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A Phase 1b Trial of DISC-0974 in Patients with Myelofibrosis and Anemia

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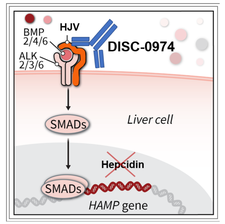
INTRODUCTION

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]

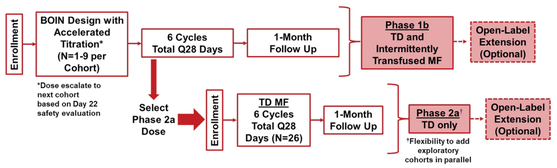


AIM

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 was administered SC every 28 days for up to 6 cycles. 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. Participants 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.

Hematologic Response Definitions: For TD participants, transfusion-independence (TI) for any 12-week period. For non-transfusion-dependent (nTD) participants, ≥1.5 g/dL hemoglobin increase from baseline at any time point; durability is evaluated as mean hemoglobin ≥1.5 g/dL above baseline during any 12-week period.

RESULTS

Table 1. Baseline and demographic information

	14 mg DISC-0974 (N=1)	28 mg DISC-0974 (N=7)	50 mg DISC-0974 (N=12)	75 mg DISC-0974 (N=8)	100 mg DISC-0974 (N=6)
Age, median (range), years	70	71 (57, 89)	70.5 (31, 83)	74 (58, 84)	67.5 (53, 79)
Men, n (%)	0	5 (71.4)	8 (66.7)	6 (75.0)	4 (66.7)
Disease diagnosis, n (%) PMF Post-ET MF Post-PV MF	 0 1 (100) 0	 4 (57.1) 3 (42.9) 0	 10 (83.3) 0 2 (16.7)	 5 (62.5) 3 (37.5) 0	 4 (66.7) 0 2 (33.3)
Time since MF diagnosis, median (range), years	1	6 (0,18)	2.5 (0,14)	4 (0, 12)	1 (0, 2)
DIPSS risk level, n (%) Intermediate-2 High	 1 (100) 0	 6 (85.7) 1 (14.3)	 11 (91.7) 1 (8.3)	 6 (75) 2 (25)	 5 (83.3) 1 (16.7)
Concomitant medication, n (%) JAK inhibitor Hydroxyurea	 0 1 (100)	 4 (57.1) 0	 5 (41.7) 0	 1 (12.5) 1 (12.5)	 0 0
Transfusion dependent#, n (%)	0	2 (28.6)	1 (8.3)	0	1 (16.7)
Baseline hepcidin, median (range), ng/mL	48.2	93.3 (21.4, 171.1)	90.2 (8.7, 155.7)	46.6 (23.7, 188.2)	64.4 (11.5, 374.7)
Baseline hemoglobin, median (range), g/dL	8.2	8.4 (6.8, 9.3)	8.6 (6.1, 10.3)	8.9 (6.7, 9.9)	8.2 (5.5, 9.4)

Data as of 29 Apr 2024. Abbreviations: DIPSS = Dynamic International Prognostic Scoring System; JAK = Janus kinase; PMF = primary myelofibrosis; post-ET MF = post-essential thrombocythemia myelofibrosis; post-PV MF = post-polycythemia vera myelofibrosis; PRBC = packed red blood cells; RBC = red blood cells.
Defined as an RBC transfusion frequency of ≥6 units 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] One participant treated with 28 mg discontinued DISC-0974 early due to physician decision.

Table 2. Adverse events at least possibly related to DISC-0974

	14 mg DISC-0974 (N=1)	28 mg DISC-0974 (N=7)	50 mg DISC-0974 (N=12)	75 mg DISC-0974 (N=8)	100 mg DISC-0974 (N=6)
Participants with event (n)	**0**	**3**	**5**	**1**	**1**
Diarrhea	0	1	2	1	0
Injection site bruising	0	1*	0	0	0
Pyrexia	0	1*	0	0	0
Blood bilirubin increased	0	0	0	0	1
Platelet count decreased	0	0	1*	0	0
Anemia	0	0	1*	0	0
Urinary tract infection	0	1*	0	0	0
Headache	0	0	1	0	0
Hot flush	0	0	1	0	0

Abbreviations: AE = adverse event; JAKi = Janus kinase inhibitor.
Grade 3 AEs include headache reported in 1 participant treated at 28 mg (unlikely related to DISC-0974) and Grade 3 anemia reported in 2 participants treated at 28 mg and 4 participants treated at 50 mg (one at 50 mg was deemed related to DISC-0974; all others were deemed not related). Serious AE: Grade 2 arthralgia was reported in 1 participant treated at 28 mg (not related to DISC-0974). There were no ≥ Grade 4 AEs reported. Liver iron concentration was obtained at baseline and end of study; for available participants (n=10), median change from baseline was 0.3 mg/g dry weight, range (-0.5 to 16.2). * indicates AE in a participant receiving concomitant JAKi therapy.

