A PHASE 1B DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF DISC-0974, AN ANTI-HEMOJUVELIN ANTIBODY, IN PATIENTS WITH NON-DIALYSIS DEPENDENT CHRONIC KIDNEY DISEASE AND ANEMIA

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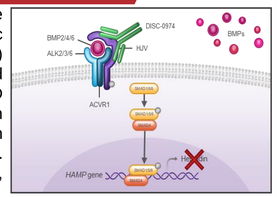
INTRODUCTION

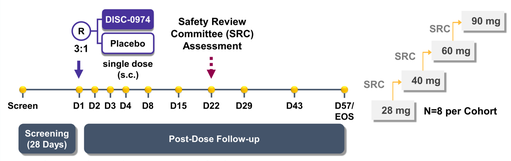
Anemia affects 30 to 40% of the non-dialysis dependent chronic kidney disease (NDD-CKD) population.[1,2] Inflammation and impaired renal clearance in CKD increases plasma hepcidin, which regulates absorption of dietary iron and systemic iron distribution. DISC-0974 is an investigational, monoclonal antibody that suppresses hepcidin. Reducing hepcidin and mobilizing iron is a novel approach to treatment of anemia in CKD. A healthy-volunteer study demonstrated dose-dependent reductions in serum hepcidin, increases in serum iron, and increasing trends in hemoglobin with a favorable safety profile.[3]



AIM

To evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and single-dose efficacy of subcutaneous (SC) administration of DISC-0974 in participants with CKD and anemia.

METHODS



s.c.=subcutaneously; R=randomization; EOS=end of study

Study Design:

- Phase 1b, multi-center, double-blind, ascending dose study
- Enrolling ~ 36 participants with CKD

Key Eligibility Criteria:

- Stage 2-5 CKD
- Hemoglobin < 11 g/dL
- Serum ferritin ≥ 75 µg/L
- Transferrin saturation ≤ 35%

Endpoints:

- Primary: Safety and tolerability of DISC-0974 as assessed by treatment-emergent adverse events, vital signs, physical exam, electrocardiogram, and laboratory testing.
- Secondary: PK/PD markers of iron regulation and hematologic parameters.

RESULTS

Table 1. Baseline and demographic information

	28 mg DISC-0974 (n=9)	40 mg DISC-0974 (n=6)	60 mg DISC-0974 (n=6)	Pooled Placebo (n=7)
Age, median (range), years	69 (55, 78)	61.5 (37, 80)	69.5 (57, 82)	71 (60, 76)
Sex				
Male, n (%)	3 (33.3)	3 (50.0)	1 (16.7)	2 (28.6)
Female, n (%)	6 (66.7)	3 (50.0)	5 (83.3)	5 (71.4)
CKD Stage, n (%)				
Stage 2	0	1 (16.7)	1 (16.7)	0
Stage 3	2 (22.2)	0	2 (33.3)	2 (28.6)
Stage 4	5 (55.6)	5 (83.3)	3 (50.0)	5 (71.4)
Stage 5	2 (22.2)	0	0	0
Baseline[a] hepcidin, median (range), ng/mL	57.7 (24.0, 170.6)	63.2 (50.0, 109.6)	57.8 (29.2, 156.9)	76.3 (36.8, 122.3)
Baseline[a] hemoglobin, median (range), g/dL	9.8 (8.6, 10.6)	10.6 (10.0, 11.2)	10.8 (10.1, 11.0)	9.6 (9.0, 10.9)

CKD=chronic kidney disease; [a]Baseline is an average of screening and pre-dose measurements.

Table 2. Adverse events by preferred term occurring in ≥2 participants at any dose level

	28 mg DISC-0974 (n=9)	40 mg DISC-0974 (n=6)	60 mg DISC-0974 (n=6)	Pooled Placebo (n=7)
Metabolic Acidosis	1 (11.1)	1 (16.7)	1 (16.7)	1 (14.3)
Hyperkalemia	0	1 (16.7)	2 (33.3)	0
Anemia	2 (22.2)	0	0	2 (28.6)
Atrial fibrillation	1 (11.1)	0	1 (16.7)	0
Hypertension	0	0	0	2 (28.6)

