

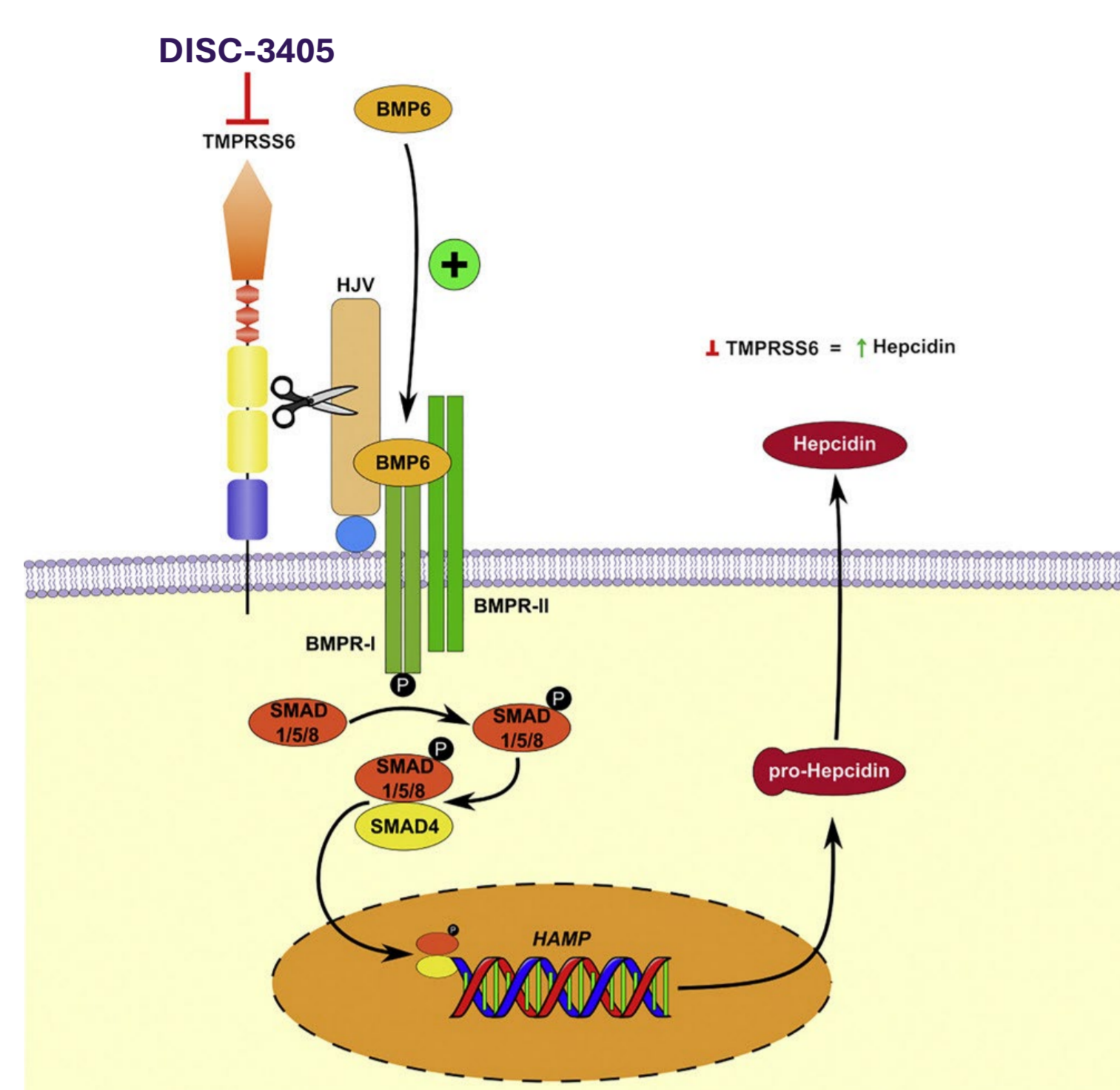
# Phase 1 Healthy Volunteer Study of DISC-3405, a Recombinant Humanized Antibody Targeting TMPRSS6

