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 lymphocytes in bone marrow.
- WHIM syndrome is characterized by severe neutropenia (induced ANC), lymphopenia (induced 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.

X4P-001

- X4P-001 is a small, selective molecule antagonist of CXCR4 that binds allosterically to the extracellular region of the receptor and inhibits CXCL12 stimulation of different intracellular variants of CXCR4.
- X4P-001 is orally bioavailable with a long half-life ($T_{1/2}$ = 23 hours), allowing once-daily dosing.

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

Study Design

This is a preliminary report from the Phase 2 part of an ongoing Phase 2/3 study of X4P-001 for treating WHIM syndrome.

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.

Eligibility Criteria

Inclusion:
- < 18 years
- Genetically confirmed CXCR4 mutation
- Confirmed ANC < 4000/µL or ALC < 1000/µL (or both)

Exclusion:
- Recent plerixafor treatment (< 2 months)
- Recent CXCR4 antagonists for WHIM (WHIM) syndrome.

As of October 16, 2017, five patients have been enrolled.

X4P-001 Pharmacokinetics

- X4P-001 is a novel molecularly-targeted oral therapy for WHIM Syndrome
- X4P-001: A Novel Molecularly-Targeted Oral Therapy for WHIM Syndrome
- David C. Dale, Audry Anna Bolyard, Emily Dick, Merideth L. Kelley, Vahagn Makaryan, Ramsey Johnson, Lu Gan, and Sudha Parasuraman

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

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>ANC (x10³/µL)</th>
<th>ALC (x10³/µL)</th>
<th>CRP (µg/mL)</th>
<th>BUN (mg/dL)</th>
<th>Creatinine (mg/dL)</th>
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<td>0.06</td>
<td>20.1</td>
<td>0.71</td>
</tr>
</tbody>
</table>

PK-PD Correlation

- y(t) = 3465 + 0.885*t

Adverse Events (AEs)

- All patients demonstrated a dose-dependent increase in ANC and ALC from screening values, with ANC increasing in greater proportion than ALC.
- No severe or life-threatening events were reported.
- The most common X4P-001-related AEs were dry mouth and nausea (2 each); dry eye, nasal dryness, dyspepsia, conjunctivitis, and rhinitis (1 each).

Conclusions

X4P-001 was well-tolerated, with no severe AEs reported at the doses tested.

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References:

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