PRECLINICAL PHARMACOKINETICS AND PHARMACODYNAMICS OF DISC-0998, A HUMANIZED ANTI-HEMOJUVELIN (HJV) MONOCLONAL ANTIBODY TO SUPPRESS THE PRODUCTION OF HEPCIDIN

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INTRODUCTION

Anemia of inflammation (AI) is an immune-driven disorder that displays reduced erythropoietic activity and dysregulation of iron homeostasis. It is associated with a number of underlying diseases, including myelofibrosis (MF) and chronic kidney disease (CKD), and caused by inflammatory cytokine-driven increases in hepcidin levels. Increased hepcidin causes to sequestration of iron in macrophages, decreased iron absorption, and decreased serum iron, which leads to iron-restricted erythropoiesis and anemia.[1]

DISC-0974, a monoclonal antibody (mAb) targeting hemojuvelin (HJV), which positively regulates hepcidin, has been recently evaluated in a Phase 1 clinical study in healthy volunteers. Administration of DISC-0974 has resulted in suppression of hepcidin and increases in serum iron, with the overall PK/PD profile supporting monthly subcutaneous dosing.[2]

DISC-0998 is a potent and highly selective HJV mAb engineered with the mutation combination of T250Q/M429L (QL-mutation) in the Fc region, which aimed to alter binding to the FcRn receptor and increase PK half-life. Preclinical studies have demonstrated that DISC-0998 has biological activity, low immunogenicity potential, and desirable pharmacokinetic (PK) and pharmacodynamic (PD) properties.

OBJECTIVES

To evaluate the PK/PD relationships of DISC-0998 with hepcidin, serum iron, and transferrin saturation (TSAT) in male cynomolgus monkeys to inform drug development strategy.

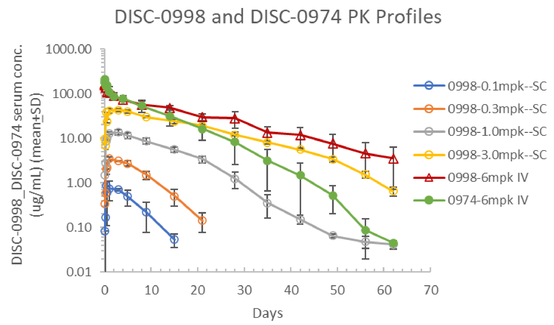
METHOD

Male cynomolgus monkeys (n = 3 per group) were randomized to different dose groups and received single 0.1, 0.3, 1.0, and 3.0 mg/kg subcutaneous (SC), or 6 mg/kg intravenous (IV) doses of DISC-0998, or 0.3 and 1.0 mg/kg subcutaneous (SC) or 6 mg/kg intravenous (IV) doses of DISC-0974. Blood samples were obtained at predefined time points for PK, hepcidin-25, serum iron, and total iron binding capacity (TIBC) measurements. Concentrations of serum hepcidin-25 were analyzed using a qualified LC-MS/MS method. Concentrations of serum iron and TIBC were analyzed using a HITACHI7180 Chemistry Analyzer. Serum DISC-0998 concentrations were analyzed using a qualified MesoScale Discovery (MSD) method.

WinNonlin (PhoenixTM,version8.1) was used for PK/PD calculations.

The PK/PD relationship was investigated using an Emax model.

