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.1,2
- 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.3
- CXCR4 antagonists are under investigation as specific, mutation-targeted therapies.4-6

X4P-001

- Non-competing, allosteric, small molecular antagonist of CXCR4.
- Orally bioavailable with a mean terminal half-life (t1/2) 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.

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 AUC0-inf and AUC0-t were calculated using the trapezoidal method (AUC0-t). For AUC0-t, the AUCs were calculated relative to a pre-specified threshold of 600 cells/µL and 1000 cells/µL for ANC and ALC, respectively.

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

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.

References: