Single- and Multiple-Ascending Doses of DISC-3405, a Recombinant Humanized Antibody Targeting TMPRSS6, Increased Hepcidin and Reduced Iron and Hematocrit in Healthy Volunteers

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Introduction

- DISC-3405 is a novel, investigational humanized monoclonal antibody (mAb) inhibiting transmembrane serine protease 6 (TMPRSS6), which downregulates hepcidin expression through the BMP/SMAD pathway by cleaving the membrane-bound co-receptor hemojuvelin (HJV).[1,2] Hepcidin is a key regulator of iron homeostasis, regulating iron sequestration and dietary iron absorption.[3,4]
- As iron restriction has emerged as an effective mechanism for managing hematocrit (HCT) and quality of life in patients with polycythemia vera (PV), DISC-3405 is in development for the treatment of PV, and a study in healthy volunteers was completed (NCT06050915).

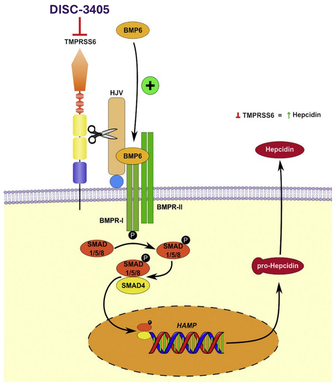


Figure 1: Proposed Mechanism of Action for DISC-3405

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]

Methods

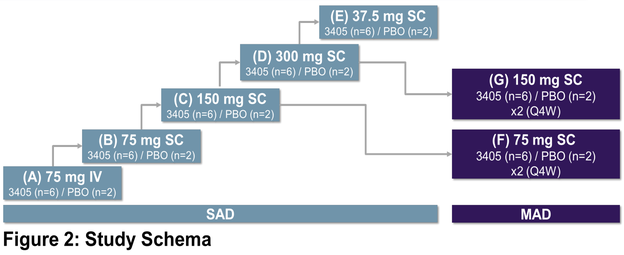


Figure 2: Study Schema

- Healthy male and female participants ages 18 to 65 years were enrolled in this study, which consisted of a screening period (up to 28 days), a treatment period (1 day for the single-ascending dose [SAD] cohorts or 29 days for the multiple-ascending dose [MAD] cohorts), and a follow-up period (70 days for the SAD cohorts or 98 days for the MAD cohorts).
- In the SAD cohorts, participants were administered DISC-3405 (n=6) or placebo (PBO; n=2) as a single intravenous (IV) infusion or subcutaneous (SC) injection after an overnight fast. A 37.5 mg dose cohort was added to better characterize pharmacokinetic/ pharmacodynamic (PK/PD) profiles.
- For the MAD cohorts, participants were administered DISC-3405 (n=6) or PBO (n=2) as SC injections once every 4 weeks (Q4W) for a total of 2 doses.
- The ***primary endpoint*** of safety and tolerability included adverse events, clinical laboratory assessments, vital signs, physical examinations, and electrocardiograms. The Safety Review Committee met after Study Visit Day 15 for each cohort.
- ***Secondary endpoints*** included PK and PD parameters. PD parameters included serum hepcidin, serum iron, serum ferritin, reticulocyte hemoglobin content (CHr), hemoglobin, and HCT.

Results

Table 1: Healthy Volunteer Baseline Characteristics

Characteristic	Placebo n=14	Dosed n=42
Age (years) Median (range)	45 (39, 62)	43.5 (22, 65)
Female, n (%)	4 (28.6)	19 (45.2)
Race White, n (%) Black, n (%) Asian, n (%)	10 (71.4) 4 (28.6) 0 (0)	36 (85.7) 5 (11.9) 1 (2.4)
Hepcidin (ng/mL), Mean (range)	15.0 (5.2, 50.1)	19.5 (2.0, 84.2)
Serum Iron (ug/dL), Mean (range)	91.6 (41, 180)	93.0 (33, 154)
Hemoglobin (g/dL), Mean (range)	14.5 (12.2, 16.0)	14.2 (10.7, 17.7)
Hematocrit (%), Mean (range)	42.7 (38.3, 47.1)	42.0 (34.3, 50.5)
RBC (10^{12}/L), Mean (range)	4.8 (4.1, 5.8)	4.7 (3.8, 5.8)

Results (Continued)

