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PHASE 1 HEALTHY VOLUNTEER STUDY OF DISC-3405, A RECOMBINANT HUMANIZED ANTIBODY TARGETING TMPRSS6

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INTRODUCTION

- Hepcidin is a key regulator of iron homeostasis, regulating iron sequestration and dietary iron absorption.[1,2]
- Transmembrane serine protease 6 (TMPRSS6, also referred to as matriptase-2) downregulates hepcidin expression by cleaving the membrane bound co-receptor hemojuvelin (HJV).[3,4]
- DISC-3405 is a novel humanized monoclonal antibody (mAb) targeting TMPRSS6 with subsequent upregulation of hepcidin.
- In preclinical studies, DISC-3405 significantly increased hepcidin production, suppressed iron levels, and demonstrated efficacy in disease models including beta-thalassemia and polycythemia vera (PV).
- DISC-3405 is currently being evaluated in a Phase 1 study of healthy volunteers.

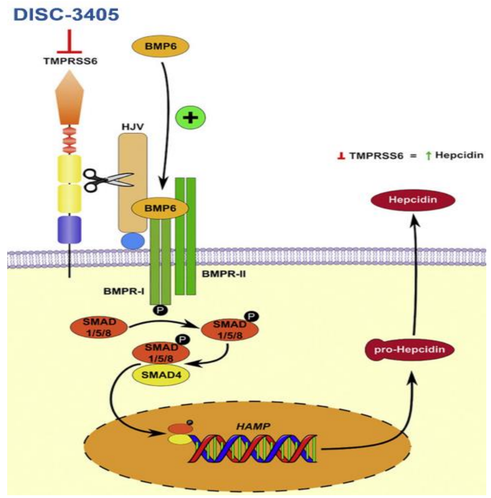
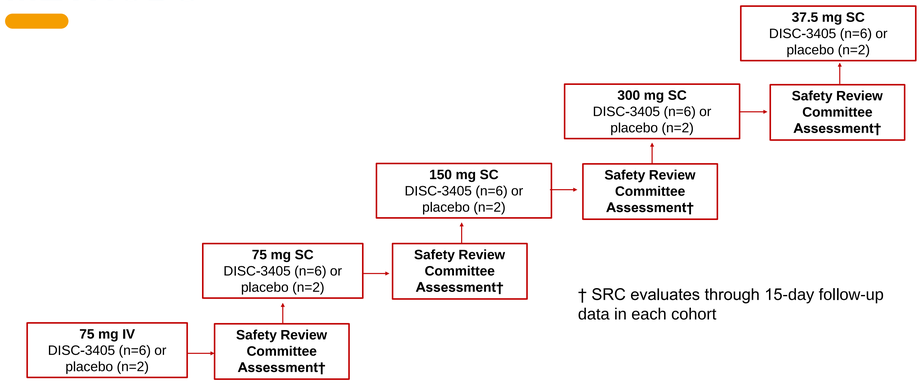


Fig. 1. Proposed Mechanism of Action for DISC-3405
BMP = bone morphogenetic protein; **BMPR** = bone morphogenetic protein receptor; **HJV** = hemojuvelin; **P** = phosphorylated; **TMPRSS6** = transmembrane serine protease 6; **SMAD** = suppressor of mothers against decapentaplegic
Modified from Béliveau,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

This is a Phase 1, double-blind, placebo-controlled single-ascending dose study to evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics of DISC-3405 (NCT06050915)

METHODS



† SRC evaluates through 15-day follow-up data in each cohort

- Healthy males and females ages 18 to 65 were given a single dose of placebo or DISC-3405 75 mg intravenously (IV), 37.5 mg subcutaneously (SC), 75 mg SC, 150 mg SC, or 300 mg SC.
- Safety Review Committee (SRC) assessed data through Day 15 for each cohort. Two sentinel participants were enrolled in each cohort except for the 37.5 mg SC cohort, which was added after the 300 mg SC dose after emerging PK/PD data.
- Primary endpoints for the safety and tolerability objectives included adverse events, clinical laboratory assessments, vital signs, physical examinations, and electrocardiograms.
- Secondary endpoints included pharmacokinetics; pharmacodynamic parameters including but not limited to serum hepcidin, serum iron, and ferritin; and hematological parameters (reticulocyte hemoglobin content [CHr]), hemoglobin, and hematocrit).
- Serum samples were analyzed for DISC-3405 concentrations using a validated method.
- Data reported here are interim data (19 Apr 2024) and are summarized using descriptive statistics.

