DISC-0974, AN ANTI-HEMOJUVELIN ANTIBODY, REDUCES HEPCIDIN AND MOBILIZES IRON IN HEALTHY VOLUNTEERS

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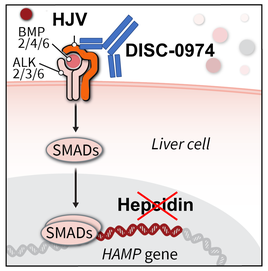
INTRODUCTION

DISC-0974 is a monoclonal antibody developed to target hemojuvelin (HJV), a key regulator of hepcidin and iron homeostasis. HJV is a BMP ligand co-receptor that facilitates BMP/SMAD signaling to increase expression of HAMP, the gene encoding hepcidin. Loss-of-function mutations in HJV seen in juvenile hemochromatosis provide a rationale for HJV as a target for therapeutic intervention. HJV mutations are associated with low hepcidin and elevated serum iron levels. These mutations are phenotypically indistinguishable from loss-of-function mutations in HAMP. Therefore, targeting HJV is anticipated to reduce hepcidin and increase serum iron, representing a new approach for treating conditions with elevated hepcidin and low circulating iron, such as anemia of inflammation.

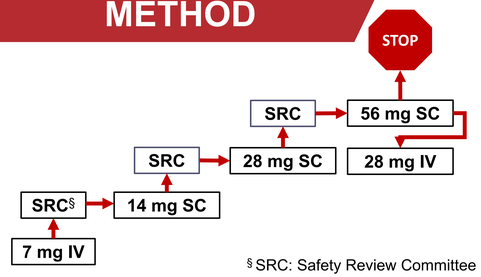


AIM

First-in-human, Phase 1a, double-blind, placebo-controlled, single ascending dose study (NCT04999527) that evaluates DISC-0974 in healthy volunteers for:

- **Safety and tolerability**
- **Pharmacokinetics (PK)**
- **Pharmacodynamics (PD)**

METHOD



§ SRC: Safety Review Committee

- *Population:* Healthy males and females (18-65 years old)
- *Randomization:* 3:1 active:placebo, N = 8
- *Dose escalation stopping criteria:*
  - TSAT > 40% in 2 subjects for 13 days
  - TSAT > 50% in 1 subject for 13 days

RESULTS

Parameter	Placebo* N = 10	7 mg IV N = 8	14 mg SC N = 6	28 mg SC N = 6	56 mg SC N = 6	28 mg IV N = 6
Age, years §	56.5 (20, 64)	51.5 (41, 62)	55.0 (19, 59)	55.5 (23, 62)	41.5 (29, 60)	54.0 (34, 59)
Gender, F †	4 (40.0)	4 (50.0)	3 (50.0)	3 (50.0)	2 (33.3)	3 (50.0)

Table 1. Demographics.
* Placebo is pooled IV and SC. § Age is presented as median (range).
† Gender (female) is presented as number (percent).

Preferred term	Placebo N = 10	7 mg IV N = 8	14 mg SC N = 6	28 mg SC N = 6	56 mg SC N = 6	28 mg IV N = 6
Diarrhea	1 (10.0)	0	0	0	0	0
Dizziness	0	0	0	0	1 (16.7)§	1 (16.7)
Dyspepsia	0	0	0	0	1 (16.7)	0
Eye pruritis	0	0	0	1 (16.7)	0	0
Headache	0	0	0	1 (16.7)	0	0
Myalgia	0	0	0	0	1 (16.7)	0
Nasal congestion	0	0	0	0	1 (16.7)	0
Pain in extremity	1 (10.0)	0	0	0	0	0
Peripheral swelling	0	0	0	0	0	1 (16.7)§
Seasonal allergy	0	0	0	1 (16.7)	0	0
Vessel puncture site bruise	1 (10.0)	0	0	0	0	0
Vomiting	1 (10.0)	0	0	0	0	0

Table 2. Safety and tolerability is comparable between placebo and DISC-0974 treated groups. Adverse events (AEs) are displayed as number (percent) of participants affected. No serious AEs, ≥ Grade 2 AEs, or AEs leading to study withdrawal were reported. § Two mild (Grade 1) AEs that occurred and resolved within 72 hours of dosing were considered possibly related to study drug.

