A Phase 1b Trial of DISC-0974, an Anti-Hemojuvelin Antibody, in Patients with Myelofibrosis and Anemia

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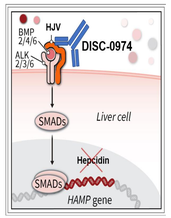
INTRODUCTION



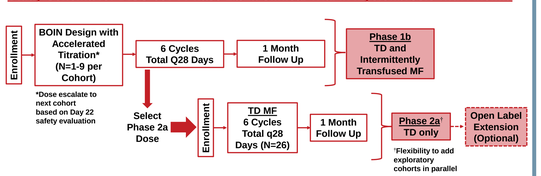
Hepcidin, a central regulator of iron homeostasis, is pathologically elevated in patients with myelofibrosis (MF) and anemia. DISC-0974 is an investigational, first-in-class, monoclonal antibody that blocks hemojuvelin, a co-receptor in the bone morphogenetic protein-signaling pathway driving hepcidin expression. Preclinical studies have shown that DISC-0974 suppresses hepcidin and increases serum iron. A healthy volunteer study has demonstrated dose-dependent reductions in serum hepcidin, increases in serum iron, and increasing trends in hemoglobin with a favorable safety profile.[1]

AIM

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

METHODS

Study Schema for DISC-0974 Phase 1b/2a Clinical Trial in Myelofibrosis with Anemia



Study Design: This is a Phase 1b/2a, multi-center, open-label, ascending-dose study with expansion cohorts. In the Phase 1b (dose-escalation) portion of the study, DISC-0974 will be administered SC every 4 weeks for up to 6 treatments. The 1b portion of the study employs a Bayesian optimal interval (BOIN) design with accelerated titration.

Key Eligibility Criteria: Eligible participants are adults with primary, post-essential thrombocythemia, or post-polycythemia vera MF with intermediate-2 or high-risk disease and hemoglobin <10 g/dL on ≥3 assessments over 84 days or transfusion dependent (TD). Washout prior to screening for androgens, erythropoietin, cladribine, immunomodulators, and interferon-α is required. Concomitant stable Janus kinase inhibitor or hydroxyurea use is allowed. Subjects with anemia due to infection, bleeding, or iron, vitamin B12, or folate deficiency are excluded.

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

	14 mg DISC-0974 (N=1)	28 mg DISC-0974 (N=7)	50 mg DISC-0974 (N=3)
Age, median (range), years	70	71 (57, 89)	66 (31, 71)
Men, n (%)	0	5 (71.4)	2 (66.7)
Disease diagnosis, n (%)			
PMF	0	4 (57.1)	2 (66.7)
Post-ET MF	1 (100)	3 (42.9)	0
Post-PV MF	0	0	1 (33.3)
Time since MF diagnosis median (range), years	1	6 (0,18)	2 (0,14)
DIPSS risk level, n (%)			
Intermediate-2	1 (100)	6 (85.7)	3 (100)
High	0	1 (14.3)	0
Prior JAK inhibitor use, n (%)	1 (100)	2 (28.6)	0
Concomitant medication, n (%)			
JAK inhibitor	0	4 (57.1)	0
Hydroxyurea	1 (100)	2 (28.6)	0
Transfusion dependent#, n (%)	0	2 (28.6)	0
Baseline hepcidin, median (range), ng/mL	48.2	93.3 (27.3, 171.1)	77.1 (34.8, 119.3)

Abbreviations: PMF = primary myelofibrosis; post-ET MF = post-essential thrombocythemia myelofibrosis; post-PV MF = post-polycythemia vera myelofibrosis; DIPSS = Dynamic International Prognostic Scoring System; JAK = Janus kinase.
Defined as an RBC transfusion frequency of ≥6 units packed RBCs (PRBC) over the 84 days immediately prior to Screening. There must not be any consecutive 42-day period without an RBC transfusion in the 84-day period, and the last transfusion must be within 28 days prior to Screening.[2]

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

	14 mg DISC-0974 (N=1)		28 mg DISC-0974 (N=7)		50 mg DISC-0974 (N=3)	
	Any Grade	Grade 3	Any Grade	Grade 3	Any Grade	Grade 3
Subjects with event (n)	**0**	**0**	**6**	**3**	**2**	**1**
Fatigue	0	0	3	0	0	0
Anemia	0	0	4	2	1	1
Diarrhea	0	0	2	0	1	0
Nausea	0	0	2	0	0	0

Related AEs: 1 subject with Grade 2 diarrhea treated at 50 mg. Grade 3 AE: headache was reported in 1 subject treated at 28 mg, unlikely related to DISC-0974. Serious AE: Grade 2 hip pain was reported in 1 subject treated at 28 mg, not related to DISC-0974. There were no ≥ Grade 4 AEs reported.

