EUROPEAN HEMATOLOGY ASSOCIATION

DISC-B, A SELECTIVE MATRIPTASE-2 INHIBITOR, ELICITED ROBUST INCREASE IN HEPCIDIN-25 AND REDUCTION IN SERUM IRON IN CYNOMOLGUS MONKEYS

disc medicine

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INTRODUCTION

Hepcidin is known as the master regulator of systemic iron homeostasis with reduction in synthesis leading to the development of iron overload. Hepcidin gene expression is negatively modulated by matriptase-2 (MT-2), a liver-specific type II transmembrane serine protease. MT-2 cleaves hemojuvelin (HJV), leading to the extracellular release of soluble HJV (sHJV) fragments and suppression of hepcidin expression. Therefore, inhibition of MT-2 represents a potential therapeutic strategy for diseases caused by inappropriately low hepcidin leading to iron overload or where therapeutic iron restriction may be used to control excessive erythrocytosis. DISC-B is a potent (MT-2 Ki =14 nM) and selective small molecule MT-2 inhibitor.

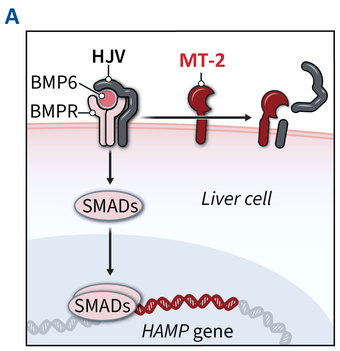


Figure 1A. *Normal BMP/SMAD/hepcidin signaling pathway*

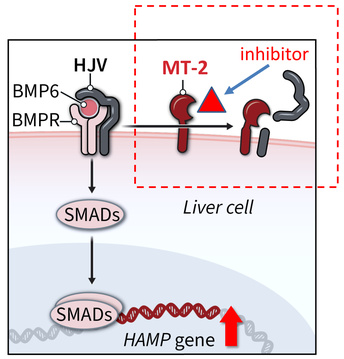


Figure 1B. *MT-2 small molecule inhibitor increases hepcidin expression through HJV*

OBJECTIVES

To examine the exposure-dependency of acute treatment of DISC-B on the key PD markers (hepcidin-25, sHJV, serum iron) in cynomolgus monkeys.

To determine the time to maximum decrease in serum iron upon multiple dosing.

To evaluate the effect of chronic treatment on key hematologic parameters.

METHODS

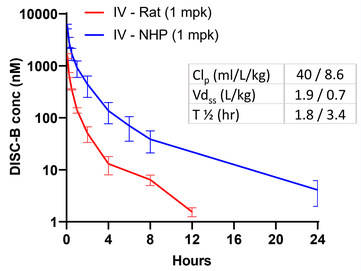
A cross-over study was conducted in male cynomolgus monkeys (2-4-year-old; N=6). Animals were administered a single subcutaneous (SC) dose of DISC-B at 5, 15, 50 mg/kg or vehicle control, followed by administration of DISC-B once a day for 7 consecutive days; the washout period in between treatments was 2 weeks. For the single-dose treatments, blood samples were collected 48-hr prior to treatment (baseline) and at various time points after dosing. For the multiple dose part of the study, blood samples were collected 48-hr prior to dosing (baseline) and at various time points after the 1st and the 7th dose. All blood samples were processed to serum and sHJV, hepcidin-25, serum iron and total iron binding capacity (TIBC) were quantified. In addition, for the multiple dose part of the study, reticulocyte hemoglobin was determined at baseline and on Day 7. TSAT was calculated as the ratio of serum iron/TIBC x 100.

RESULTS

DISC B: A Potent and Selective MT-2 Inhibitor		
Potency	MT-2 Ki	14 nM
Selectivity	Proteases	> 40-fold
	Safety panel	No hits
DDI potential	CYP inh IC_{50}	>50 uM
	CYP ind 3A4	No
	Transpt substrate	No
Safety	Ion channels	>30 uM
	Safety panel	No hits
	Ames	Negative

Table 1. *Drug-like properties of DISC-B*
- Potent and selective against proteases (FXa, Thrombin, etc.) and 78 targets safety
- Low DDI potential and favorable safety profile

Favorable PK rat/NHP



SINGLE DOSE OF DISC-B IN CYNOMOLGUS MONKEYS LED TO ROBUST ↑ HEPCIDIN-25 AND ↓ SERUM IRON

NHP PK (SC)

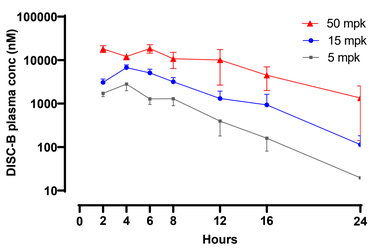


Figure 2A. *Dose-dependent exposure of DISC-B upon single SC dose of DISC-B at 5, 15, and 50 mg/kg*