RESULTS

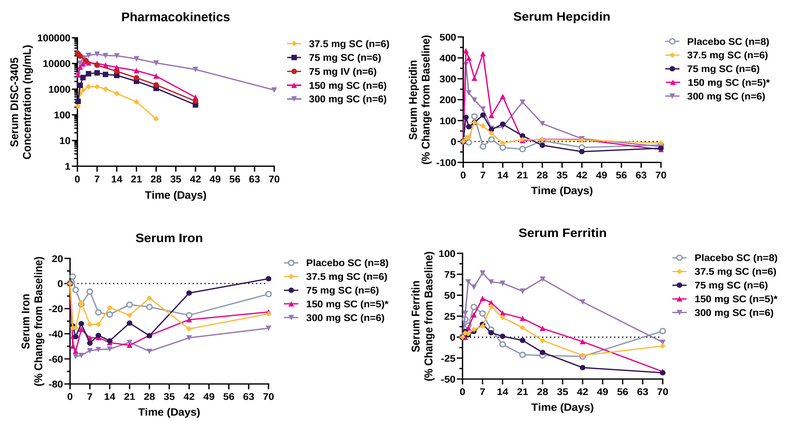
Characteristic	Placebo n = 10	37.5 mg SC n = 6	75 mg IV n = 6	75 mg SC n = 6	150 mg SC n = 6	300 mg SC n = 6
Age, years	48.6 (39-62)	52.7 (42-64)	36.8 (23, 49)	57.3 (49, 61)	44.0 (25, 57)	34.0 (22, 38)
Gender, Female, n (%)	2 (20)	5 (83.3)	3 (50.0)	4 (66.7)	2 (33.3)	0 (0)
Hepcidin, ng/mL	14.1 (5.2, 28.8)	41.7 (6.1, 177.2)	19.4 (2.0, 36.6)	32.6 (7.2, 69.8)	15.2 (8.7, 20.2)	18.7 (8.6, 45.0)
Serum Iron, ug/dL	97.2 (50, 180)	88.7 (43, 127)	99.2 (74, 127)	95.7 (67, 137)	85.7 (43, 138)	106.2 (54, 135)
Hemoglobin, g/dL	14.9 (13.1, 16.0)	13.2 (10.7, 17.7)	13.8 (12.1, 15.6)	13.8 (12.7, 16.0)	14.2 (13.0, 14.9)	15.4 (14.4, 16.7)
Hematocrit, %	43.6 (38.9, 47.1)	39.7 (34.3, 50.2)	41.5 (37.1, 45.5)	41.0 (38.7, 45.0)	42.3 (39.4, 46.2)	45.2 (42.3, 48.2)
RBC, 10^{12}/L	4.9 (4.2, 5.8)	4.5 (3.9, 5.7)	4.6 (3.8, 5.2)	4.5 (4.2, 5.0)	4.7 (3.9, 5.1)	5.1 (4.8, 5.8)

Table 1. Baseline characteristics.
Baseline is defined as the last non-missing value before the participant receives study drug. Data are expressed as mean (range) at pre-dose, except for "Gender," where "number (n) " is shown. Abbreviations include red blood cell (RBC) count. Participant number per group is indicated with "n."

Adverse Event	Placebo n = 10	37.5 mg SC n = 6	75 mg IV n = 6	75 mg SC n = 6	150 mg SC n = 6	300 mg SC n = 6
Sore Throat	0	0	1	0	0	0
Nausea	0	1	0	1	0	0
Headache	1	1*	0	0	0	0
Cough	0	0	0	0	1	0
Rhinorrhea	0	0	0	0	1	0
Lightheadedness	0	0	0	1	0	0
Increased ALT	0	0	0	0	1*	0
Increased AST	0	0	0	0	1*	0

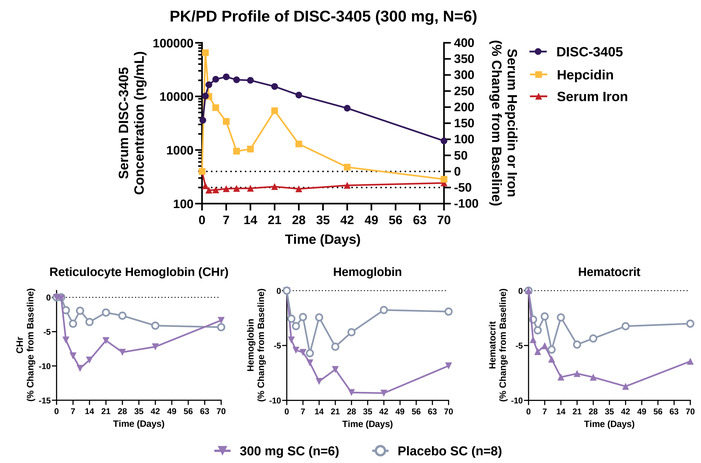
Table 2. Adverse events (AEs) considered possibly related.
No serious AEs, > Grade 2 AEs, or AEs leading to study withdrawal were reported.
** Grade 2 AEs; one participant reported a self-limited headache; one participant observed to have isolated, self-limited elevations of AST and ALT.*

Fig 2. Mean Pharmacokinetic and Pharmacodynamic (Serum Hepcidin, Iron, and Ferritin) Profiles



**One participant randomized to 150 mg SC was excluded from PD analysis due to history of anemia and recent hemorrhoidal bleeding, not disclosed prior to enrollment, deeming the subject ineligible.*

Fig 3. Mean PK/PD and Hematological Parameters following a Single Dose of DISC-3405 300 mg SC



CONCLUSIONS

- DISC-3405 was well tolerated in healthy volunteers.
- Subcutaneous administration of DISC-3405 resulted in dose-dependent PK profiles with a terminal half-life of more than 11 days at the 300-mg dose.
- DISC-3405 produced dose-related hepcidin increases and corresponding serum iron reductions across all dose levels.
- Mean serum iron reduction of more than 50% from baseline were achieved for both 150- and 300-mg doses.
- Mean serum iron reduction of more than 50% was sustained for at least 4 weeks for the 300-mg dose, with meaningful reduction of selective hematological parameters (CHr, hemoglobin, and hematocrit).
- DISC-3405 is a promising treatment with a convenient dosing regimen for conditions that would benefit from iron restriction.

REFERENCES

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