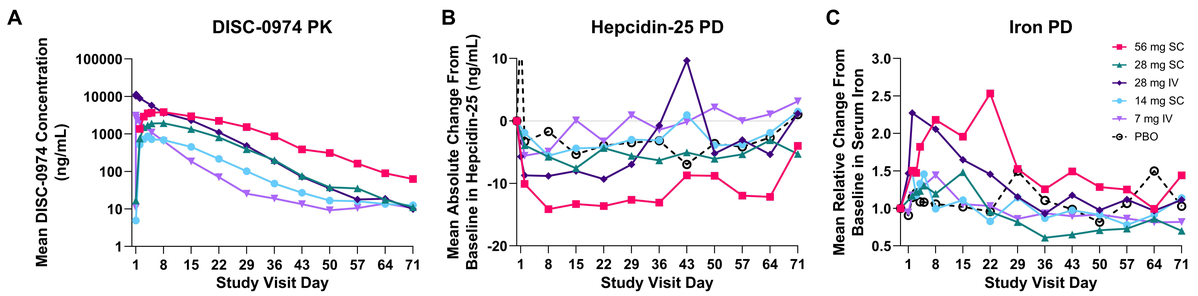


Figure 1. DISC-0974 lowers serum hepcidin-25 and raises serum iron in a dose dependent manner.
Mean (A) DISC-0974 concentration, (B) absolute change from baseline in hepcidin-25 (value - baseline) and (C) relative change from baseline in iron (value/baseline) for pooled placebo (PBO) (N = 10), 7 mg IV (N = 8), 14 mg SC (N = 6), 28 mg SC (N = 6), and 56 mg SC (N = 6) and 28 mg IV (N=6). Multivariate regression modeling showed that baseline ferritin was a statistically significant predictor of iron response. Average ferritin levels also consistently decreased (-20 to -50 ng/mL) in response to DISC-0974 treatment. Average erythropoietin changes were comparable across all groups (+ 1 to + 2 mIU/mL from baseline to Day 15), except for 28 mg IV where an average decline (- 1 mIU/mL) was seen.

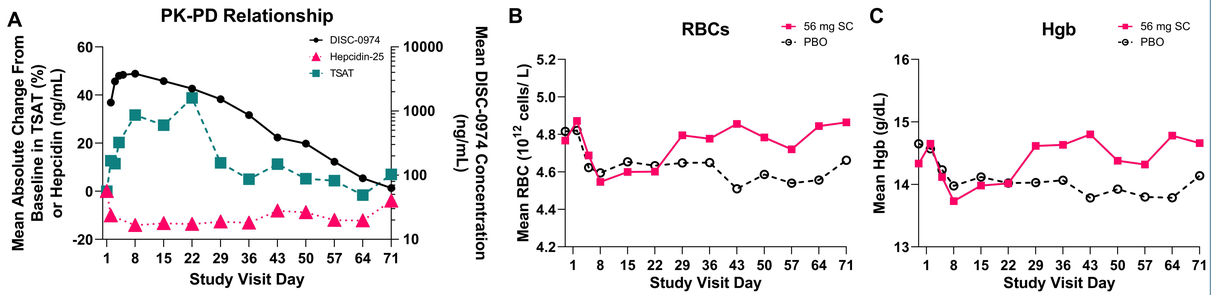


Figure 2. 56 mg SC DISC-0974 lowers serum hepcidin-25, raises iron, lowers ferritin, and increases RBC and Hgb production when compared to placebo.
(A) Mean DISC-0974 concentration and mean absolute changes from baseline in transferrin saturation and hepcidin-25 in the 56 mg SC dose cohort (N = 6). Mean (B) red blood cell (RBC) count and (C) hemoglobin (Hgb) in the 56 mg SC (N = 6) and placebo (N = 10) groups.

CONCLUSIONS

This healthy volunteer study provides clinical proof of mechanism that inhibiting hemojuvelin with DISC-0974 reduces hepcidin and increases circulating iron availability

- **Single dose of DISC-0974** in healthy volunteers demonstrated **acceptable safety and tolerability**, with only Grade 1 AEs observed
- Serum exposure was dose-related in the 14 to 56 mg SC range
- **DISC-0974** dosing resulted in **decreased hepcidin and increased TSAT**
- Exploratory biomarkers showed iron mobilization from iron stores into RBC hemoglobin
- At the 56 mg SC dose, increased erythropoiesis with **higher hemoglobin** in comparison to placebo was observed by Day 29 and sustained through Day 71
- Studies of **once monthly dosing** are ongoing in myelofibrosis and anemia (NCT05320198) and planned in other diseases with **anemia of inflammation**

REFERENCES

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CONTACT INFORMATION

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