↑ Hepcidin-25 (AUC)

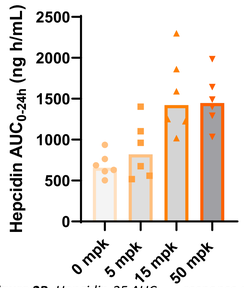


Figure 2B. *Hepcidin-25 $AUC_{0\text{-}24h}$ response shows that the magnitude of hepcidin-25 modulation was similar at 15 and 50 mg/kg dose.*

↓ Serum Iron (AUC)

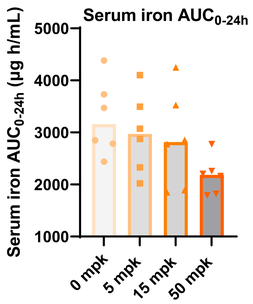


Figure 2C. *DISC-B reduces serum iron $AUC_{0\text{-}24h}$ in a dose-dependent manner.*

↓ Serum Iron – 15 and 50 mg/kg

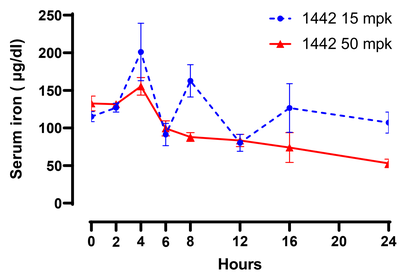


Figure 2D. *Effect of DISC-B at 15 and 50 mg/kg on serum iron*
- Maximum iron reduction from baseline was 25% and 50% for 15 and 50 mg/kg.
- Responses were more consistent across different animals at 50 mg/kg.

MULTIPLE DOSES OF DISC-B RESULTED IN CUMULATIVE ↓ SERUM IRON AND ↓ RETICULOCYTE HEMOGLOBIN

↑ Hepcidin-25 - 7-day study

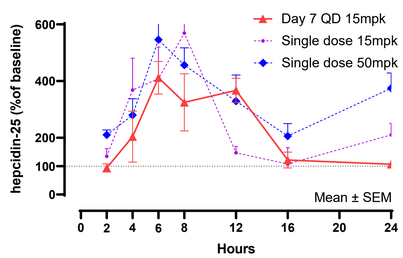


Figure 3A. *After 7 days of treatment with DISC-B hepcidin-25 increase over baseline was comparable to those of single dose 15 and 50 mg/kg.*

↑ Hepcidin-25 ↓ sHJV

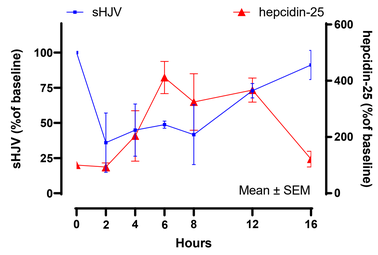


Figure 3B. *Effect on sHJV and hepcidin-25*
- Up to 60% reduction in sHJV observed at 2-hr.
- Maximum increase in hepcidin-25 achieved at 6-hr, following a 4-6 hour delay from sHJV reduction.

↓ Serum Iron- 7-day study

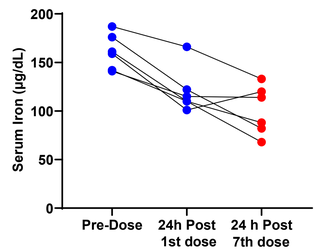


Figure 3C. *Effect on serum iron at day 7 compared to day 1*
- *Responses were more consistent after 7 doses at 15 mg/kg compared to a single dose.*
- *Accumulated reduction in serum iron after 7 doses at 15 mg/kg, reaching maximum 40-45% reduction.*

↓ Reticulocyte Hgb

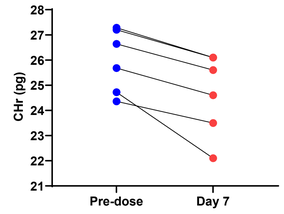


Figure 3D. *All animals showed a reduction in reticulocyte hemoglobin (CHr) with a mean reduction of 1.3 pg (± 0.6) on day 7 compared to their baseline levels, suggesting the induction of iron-restricted erythropoiesis.*

CONCLUSIONS

- DISC-B modulates serum hepcidin-25 levels and iron homeostasis in cynomolgus monkeys in a dose-dependent manner.
- The consistent increase in hepcidin-25 and the increasing reduction in serum iron after 7 doses of DISC-B suggest that prolonged inhibition of MT-2 can lead to sustained, therapeutically relevant reduction in serum iron.
- Our data demonstrate that MT-2 can be successfully inhibited by a selective small molecule to reduce sHJV, increase hepcidin, and decrease serum iron.
- The favorable pharmacokinetics and drug-like properties suggest compounds from these chemical series have the potential for clinical therapeutic benefit.

CONTACT INFORMATION

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