Abstract: P1059

Title: A PHASE 1B TRIAL OF DISC-0974, AN ANTI-HEMOJUVELIN ANTIBODY, IN PATIENTS WITH MYELOFIBROSIS AND ANEMIA

Abstract Type: Poster Presentation

Topic: Myeloproliferative neoplasms - Clinical

Background:

Hepcidin, a central regulator of iron homeostasis, is pathologically elevated in patients with myelofibrosis (MF) and anemia. Chronic elevations in hepcidin limit iron availability for red cell production and contribute to the onset and severity of anemia, for which there is a large unmet need for safe and effective treatments. DISC-0974 is an investigational, first-in-class, monoclonal antibody that blocks hemojuvelin, a co-receptor in the bone morphogenetic protein-signaling pathway driving hepcidin expression. A completed healthy volunteer study demonstrated dose-dependent reductions in serum hepcidin, increases in serum iron and increasing trends in reticulocyte count, reticulocyte hemoglobin, mean corpuscular hemoglobin, total hemoglobin (Hgb), and red blood cell count. No safety signal was identified.

Aims:

This Phase 1b/2, open-label, multiple-ascending dose study (NCT05320198), assesses the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and initial efficacy of DISC-0974 in patients with MF and anemia.

Methods:

Eligible participants are over 18 years of age with intermediate-2 or high-risk MF and anemia. MF is confirmed using the World Health Organization 2016 criteria. Anemia is defined as Hgb < 10 g/dL or transfusion dependence, as defined by the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT). A stable dose of concomitant hydroxyurea and/or Janus kinase (JAK) inhibitor is allowed. Major exclusion criteria include liver iron concentration ≥ 7 mg/g dry weight; splenectomy; and nutritional, genetic, infectious, or autoimmune causes of anemia. Dose-escalation is based on a Bayesian optimal interval design with accelerated titration. DISC-0974 was administered subcutaneously monthly for a total of 6 doses. Primary endpoints include safety and tolerability of DISC-0974. Secondary endpoints include PK/PD markers of iron regulation and hematologic parameters. All data are summarized using descriptive statistics.

Results:

At the time of data cut, 11 patients were treated with DISC-0974. Four of seven (57%) evaluable non-transfusion-dependent (NTD) patients treated at the 28 mg and 50 mg dose levels had a ≥1.5 g/dL hemoglobin increase from baseline after starting DISC-0974. One of two transfusion-dependent (TD) patients achieved transfusion independence by Gale Criteria. Hematologic activity was observed regardless of concomitant JAK inhibitor use. Treatment with DISC-0974 resulted in meaningful, dose-dependent, and sustained reductions in hepcidin across all treated patients to date (typically >75% reduction). These reductions in hepcidin were generally sustained for >2 weeks following DISC-0974 administration and corresponded to dose-dependent increases in serum iron. Adverse events (AEs) reported in two or more subjects were fatigue, anemia, diarrhea, and nausea. Grade 3 AEs included anemia in three patients and headache in one patient and were deemed not related to DISC-0974. One serious adverse event of worsening hip pain was reported and deemed not related to DISC-0974.

Summary/Conclusion: DISC-0974 demonstrated acceptable safety and tolerability at all evaluated dose levels. Anemia responses were achieved in NTD and TD participants, regardless of concomitant JAK inhibitor use. Sustained and substantial hepcidin reduction with DISC-0974 leads to increased serum iron that precedes anemia responses. Additional Phase 1b data, including longer follow up and results from additional escalation

cohorts will be presented.

Keywords: Hepcidin, Myelofibrosis, Anemia