An Iron Pulse Study to Assess Oral Iron Absorption Following Treatment With DISC-3405 in Healthy Volunteers

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INTRODUCTION

- Hepcidin plays a central role in maintaining iron homeostasis by controlling both iron sequestration and dietary iron absorption.[1,2]
- Transmembrane serine protease 6 (TMPRSS6) suppresses hepcidin expression via the BMP/SMAD signaling pathway through cleavage of the membrane-bound co-receptor hemojuvelin (HJV).[3,4]
- DISC-3405 is a novel humanized monoclonal antibody (mAb) designed to target TMPRSS6 and upregulate hepcidin expression (Figure 1).
- The resulting elevation in hepcidin levels is anticipated to reduce dietary iron absorption (Figure 2).
- An iron pulse study was conducted to evaluate the effectiveness of DISC-3405 in inhibiting dietary iron uptake (Figure 3).

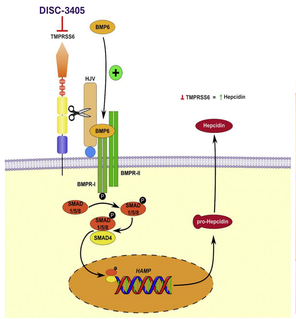


Figure 1: DISC-3405 Proposed Mechanism of Action
BMP = bone morphogenetic protein;
BMPR = bone morphogenetic protein receptor;
HJV = hemojuvelin; **P** = phosphorylated;
SMAD = suppressor of mothers against;
TMPRSS6 = transmembrane serine protease 6
decapentaplegic
Modified from Béliveau, 2019[5]

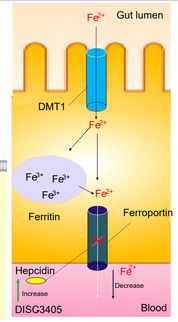
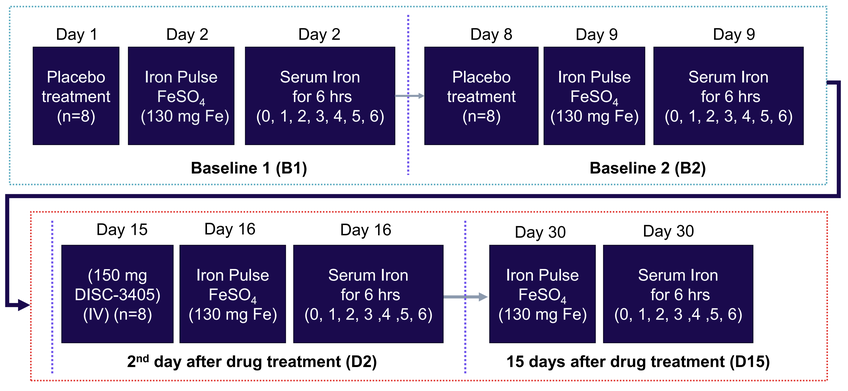


Figure 2: DISC-3405 Inhibits Iron Absorption in the Gut by Hepcidin Induction
DMT1 = Divalent Metal Transport-1

METHODS

Figure 3: Sequential Iron Pulse Study with Control Periods for Within-Participant Variability



- Eight healthy volunteers received oral ferrous sulfate ($FeSO_4$) tablets (2 × 325 mg, containing 130 mg of iron) on each indicated occasion. Participants fasted for at least 8 hours prior to dosing and consumed the iron supplement with orange juice (12 oz).
- Two sequential placebo occasions (1 week apart) were included to assess intra-participant iron absorption variability.
- Blood samples were collected at baseline (pre-dose) and 1, 2, 3, 4, 5, and 6 hours post-dose to monitor serum iron.
- Iron absorption was assessed using $AUC_{0\text{-}6h}$ as a surrogate marker, which may underestimate total absorption, as serum iron levels continued to rise beyond 6 hours.
- Baseline blood samples were also analyzed for hepcidin levels to explore the relationship between pre-dose hepcidin concentration and iron absorption.

RESULTS

Figure 4: Representative Serum Iron Profiles of One Participant Following Four Iron Pulses

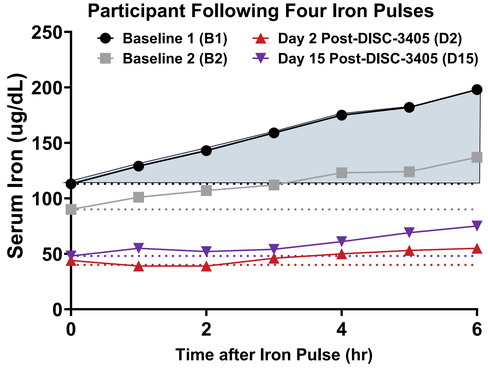


Figure Notes: Each dotted line represents the baseline for each group. $AUC_{0\text{-}6h}$ was determined for each group using respective baselines. A shaded example is shown for the B1 group.

