P1559 DISC-0974, A FIRST-IN-HUMAN ANTI-HEMOJUVELIN MONOCLONAL ANTIBODY, REDUCES SERUM HEPcidIN LEVELS AND MOBILIZES IRON IN HEALTHY PARTICIPANTS

Topic: 29. Iron metabolism, deficiency and overload

Natasha Novikov, MD, PhD1, Hua Yang, PhD1, Sophia Nguyen, MS1, Akshay Buch, PhD1, Sarah Tuller, JD, RAC1, Michelle Andruk, MBA1, Katherine Chan, PhD, MPH, MBA1, Min Wu, PhD1, Richard Rodriguez1, Rajiv Panwar, PhD1, Haley Howell1, Brian MacDonald, MBChB, PhD1, Will Savage, MD, PhD1

1 Disc Medicine, Watertown, United States

Background: Hepcidin-induced iron restriction results from inflammatory stimuli and can cause anemia of inflammation. Hemojuvelin (HJV) is a glycosylphosphatidylinositol-anchored membrane protein expressed in iron-loading tissues that binds Bone Morphogenetic Protein (BMP) family ligands as a central regulator of hepcidin expression. DISC-0974 is a monoclonal antibody developed to target HJV and block binding of HJV with BMP ligands to reduce hepcidin production and treat anemia of inflammation.

Aims: This is a first-in-human, Phase 1a, double-blind, placebo-controlled single-ascending dose study of intravenous (IV) and subcutaneous (SC) DISC-0974 in healthy volunteers to evaluate safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD).

Methods: Eligible participants include healthy females of non-reproductive potential and males 18-65 years old with normal baseline red blood cell parameters, serum iron, and Total Iron Binding Capacity (TIBC), morning transferrin saturation (TSAT) <30%, and serum ferritin ≥30 ng/mL. Dosing is planned at the 7 mg IV, 14 mg SC, 28 mg SC, and 56mg SC doses, with Safety Review Committee assessment of data through Day 15, followed by unblinding in each cohort. Treatment is allocated in a 3:1 ratio with 8 participants planned per cohort. The primary endpoints are safety and tolerability. Secondary endpoints include PK of DISC-0974 and PD response evaluated using serum iron, TSAT, and hepcidin-25. Endpoints are summarized using descriptive statistics.

Results: The 7mg IV and 14mg SC cohorts have been unblinded, with a total of 18 participants dosed. Fourteen participants received DISC-0974, and 4 received placebo. In the active treatment group, the median age was 54 years [range: 19-62], 50% were females, and median baseline hemoglobin (Hgb) was 14.0 g/dL [11.7 – 17.3]. The placebo group had median age of 47 years [29 -64], 25% females, and median baseline Hgb of 15.1 [13.6 – 16.2]. No serious AEs, Grade >= 2 AEs, and AEs leading to study withdrawal were reported. Four Grade 1 AEs were seen in two placebo participants. No AEs related to DISC-0974 were reported.

Based on preliminary analysis, PK profiles showed anticipated patterns, with lower Cmax and longer Tmax in SC as compared to IV. Dose-related increases in serum iron and TSAT as well as hepcidin reduction were seen in participants treated with DISC-0974 as compared to placebo. The 7mg IV group had no appreciable difference from placebo, whereas the 14mg SC group had increased mean and median serum iron and TSAT between baseline and Day 8 as compared to placebo (Fig 1A). TSAT escalation stopping rules were not met in any subject, but in the 14mg group, two subjects had a majority of individual TSAT values >40% through Day 15, as compared to none in the 7mg group. Consistent with the iron data, a dose related decrease in hepcidin, as measured by area under the curve (AUC) calculations between baseline and Day 15, was observed (Fig 1B). Updated data will be presented at the meeting.

Image:
Summary/Conclusion: Preliminary analysis of data from the 7 mg IV and 14 mg SC DISC-0974 cohorts shows an acceptable safety and tolerability profile, as well as evidence of target engagement and iron mobilization. Higher doses of DISC-0974 are under investigation and potentially represent a new therapeutic approach for patients with functional iron deficiency in a variety of disease states.