Figure 2: Mean PK/PD Profiles for SAD (300 mg) and MAD (75 mg, 150 mg) Cohorts

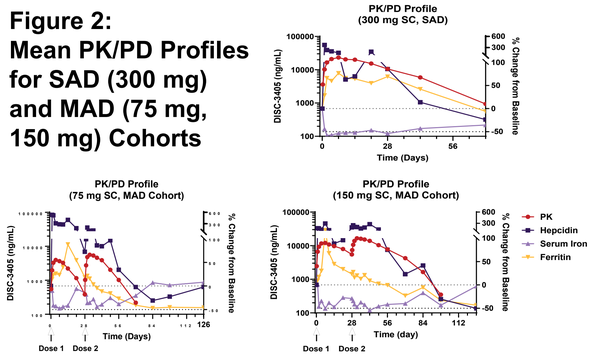


Figure 3: Select Hematological Parameters for SAD and MAD Cohorts

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

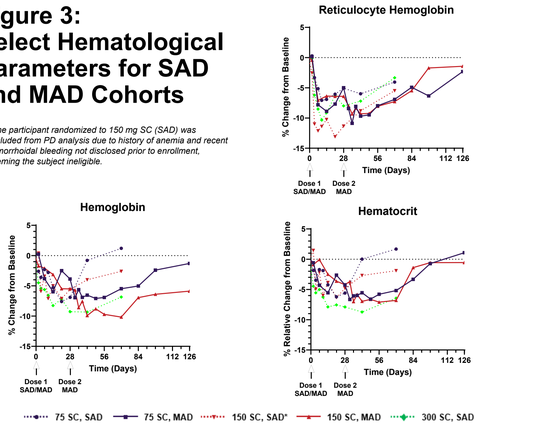
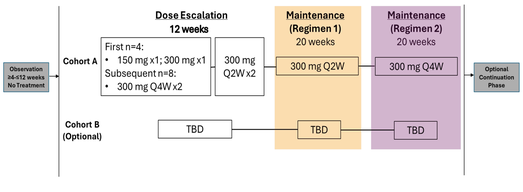


Table 2: Adverse Events Considered Related to Study Drug

Adverse Event	Placebo n=14	37.5 mg SC SAD n=6	75 mg IV SAD n=6	75 mg SC SAD n=6	150 mg SC SAD n=6	300 mg SC SAD n=6	75 mg SC MAD n=6	150 mg SC MAD n=6
Sore Throat	0	0	1	0	0	0	0	0
Nausea	0	1	0	1	0	0	1	0
Headache	1	1*	0	0	0	0	1	1
Cough	0	0	0	0	1	0	0	0
Rhinorrhea	0	0	0	0	1	0	0	0
Lightheadedness	0	0	0	1	0	0	0	0
Increased ALT	0	0	0	0	1*	0	0	0
Increased AST	0	0	0	0	1*	0	0	0
Fatigue	0	0	0	0	0	0	0	2

No serious AEs, >Grade 2 AEs, or AEs leading to study withdrawal were reported.
** Grade 2 AEs; 1 participant reported a self-limited headache; 1 participant was observed to have isolated, self-limited elevations of AST and ALT.*

Figure 4: DISC-3405 PV Phase 2 Study Design



Note: Cohort B is optional and intended as an expansion of Cohort A or to explore additional dose levels and dose regimens. (TBD = To Be Determined)

Conclusions

- DISC-3405 was well tolerated in healthy volunteers and repeated SC dosing provided the anticipated PK/PD profile.
- As reported previously,[6,7] SC 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, and produced dose-related increases in serum hepcidin, with corresponding reductions in serum iron across all dose levels.[6,7]
- DISC-3405 resulted in deep reductions in serum iron (ranging from 50-80% from baseline) and HCT that were sustained and support a once-monthly SC dosing regimen.[6,7]
- Overall, the favorable tolerability and PK/PD profiles support future clinical studies in patient populations that could benefit from iron restriction. A Phase 2 study in PV is active and recruiting (NCT06985147).

References

1. Du X, et al. *Science.* 2008;320:1088-1092. 2. Giannini S, et al. European Iron Club Annual Conference, 2024, Apr 23-26, Toulouse, France. 3. Nemeth E, et al. *Science.* 2004;306(5704):2090-2093. 4. Andrews NC. *N Engl J Med.* 2012;366:376-377. 5. Béliveau, et al. *Cell Chem Biol.* 2019;26(11):1559-1572.e9. 6. Liu G, et al. EHA, 2024, June 13-16, Madrid. 7. Liu G, et al. ASH, 2024, Dec 7-10, San Diego.

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