Figure 5: Average Pre-Iron Hepcidin

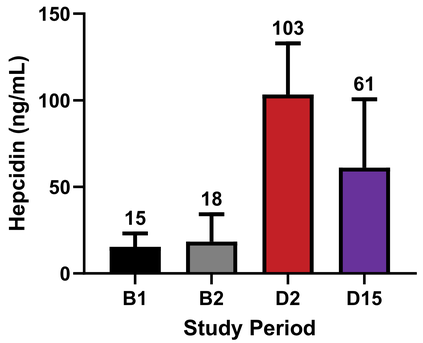


Figure Notes: Data presented as mean ± SD. Value above bars are means.

Figure 6: Average Serum Iron $AUC_{0\text{-}6h}$

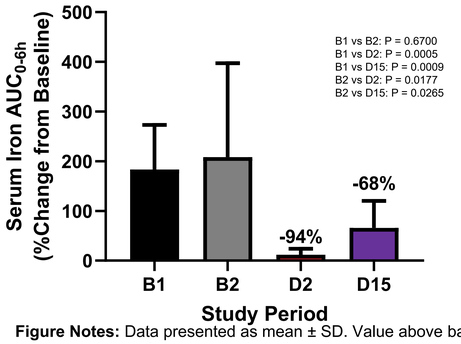


Figure Notes: Data presented as mean ± SD. Value above bars are mean change from average baseline.

Figure 7: Inverse Relationship between Pre-Iron Hepcidin Level and Iron Absorption

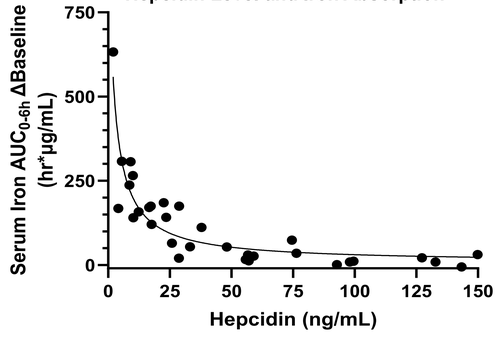


Table 1: Individual Pre-Dose Serum Hepcidin and Serum Iron Increases from Baseline ($AUC_{0\text{-}6h}$)

Participant[1]	1	2	3	4	5	6	7	8
B1 Pre-dose Hepcidin (ng/mL)	22.5	8.60	28.7	10.0	5.50	12.4	17.6	17.3
B1 $AUC_{0\text{-}6h}$ (hr*µg/mL)	185	237	20.0	266	308	158	121	175
B2 Pre-dose Hepcidin (ng/mL)	33.2	9.10	16.6	10.2	2.00	4.10	23.5	48.1
B2 $AUC_{0\text{-}6h}$ (hr*µg/mL)	54.0	307	171	141	633	168	142	53.5
B1/B2 Mean $AUC_{0\text{-}6h}$ (hr*µg/mL)	120	272	95.3	203	470	163	131	114
D2 Pre-dose Hepcidin (ng/mL)	133	99.5	143	57.0	76.4	127	92.8	98.0
D2 $AUC_{0\text{-}6h}$ (hr*µg/mL)	9.00	11.0	-5.50	12.5	35.0	21.5	1.00	9.00
% Inhibition[2]	-92.5	-96.0	-100	-93.8	-92.6	-86.8	-99.2	-92.1
D15 Pre-dose Hepcidin (ng/mL)	74.5	37.9	56.7	25.9	28.8	150	59.0	55.8
D15 $AUC_{0\text{-}6h}$ (hr*µg/mL)	74.0	112	29.5	64.5	175	31.0	26.5	16.0
% Inhibition[2]	-38.1	-59.0	-69.0	-68.2	-62.9	-81.0	-79.8	-86.0

[1]Baseline characteristics of participants: 25% female (n=2), white (75%, n=6), African American (25%, n=2). The median age is 36.0 years with a range of 20 to 49. Body mass index (kg/m^2) for all participants ranges from 18.87 to 31.27 with a median of 26.84.
[2]%Inh: D1 or D2 relative to the average of B1 and B2 according to the formula below:
%Inh = 100* (($AUC_{0\text{-}6h}$-Avg)/Avg -1), when $AUC_{0\text{-}6h}$ is negative, the % inhibition was set as -100%

CONCLUSIONS

- **Hepcidin levels remained relatively stable following placebo administration but increased markedly after a 150 mg IV dose of DISC-3405.**
- **DISC-3405 demonstrated strong inhibition of iron absorption in all participants:**
  - **Day 2 post-dose: Iron absorption inhibited by 86.8% to 100%, with an average reduction of 94.1%.**
  - **Day 15 post-dose: Iron absorption inhibition ranged from 38.1% to 86.0%, with an average reduction of 68.0%.**
- **Significant variability in iron absorption was observed within and between participants following sequential placebo doses, but statistically significant reduction of iron absorption was observed following drug treatment.**
- **A clear inverse correlation was observed between baseline hepcidin levels and the amount of iron absorbed.**
- **Collectively, these findings demonstrate that DISC-3405 effectively blocks dietary iron absorption, supporting its potential usage in treating iron overloading conditions, such as hemochromatosis, which is characterized by excessive iron uptake.**

References

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