Interim Results From a Phase 1/2, Open-Label, Dose-Escalation Trial of IMO-8400 in Patients with Relapsed or Refractory Waldenström’s Macroglobulinemia

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Rationale for Toll-like Receptor Antagonism as a Potential Therapeutic Approach in Waldenström’s Macroglobulinemia

- Waldenström's macroglobulinemia (WM) is a rare, indolent, B-cell lymphoma characterized by the production of monoclonal immunoglobulin M (IgM) and large, non-terminal B-cells that express CD22
- The disease is characterized by a monoclonal population of B-cells that produce a dysfunctioning immunoglobulin M (IgM) monoclonal protein
- The monoclonal IgM is known to contribute to the disease through several mechanisms, including: (a) binding to and activating Fcγ receptors on bone marrow-derived stromal cells, leading to proliferation and survival of the tumor cells; (b) binding to and activating the JAK/STAT pathway through the receptor FcγRIIa, leading to increased proliferation and survival of the tumor cells; and (c) binding to and activating the Toll-like receptor (TLR) pathway through the receptor TLR-4, leading to the production of cytokines that contribute to the disease

Study Objectives

Primary
- Safety and tolerability

Secondary
- Pharmacodynamics of IMO-8400 and evaluation of biomarkers for studying a clinical mechanism
- Identification of an optimal dose for further clinical evaluation
- Characterization of the pharmacokinetics of IMO-8400 levels

Eligibility Criteria

Major Inclusion Criteria
- Patient diagnosis established according to criteria of the World Health Organization
- patient at an age of 18 to 80 years old (inclusive)
- Relapsed or refractory WM according to the IWCLL criteria
- Serum-based or bone marrow-based genetic screening used to determine MYD88 L265P mutation status
- Serum collected at screening, Week 1 of every 8 week cycle, and end of course

Major Exclusion Criteria
- Major systemic or organ-threatening disease
- Active infection requiring systemic therapy
- Evidence of other active malignancy
- Active or inactive inflammatory diseases
- Active major organ dysfunction
- Current or ongoing corticosteroid use

Maximal Decrease in Serum IgM or M-protein (Best Observed of Either) in Efficacy Evaluable Patients

Change in Serum IL-10 from Baseline to Last Observation

Case Report: Partial Response in a Patient with Refractory Disease

- 80% of 60 patients received chemotherapy
- 60% of 60 patients received prednisone
- 30% of 60 patients received dexamethasone
- 20% of 60 patients received cyclophosphamide

Conclusions

- IMO-8400 was generally well tolerated at dose levels of 0.6, 1.2 and 2.4 mg/kg
- No dose-limiting toxicity was observed at any dose level
- Complete or partial response was observed in 37% of patients
- There was a significant correlation between change in M-protein and change in weight
- There was no evidence of drug accumulation at Week 13
- The pharmacokinetic and pharmacodynamic data support the continued development of IMO-8400 for the treatment of WM