced ALC), and susceptibility to bacterial and human papilloma virus (HPV) infections (warts and HPV-associated malignancies)
- CXCR4 antagonists are being evaluated as a treatment for these patients[3,4]

X4P-001

- X4P-001 is a selective, small molecule antagonist of CXCR4 that binds allosterically to the extracellular region of the receptor and inhibits CXCL12 stimulation of different intracellular variants of CXCR4[5]
- X4P-001 is orally bioavailable with a long half-life ($T_{1/2}$ ~ 23 hours), allowing once-daily dosing
- X4P-001 antagonism of CXCR4 is predicted to modulate the hyper-reactive receptor characteristic of WHIM syndrome, resulting in increased mobilization of neutrophils and lymphocytes from the bone marrow into circulation



Structure of X4P-001[5]

Study Hypothesis: *CXCR4 antagonism by X4P-001 will improve the primary pathophysiology underlying WHIM syndrome, i.e., hyperactive CXCR4 response to physiologic levels of CXCL12*

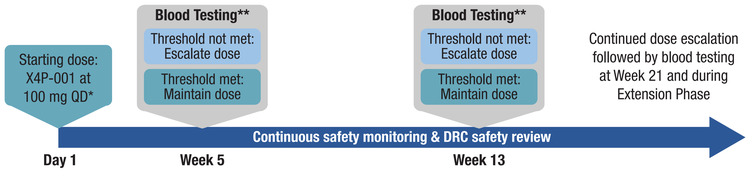
Study Design

X4P-001-MKKA:

- This is a preliminary report from the Phase 2 part of an ongoing Phase 2/3 study of X4P-001 for treating WHIM syndrome
- As of October 16, 2017, five patients have been enrolled

Primary Phase 2 Study Objectives:

- To evaluate safety and tolerability of X4P-001 in patients with WHIM syndrome
- To determine the dose required to achieve a consistent increase in absolute cell counts for neutrophils (ANC) and lymphocytes (ALC) in patient blood samples



* *The first 2 patients started at 50 mg QD but that dose was deemed to be suboptimal. Subsequent patients started at 100 mg QD*

** *24-hour AUC blood counts must meet one or both thresholds: AUC_{ANC} > 2000 cell*hr/µL or AUC_{ALC} > 5000 cell*hr/µL*

- 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 Baseline Characteristics

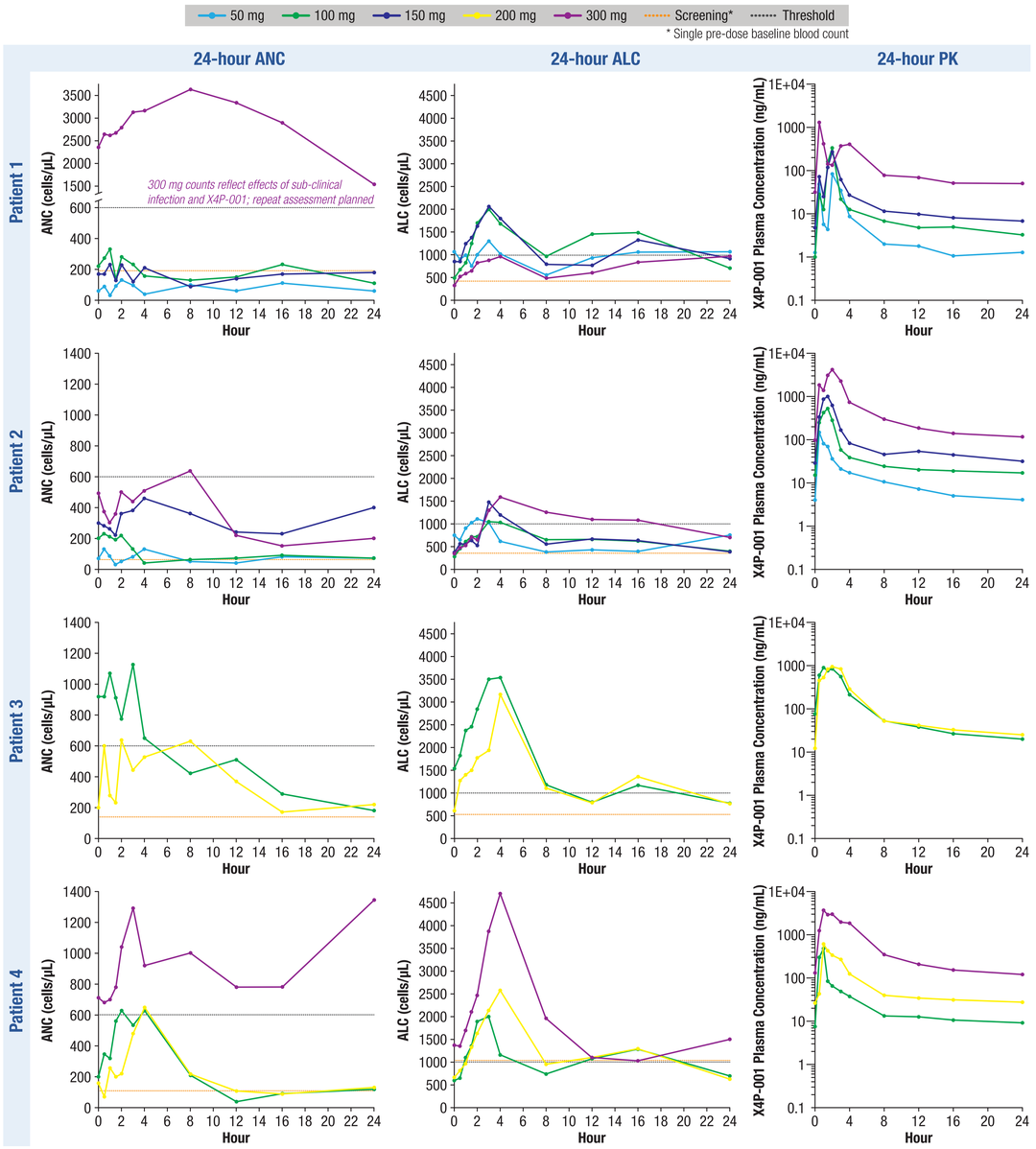
ID	Age (years)	Gender	Race	# Infections in 6 months Prior to Study	*CXCR4* Mutation	Prior WHIM-related therapies	Time on Study
1	37	Male	White	4 (otitis media, gingivitis, onychomycosis, skin infection)	R334X	IVIG, G-CSF, plerixafor	9+ months
2	57	Female	White	6 (abscess x2, cellulitis x4)	R334X	G-CSF, steroids, plerixafor	9+ months
3	19	Female	White	2 (corneal infection, oral infection)	R334X	G-CSF	4+ months
4	25	Male	White	4 (URI, sinus infection, gastroenteritis, gingivitis)	E343X	G-CSF	4+ months
5	34	Female	White	5 (recurrent warts x 3; ear infections x 2)	S365X	G-CSF, plerixafor	Developed rash ~5 days after treatment and discontinued from study