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## INTRODUCTION

- DISC-3405 is a novel humanized monoclonal antibody (mAb) targeting transmembrane serine protease 6 (TMPRSS6).
- TMPRSS6 downregulates hepcidin expression through the BMP/SMAD pathway by cleaving the membrane-bound co-receptor hemojuvelin (HJV).<sup>1,2</sup>
- Hepcidin is a key regulator of iron homeostasis, regulating iron sequestration and dietary iron absorption.<sup>3,4</sup>
- DISC-3405 has demonstrated efficacy in nonclinical disease models of beta-thalassemia and polycythemia vera (PV).
- DISC-3405 is currently being evaluated in a Phase 1 single-ascending dose/multiple-ascending dose (SAD/MAD) study in healthy volunteers.



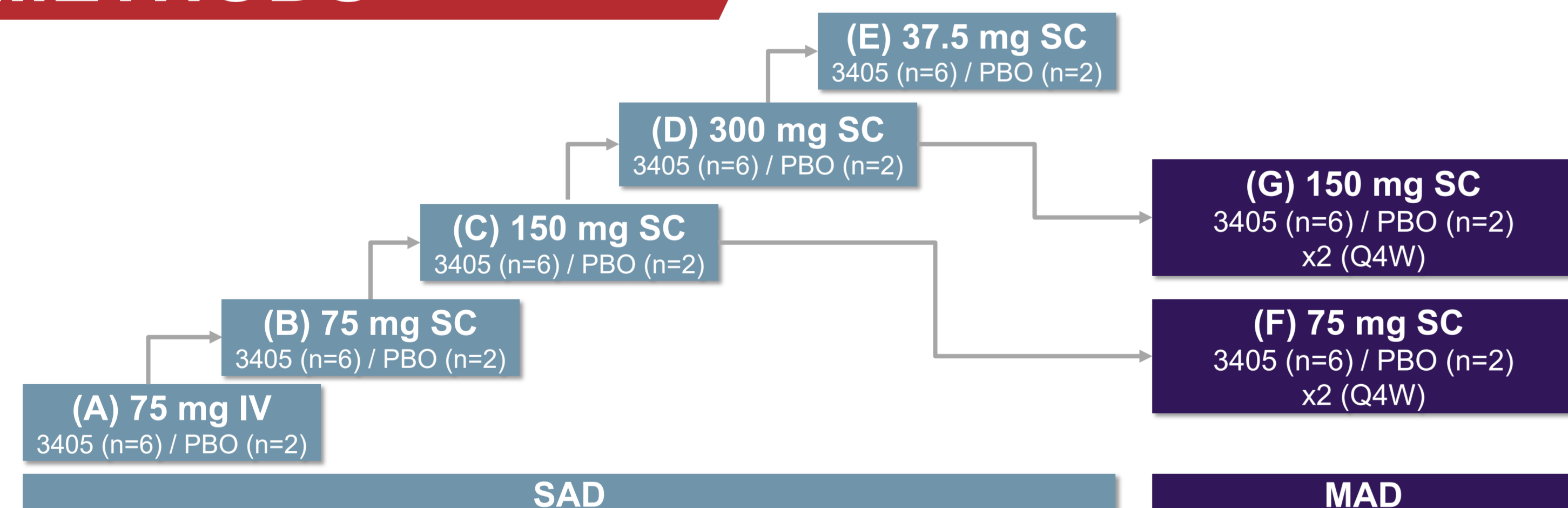
**Figure 1: Proposed Mechanism of Action for DISC-3405**

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<sup>5</sup>

## AIM

Data are presented from a Phase 1, double-blind, placebo-controlled SAD/MAD study conducted to evaluate safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of DISC-3405 in healthy volunteers (NCT06050915).