DISC-0974 reduces serum hepcidin and increases serum iron

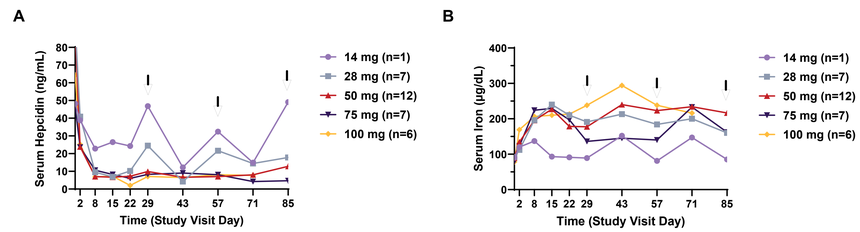
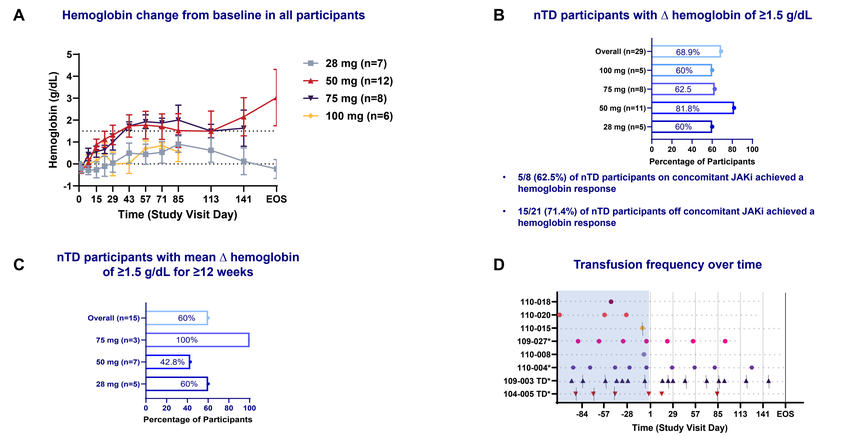


Figure 1. A) Median serum hepcidin for participants dosed at 14 mg (purple), 28 mg (light gray), 50 mg (red), 75 mg (blue), and 100 mg (yellow). B) Median serum iron for participants dosed at 14-100 mg. Arrows represent dosing days.

DISC-0974 increases hemoglobin and reduces transfusion requirements with durable hematological responses



- 5/8 (62.5%) of nTD participants on concomitant JAKi achieved a hemoglobin response
- 15/21 (71.4%) of nTD participants off concomitant JAKi achieved a hemoglobin response

Figure 2. A) Mean (±SEM) hemoglobin over time for participants dosed at 28-100 mg with evaluable participants over time. B) Percent of non-transfusion-dependent participants with a hemoglobin value of ≥1.5 g/dL above baseline at any visit during study by dose level (28-100 mg). C) Percent of non-transfusion-dependent participants with mean hemoglobin ≥1.5 g/dL above baseline for ≥12 weeks (minimum of 16-week follow-up required for inclusion and maximal follow-up of 169 days). D) Transfusion frequency of participants with baseline transfusion requirement and ≥12 weeks of follow-up through EOS. Dotted line denotes progression through study. I Indicates 2 units transfused; all other transfusions are 1 unit. One of two evaluable TD participants (104-005) achieved a TI per Gale criteria. * denotes concomitant MF-directed therapy.

CONCLUSIONS

- DISC-0974 demonstrated **acceptable safety and tolerability at all evaluated dose levels.**
- DISC-0974 dosing resulted in **decreased hepcidin and increased serum iron that was sustained for several weeks after each dose.**
- Among participants treated at 28-100 mg:
  - **Hemoglobin responses of ≥1.5 g/dL increase were achieved in 68.9% of nTD participants**.
  - **For participants who have completed study, 62.5% of nTD participants had a mean hemoglobin response of ≥1.5 g/dL above baseline sustained for at least 12 weeks.**
  - **One of two evaluable TD participants became TI** by the end of study.[3]
  - Hematologic responses were achieved in **6 of 10 participants with concomitant JAK inhibitor therapy**.
  - All evaluable participants with baseline transfusion requirement had at least a **50% reduction in transfusions over a rolling 8-week window on study compared to baseline.**
- DISC-0974 longer-term follow-up is ongoing in participants with MF and anemia with 34 participants enrolled as of this data cut.

REFERENCES

1. Novikov N, et al. *Blood.* 2022;140(Suppl 1):5339-5340.
2. Tefferi A, et al. *Blood.* 2013;122(8):1395-1398.
3. Gale RP, et al. *Leuk Res.* 2011;35(1):8-11.

CONTACT INFORMATION

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