Baseline Blood Count and Immunoglobin Parameters (Prior to X4P-001 Dosing)

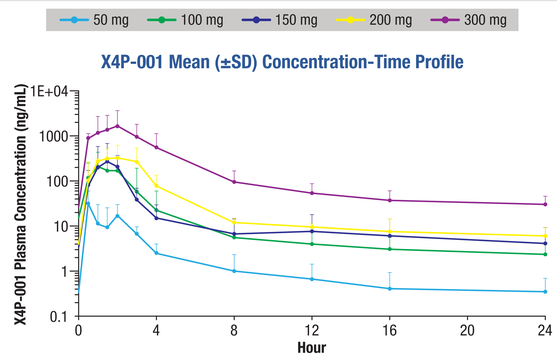
Patient ID	Hemoglobin (g/dL)	Hematocrit (%)	Platelets (x10³/µL)	WBCs (x10³/µL)	ANC (x10³/µL)	ALC (x10³/µL)	AMC (x10³/µL)	IgA** (mg/dL)	IgG** (mg/dL)	IgM** (mg/dL)
1	13.6	NA*	187	0.70	0.19	0.43	0.06	< 5	1047	74
2	11.4	NA	122	0.44	0.06	0.35	0.01	52	597	70
3	13.2	43	164	0.75	0.14	0.53	0.07	57	498	108
4	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

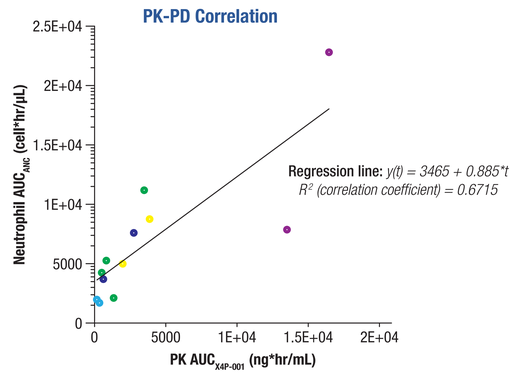
*NA: Not Available; **Day 1 values

X4P-001 Induces Dose-dependent Increases in ANC and ALC



X4P-001 Pharmacokinetics





Data from Patient 1 not included due to infection; repeat assessment planned

Safety

Adverse Events (AEs)

- As of October 16, 2017, X4P-001 was well-tolerated with no serious AEs reported at the doses tested
- Treatment emergent AEs that occurred in more than 1 patient were dry mouth and nausea (2 each)
- X4P-001-related AEs were dry mouth and nausea (2 each); dry eye, nasal dryness, dyspepsia, conjunctivitis, cholecystitis, and rash (1 each)
  - All related AEs were grade 1 except for cholecystitis, which was grade 3

Clinical Events on Study

- At week 16 examination, Patient 2 had developed one small new wart on thumb
- At week 17 examination, Patient 3 had cholecystitis requiring removal of gall bladder
- Patient 5 developed a rash around Day 5 of X4P-001 treatment and was discontinued from the study

Conclusions

- X4P-001 was well-tolerated, with no severe AEs
- All patients demonstrated a dose-dependent increase in ANC and ALC from screening values, with ALC increasing in greater proportion than ANC
- X4P-001 drug exposure showed a dose-dependent increase correlated with AUC of neutrophils
- Dose escalation continues to achieve consistent increases in ANC and ALC

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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)** 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. **4)** 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. **5)** Mosi RM, Anastassova V, Cox J, et al. The molecular pharmacology of AMD11070: an orally bioavailable CXCR4 HIV entry inhibitor. *Biochem Pharmacol.* 2012; 83(4):472-479.