## 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 SAD cohorts or 29 days for the 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 (n=2) as a single intravenous (IV) infusion or subcutaneous (SC) injection after an overnight fast.
- For the MAD cohorts, participants were administered DISC-3405 (n=6) or placebo (n=2) as SC injections once every 4 weeks 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, and the first MAD cohort (75 mg SC) did not start until the 150-mg SC SAD cohort completed the Study Day 29 visit.
- Secondary endpoints included PK and PD parameters. PD parameters included serum hepcidin, serum iron, serum ferritin, reticulocyte hemoglobin content (CHR), hemoglobin, and hematocrit.

## RESULTS

**Table 1: Healthy Volunteer Baseline Characteristics**

Characteristic	Placebo n=14	37.5 mg SC n=6	75 mg IV n=6	75 mg SC* n=12	150 mg SC* n=12	300 mg SC n=6
Age (years) Median (range)	45 (39, 62)	53.5 (42, 64)	39.5 (23, 49)	52.5 (30, 61)	40 (25, 64)	36.5 (22, 38)
Female, n (%)	4 (28.6)	5 (83.3)	3 (50.0)	6 (50)	5 (41.7)	0 (0)
Race						
White, n (%)	10 (71.4)	6 (100.0)	5 (83.3)	11 (91.7)	9 (75.0)	5 (83.3)
Black, n (%)	4 (28.6)	0 (0)	1 (16.7)	1 (8.3)	2 (16.7)	1 (16.7)
Asian, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (8.3)	0 (0)
Ethnicity						
Hispanic, n (%)	0 (0)	1 (16.7)	2 (33.3)	1 (8.3)	0 (0)	1 (16.7)
Not Hispanic, n (%)	14 (100)	5 (83.3)	4 (66.7)	11 (91.7)	12 (100)	5 (83.3)
Hepcidin (ng/mL), Mean (range)	15.0 (5.2, 50.1)	26.2 (6.1, 84.2)	19.4 (2.0, 36.6)	23.2 (4.4, 69.8)	12.8 (4.6, 27.6)	18.7 (8.6, 45.0)
Serum Iron (ug/dL), Mean (range)	91.6 (41, 180)	88.7 (43, 127)	99.2 (74, 127)	92.9 (33, 154)	85.3 (43, 138)	106.2 (54, 135)
Hemoglobin (g/dL), Mean (range)	14.5 (12.2, 16.0)	13.2 (10.7, 17.7)	13.8 (12.1, 15.6)	14.2 (12.7, 16.0)	14.3 (13.0, 17.7)	15.4 (14.4, 16.7)
Hematocrit (%), Mean (range)	42.7 (38.3, 47.1)	39.7 (34.3, 50.2)	41.5 (37.1, 45.5)	41.7 (38.7, 45.0)	42.2 (39.4, 50.5)	45.2 (42.3, 48.2)
RBC (10 <sup>12</sup> /L), Mean (range)	4.8 (4.1, 5.8)	4.5 (4.0, 5.7)	4.6 (3.8, 5.2)	4.6 (4.2, 5.2)	4.7 (4.0, 5.8)	5.1 (4.8, 5.8)

Baseline is defined as Study Day -1, prior to receiving study drug.

