DISC-0974, a First-in-Human Anti-Hemojuvelin Monoclonal Antibody, Increases Serum Iron and Transferrin Saturation in Healthy Participants

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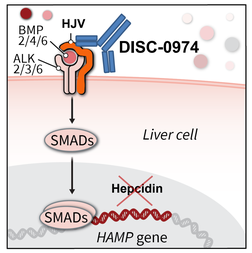
INTRODUCTION

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 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 plasma iron, representing a new approach for treating conditions with elevated hepcidin and low circulating iron, such as anemia of inflammation.

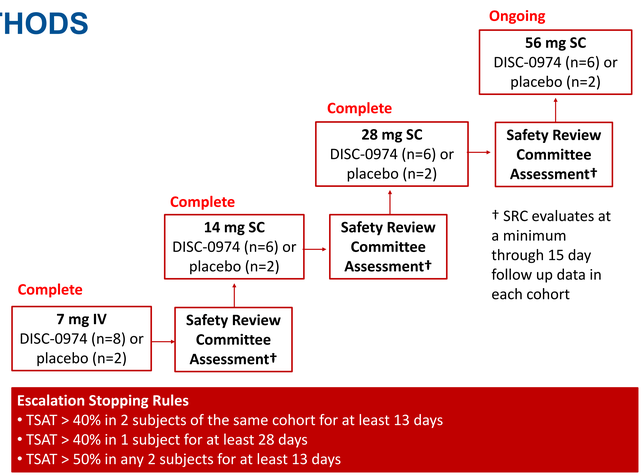


Finberg et al, (2010) Blood; Zhang et al, (2010) J Biol Chem

OBJECTIVE

The aim for this first-in-human, Phase 1a, double-blind, placebo-controlled single-ascending dose study is to evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics of DISC-0974.

METHODS



This study is a single ascending dose, double-blind, placebo-controlled trial in healthy volunteers. Eligible participants include healthy males and females of non-reproductive potential, ages 18 to 65. Dosing occurred at 7 mg IV, 14 mg SC, 28 mg SC, and 56 mg SC. Safety Review Committee assessments of data through Day 15 were held for each cohort and followed by unblinding. Treatment was allocated 3:1, with 8 participants planned per cohort. Two replacement participants were enrolled in the 7 mg IV cohort and are included in the analyses here. Primary endpoints for the safety and tolerability objectives included: adverse events, clinical laboratory assessments, vital signs, physical examinations, and electrocardiograms. Secondary endpoints included standard pharmacokinetic parameters and the following pharmacodynamic parameters: hepcidin, transferrin saturation (TSAT), and exploratory hematology biomarkers. Serum samples were analyzed for DISC-0974 concentrations using a validated electrochemiluminescence immunoassay method. Data are summarized using descriptive statistics.

RESULTS

Four dose levels of DISC-0974 have been administered

Characteristic	Placebo n = 8	7 mg IV n = 8	14 mg SC n = 6	28 mg SC n = 6	56 mg SC n = 6
Age, years	57 (29, 64)	52 (41, 62)	55 (19, 59)	56 (23, 62)	42 (29, 60)
Gender, Female / Male, N (%)	4 (50) / 4 (50)	4 (50) / 4 (50)	3 (50) / 3 (50)	3 (50) / 3 (50)	2 (33) / 4 (67)
Hepcidin, ng/mL	15.0 (7.0, 20.7)	10.3 (2.0, 22.9)	9.0 (2.0, 15.0)	12.5 (8.6, 16.6)	8.9 (5.7, 65.1)
TSAT, %	21 (14, 27)	25 (8, 37)	25 (14, 34)	27 (18, 71)	19 (16, 40)
Ferritin, ng /mL	70 (39, 118)	56 (31, 140)	51 (31 , 115)	86 (49, 156)	105 (57, 158)
CHr, pg	34 (34, 35)	34 (27, 35)	35 (32, 37)	35 (33, 36)	35 (32, 37)
MCH, pg	31 (29, 33)	30 (26, 30)	30 (29, 34)	29 (28, 31)	31 (27, 33)
Hemoglobin, g/dL	14.3 (12.9, 16.2)	14.0 (11.7, 15.1)	14.0 (12.4, 17.3)	14.2 (13.5, 15.6)	14.4 (12.6, 16.1)
Hematocrit, %	43 (39, 48)	42 (37, 47)	41 (37, 48)	42 (38, 45)	43 (38, 46)
RBC, 10^{12}/L	4.6 (4.4, 5.5)	4.7 (4.2, 5.2)	4.6 (4.3, 5.2)	5.0 (4.3, 5.1)	4.8 (4.1, 5.4)

Table 1. Baseline characteristics.
Baseline is defined as the last non-missing value before the participant receives study drug. Data are summarized using "median (range)" at pre-dose, except for "Gender" where "number (N) (percent)" is shown. Abbreviations include transferrin saturation (TSAT), reticulocyte hemoglobin (CHr), mean corpuscular hemoglobin (MCH), and red blood cell (RBC) count. Participant number per group is indicated with "n."