Related AEs: 1 participant with Grade 1 hyperkalemia treated at 60 mg; 1 participant with Grade 1 dizziness treated at 60 mg; 1 participant with Grade 2 Eosinophilia and Grade 2 Renal failure (Creatinine 1.2X baseline at day 29 with resolution by day 57). ≥ Grade 3 AEs: 1 participant treated at 28 mg with Grade 4 ESRD (dialysis eligible prior to enrollment), Grade 4 anemia and Grade 3 fluid retention; 1 participant treated at 40 mg with Grade 3 hypervolemia. Serious adverse events: 3 participants including 1 participant treated at 28 mg with Grade 4 ESRD (same as "≥ Grade 3 AE" participant with ESRD); 1 participant treated at 28 mg with Grade 2 atrial fibrillation (medical history of atrial fibrillation); 1 participant treated at 60 mg with Grade 1 atrial fibrillation (medical history of atrial fibrillation).

DISC-0974 Reduces Hepcidin and Mobilizes Iron

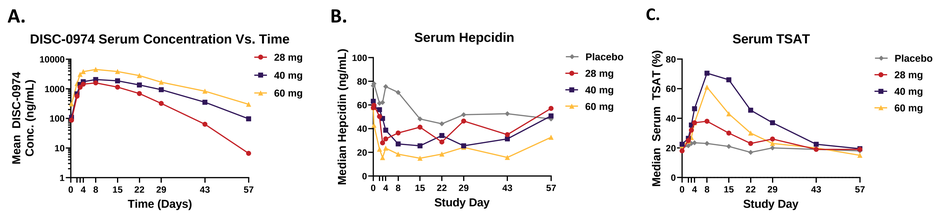


Figure 1. A) Mean DISC-0974 concentration over time; B) Median serum hepcidin after administration of placebo (gray), 28 mg DISC-0974 (red), 40 mg DISC-0974 (blue), or 60 mg DISC-0974 (yellow). C) Median serum TSAT after administration of placebo (gray), 28 mg DISC-0974 (red), 40 mg DISC-0974 (blue), or 60 mg DISC-0974 (yellow). Conc=concentration; TSAT=transferrin saturation.

Hematologic Response after DISC-0974 Dosing

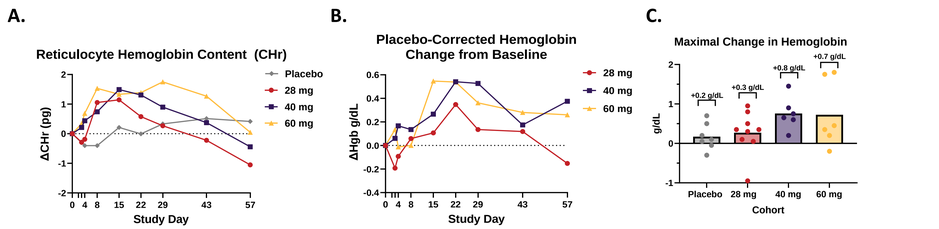


Figure 2. A) Mean change from baseline for reticulocyte hemoglobin after administration of placebo (gray), 28 mg DISC-0974 (red), 40 mg DISC-0974 (blue), or 60 mg DISC-0974 (yellow). B) Placebo-corrected hemoglobin change from baseline after administration of 28 mg DISC-0974 (red), 40 mg DISC-0974 (blue), or 60 mg DISC-0974 (yellow) using the difference of the least-squares means. C) Mean maximal change in hemoglobin from baseline after treatment through Day 29 of study with dots representing individual values.

CONCLUSIONS

- DISC-0974 demonstrated **acceptable safety and tolerability at all evaluated dose levels.**
- DISC-0974 dosing resulted in **decreased hepcidin and increased serum TSAT** when compared with placebo**.**
- DISC-0974 resulted in an increase in mean reticulocyte hemoglobin and hemoglobin compared to placebo.
- These data provide initial proof of mechanism that in the setting of CKD, hemojuvelin-targeted therapy with DISC-0974 can suppress hepcidin, mobilize iron into circulation, and can increase hemoglobin to address anemia. DISC-0974 dose escalation is ongoing in participants with NDD-CKD and anemia.

REFERENCES

1. Stauffer ME, Fan T. *PLoS One* 2014;9(1):e84943.
2. Hsu C, et al. *J Am Soc Nephrol* 2002;13:504-510.
3. Novikov N, et al. *Blood.* 2022;140(Suppl 1):5339-5340.

CONTACT INFORMATION

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DISC-0974 is an investigational drug and is not approved for use by any regulatory agency, including the US Food & Drug Administration.