\*75 and 150 mg SC include both SAD and MAD cohorts

**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

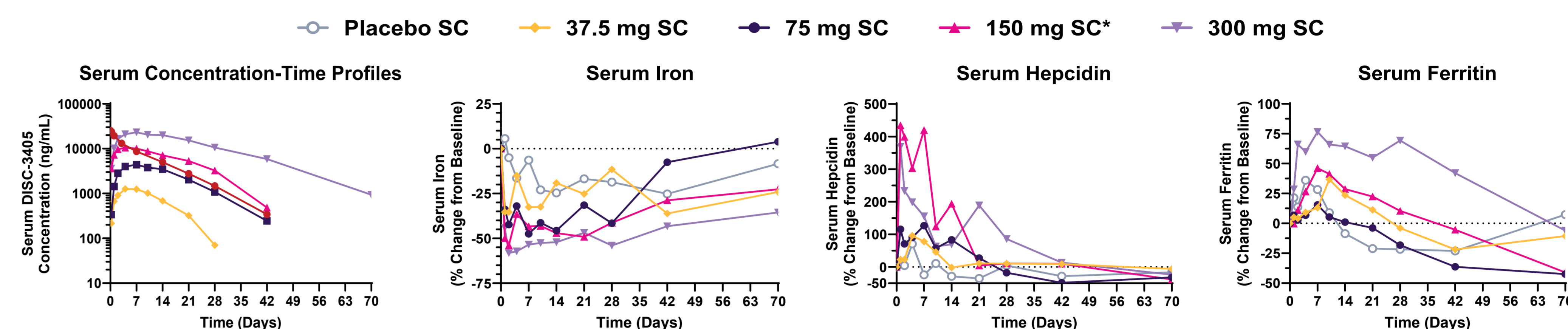
No serious AEs, >Grade 2 AEs, or AEs leading to study withdrawal were reported.

\* Grade 2 AEs; 1 participant reported a self-limited headache; 1 participant was observed to have isolated, self-limited elevations of AST and ALT.

## CONCLUSIONS

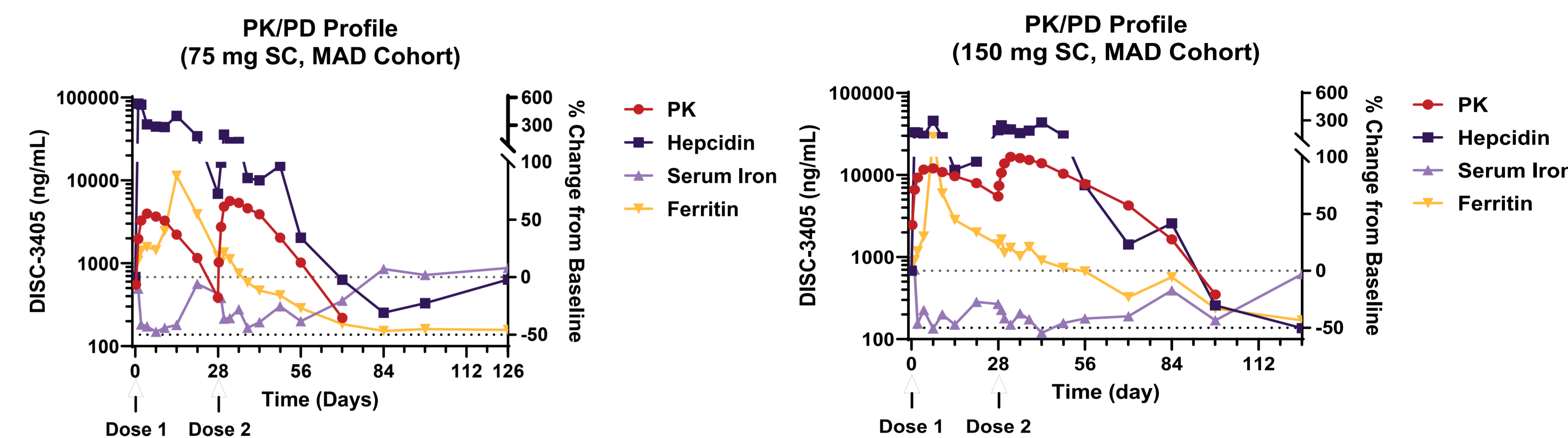
- DISC-3405 was well tolerated in healthy volunteers.
- SC administration of DISC-3405 resulted in dose-dependent PK profiles, with a terminal half-life of more than 11 days at the 300-mg dose.
- DISC-3405 produced dose-related increases in serum hepcidin, with corresponding reductions in serum iron across all dose levels.
- DISC-3405 resulted in deep reductions in serum iron (ranging from 50-80% from baseline) that were sustained and support a once-monthly SC dosing regimen
- Repeated SC dosing of DISC-3405 provided the anticipated PK/PD profile.
- Single and repeat dosing of DISC-3405 produced apparent reductions in hemoglobin, reticulocyte hemoglobin, and hematocrit.
- Overall, the favorable tolerability and PK/PD profiles demonstrated in this study with DISC-3405 support future clinical studies in patient populations that could benefit from iron restriction, including those in a planned Phase 2 study in polycythemia vera.