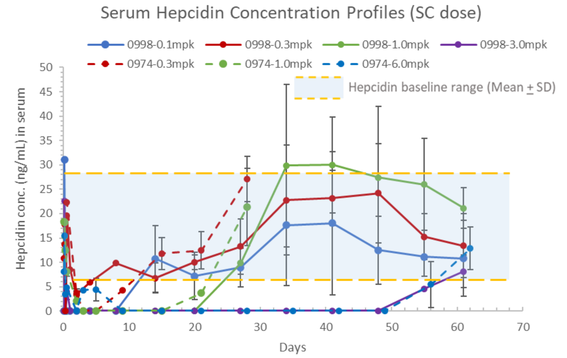
RESULTS

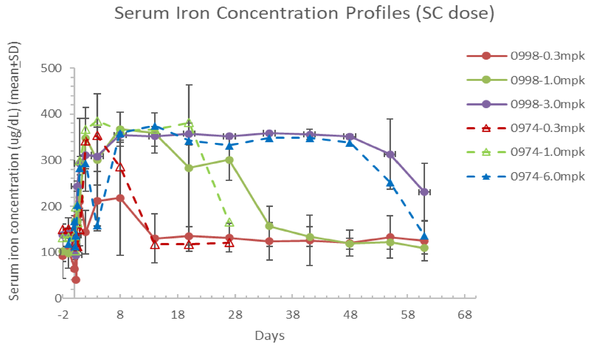


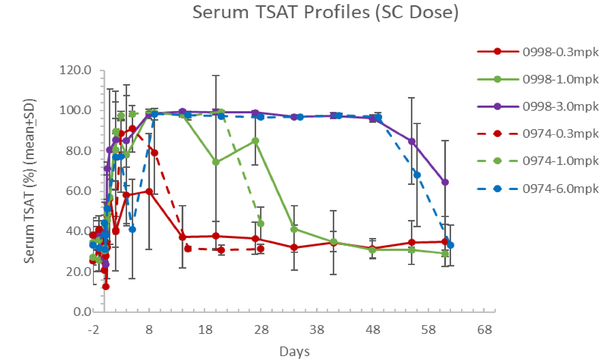
0998 SC (mpk) in monkey	C_{max} (ug/mL)	$T_{1/2}$ (days)	CL/F (mL/hr/kg)	$AUC_{0\text{-}1464hr}$ (hr*ug/mL)
0.1	0.878	3.6	0.830	114
0.3	3.46	4.0	0.440	675
1.0	13.5	6.3	0.230	4344
3.0	43.3	10.9	0.140	20630

IV @ 6 mpk in monkey	CL (mL/hr/kg)	V_{dss} (mL/kg)	$T_{1/2}$ (days)	$AUC_{0\text{-}1464hr}$ (hr*ug/mL)
0998	0.14	61.5	12.9	41989
0974	0.21	38.9	5.5	29214

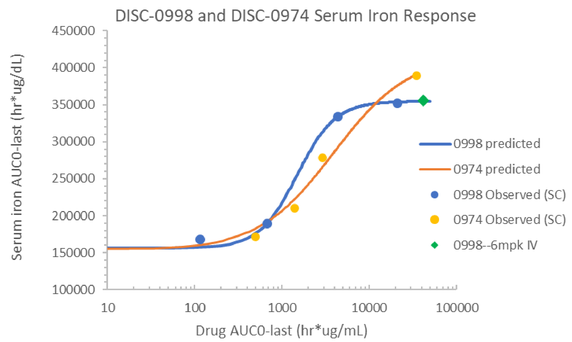
- Following single SC or IV dose, DISC-0998 exhibited low clearance (SC CL/F 0.14 – 0.83 mL/hr/kg, IV CL 0.14 mL/hr/kg), small volume of distribution (Vz 50 -104 mL/kg), and nonlinear PK as expected for a mAb.
- Compared to DISC-0974, DISC-0998 clearance was 33% lower, and half-life (t1/2) was over 2 times longer.







- Dose-dependent hepcidin-25 reduction and sustained serum iron and TSAT elevations were demonstrated in the study.
- DISC-0998 exhibited longer duration of action compared to DISC-0974



DISC-0974	Estimate	SD	CV%
AUEmax (hr*ug/dL)	264521	22957	9
EAUC50 (hr*ug/mL)	3918	1353	35
AUE0 (hr*ug/dL)	152928	15771	10

DISC-0998	Estimate	SD	CV%
AUEmax (hr*ug/dL)	198621	8219	4
EAUC50 (hr*ug/mL)	1495	181	12
AUE0 (hr*ug/dL)	156094	7738	5
Gamma	1.99	0.22	11

- Estimated $EAUC_{50}$ of DISC-0998 and DISC-0974 are 1495 hr*ug/mL and 3918 hr*ug/mL, respectively. DISC-0998 has similar or slightly better potency in monkey compared to DISC-0974.

CONCLUSIONS

DISC-0998 demonstrated a favorable PK/PD profile in monkey, allowing prediction of its PK/PD profile in humans. This, along with its extended duration of PD responses, supports further development of DISC-0998 for disorders related to anemia of inflammation, with the potential for less frequent dosing compared to DISC-0974.

REFERENCES

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2. N. Novikov, H. Yang, S. Nguyen, A. Buch, S. Tuller, M. Andruk, K. Chan, M. Wu, R. Rodriguez, R. Panwar, H. Howell, B. MacDonald, and W. Savage. 27th EHA Annual Congress 2022, EHA-1434

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