All adverse events were Grade 1, non-serious events and have resolved

Adverse Event	Total n = 34	Pooled Placebo n = 8	7 mg IV n = 8	14 mg SC n = 6	28 mg SC n = 6	56 mg SC n = 6
Diarrhoea	1 (2.9)	1 (12.5)	0	0	0	0
Dizziness	1 (2.9)	0	0	0	0	1 (16.7)
Dyspepsia	1 (2.9)	0	0	0	0	1 (16.7)
Eye pruritus	1 (2.9)	0	0	0	1 (16.7)	0
Headache	1 (2.9)	0	0	0	1 (16.7)	0
Myalgia	1 (2.9)	0	0	0	0	1 (16.7)
Nasal congestion	1 (2.9)	0	0	0	0	1 (16.7)
Pain in extremity	1 (2.9)	1 (12.5)	0	0	0	0
Seasonal allergy	1 (2.9)	0	0	0	1 (16.7)	0
Vessel puncture site bruise	1 (2.9)	1 (12.5)	0	0	0	0
Vomiting	1 (2.9)	1 (12.5)	0	0	0	0

Table 2. Adverse events (AEs).
No serious AEs, ≥ Grade 2 AEs, or AEs leading to study withdrawal were reported. One AE of dizziness that occurred and resolved on the day of dosing was considered possibly related to study drug. Data are displayed as number (percent) of participants affected.

Increasing doses of DISC-0974 decreased hepcidin and increased transferrin saturation

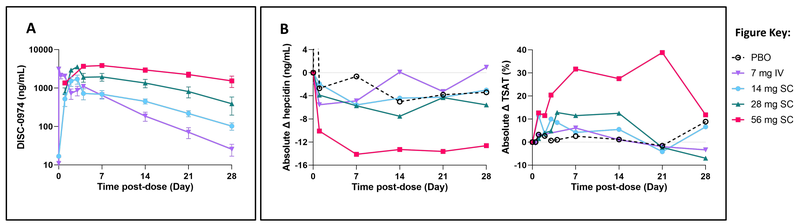


Figure 1. Pharmacokinetic and pharmacodynamic parameters.
(A) DISC-0974 concentration-time profiles plotted as mean with error bars representing standard error of the mean in 7 mg IV (purple), 14 mg SC (blue), 28 mg SC (green) and 56 mg SC (pink). (B) Mean absolute change (Δ) from baseline in hepcidin (left) and transferrin saturation (TSAT) (right). Data are shown for pooled placebo (PBO) (n = 8), 7 mg IV (n = 8), 14 mg SC (n = 6), 28 mg SC (n = 6), and 56 mg SC (n = 6).

RESULTS

DISC-0974 induced iron mobilization from ferritin iron stores to promote hemoglobin production

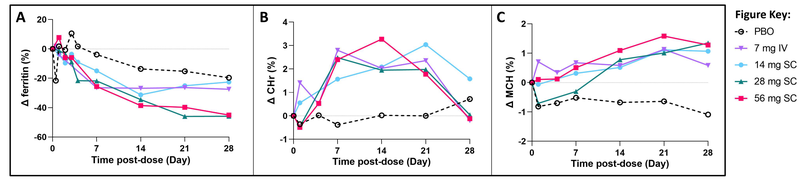


Figure 2. Ferritin and hemoglobin responses to DISC-0974 treatment.
Mean percent change (Δ) from baseline in (A) ferritin, (B) reticulocyte hemoglobin (CHr) and (C) mean corpuscular hemoglobin (MCH) in pooled placebo (PBO) (n = 8), 7 mg IV (n = 8), 14 mg SC (n = 6), 28 mg SC (n = 6), and 56 mg SC (n = 6).

A single dose of 56 mg SC DISC-0974 led to robust hepcidin and TSAT responses that increased erythropoiesis and hemoglobin in healthy volunteers

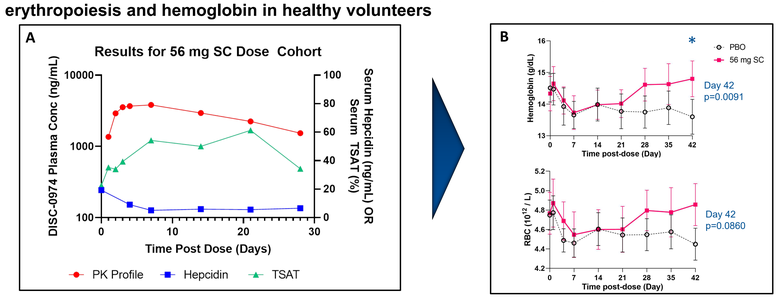


Figure 3. Robust hepcidin, TSAT, and erythropoietic responses in participants treated with 56 mg SC DISC-0974.
(A) Mean PK profile (left Y-axis) and PD response (right Y-axis) measured using hepcidin and transferrin saturation (TSAT) for the 56 mg SC cohort (n = 6). (B) Mean with error bars representing standard error of the mean for hemoglobin (top) and red blood cell (RBC) count (bottom) for pooled placebo (PBO) (n = 8) and 56 mg SC (n = 6). Asterisk (*) indicates statistically significant, two-sample t-test comparison of Day 42 hemoglobin, assessed as change from baseline.

CONCLUSIONS

- **DISC-0974** dosing in healthy volunteers demonstrated **acceptable safety and tolerability**, with only Grade 1 AEs observed
- Plasma 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** was observed
- Studies of **once monthly dosing** are planned in patients with **anemia of inflammation**

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

REFERENCES

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CONTACT INFORMATION

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