**Figure 3: Mean PK/PD Profiles for SAD Cohorts**

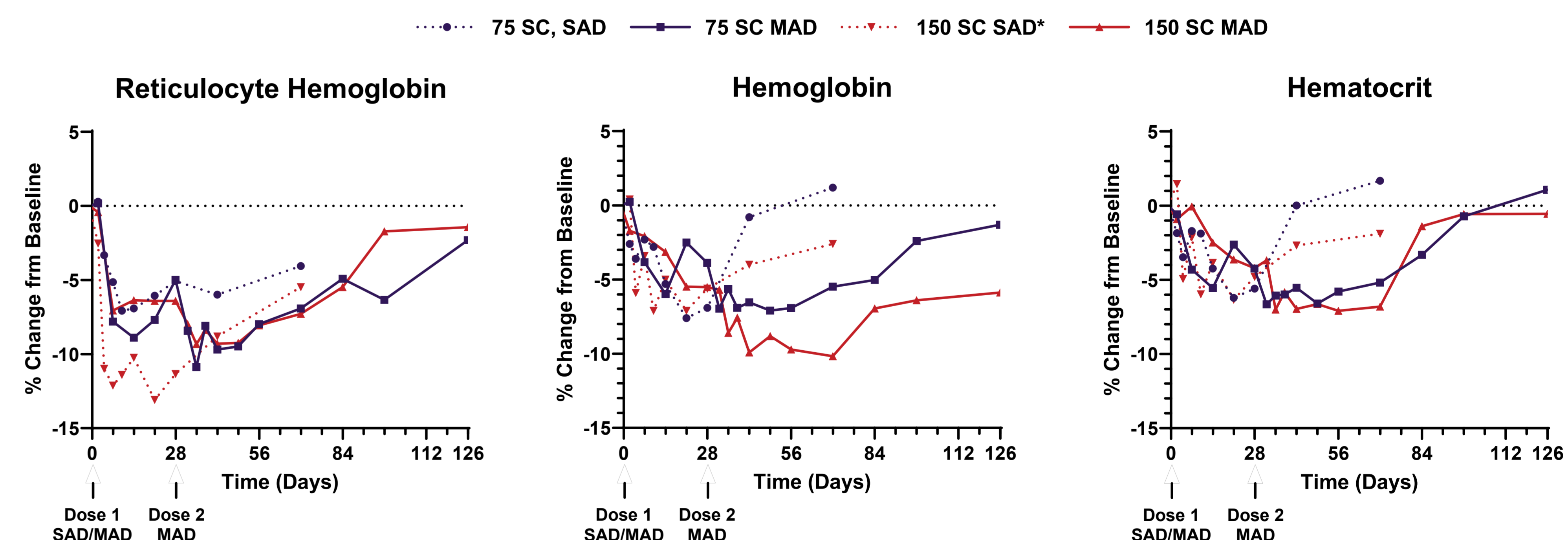


\*One participant randomized to 150 mg SC (SAD) was excluded from PD analysis due to history of anemia and recent hemorrhoidal bleeding not disclosed prior to enrollment, deeming the subject ineligible.

**Figure 4: Mean PK/PD Profiles for MAD Cohorts**



**Figure 5: 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.

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