DISC-0974 reduces serum hepcidin and increases serum iron in a dose-dependent manner

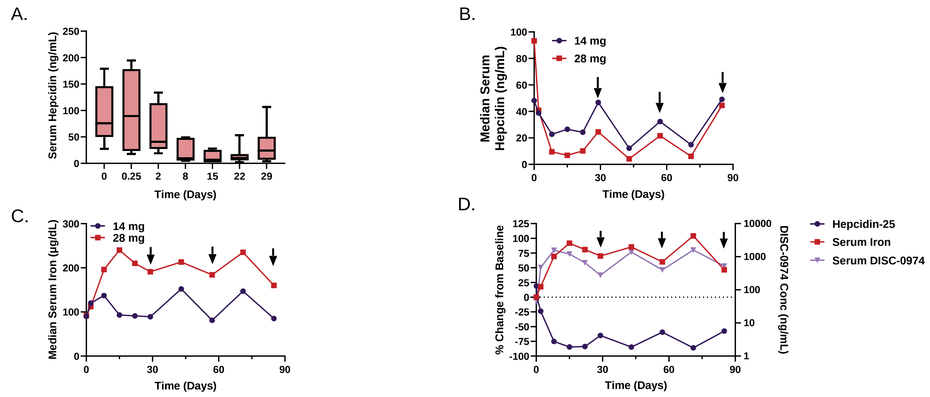


Figure 1. A) Serum hepcidin after 28 mg of DISC-0974 administration with median and range over time depicted. B) Median serum hepcidin for subjects dosed at 14 mg (blue) and 28 mg (red). C) Median serum iron for subjects dosed at 14 mg (blue) and 28 mg (red). D) Percent change from baseline for hepcidin (blue) and serum iron (red) compared with DISC-0974 concentration (purple) for subjects dosed at 28 mg. Arrows represent dosing days.

Hematologic response in transfusion-dependent and non-transfusion-dependent subjects

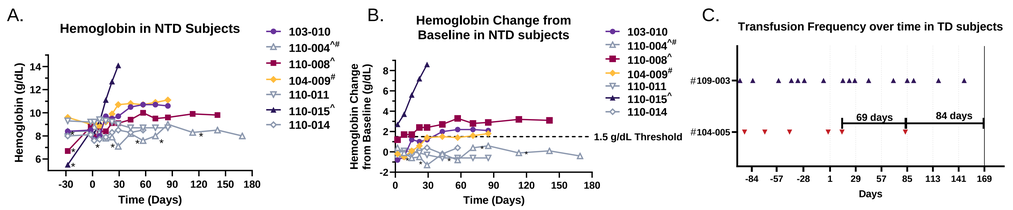


Figure 2. Anemia response was evaluated by change in hemoglobin for non-transfusion-dependent subjects (NTD) and transfusion frequency in transfusion-dependent (TD) subjects at 28 and 50 mg dosing. A) Hemoglobin values of NTD subjects over time. Five subjects received 28 mg (103-010, 110-008, 104-009, 110-011) and two subjects received 50 mg (110-014, 110-015) of DISC-0974 for more than 28 days as of the data cut. B) Hemoglobin increase from baseline (defined as average of available within 4 weeks of Day 0 but excluding values within 14 days of RBC transfusion). Four of seven subjects had ≥1.5 g/dL hemoglobin increase from baseline after starting DISC-0974. C) Transfusion frequency for 2 TD subjects receiving 28 mg DISC-0974. One subject achieved transfusion independence (Gale criteria). †Indicates transfusion. ^ Indicates transfusion during screening. # Indicates concomitant JAK inhibitor use.

CONCLUSIONS

- DISC-0974 demonstrated **acceptable safety and tolerability at all evaluated dose levels.**
- DISC-0974 dosing resulted in **decreased hepcidin and increased serum iron** in a dose-dependent manner**.**
- Among patients with at least 1 month follow-up at the 28- and 50-mg dose levels:
  - **Hemoglobin responses of ≥1.5 g/dL increase were achieved in 4 of 7** non-transfusion-dependent subjects.
  - One transfusion-dependent subject became transfusion-independent by the end of study.[3]
- DISC-0974 dose escalation is ongoing in subjects with myelofibrosis and anemia with 11 subjects enrolled as of this data cut.
- These data provide initial proof of concept that hemojuvelin-targeted therapy with DISC-0974 can suppress hepcidin greater than 75%, can mobilize iron into circulation, and can increase hemoglobin to address anemia.

REFERENCES

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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.