A Phase 1b/2 Study of DISC-0974, an Anti-Hemojuvelin Antibody, in Patients with Myelofibrosis and Anemia

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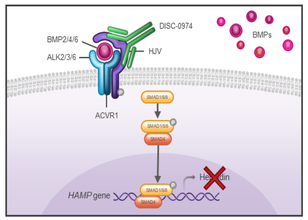
INTRODUCTION

Hepcidin, a central regulator of iron homeostasis, is pathologically elevated in patients with myelofibrosis (MF) and anemia.[1] 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.[2] This Phase 1b/2, open-label, multiple-ascending dose study (NCT05320198) assesses safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy of DISC-0974 in patients with MF and anemia.



METHODS

Study Population

- N=35
- Primary, post-essential thrombocythemia, or post-polycythemia vera MF
- Intermediate-2 or high-risk disease
- Hemoglobin (Hgb) <10 g/dL on ≥3 assessments over 84 days or transfusion dependent (TD)
- Washout prior to screening for androgens, erythropoietin, cladribine, immunomodulators, and interferon alpha is required
- Concomitant stable Janus kinase (JAK) inhibitor or hydroxyurea use is allowed

Phase 1b Study Design

Screening (28 Days) → Treatment Period (6 Cycles q28 Days) → Follow-Up (28 Days) → Continuation Treatment (q28 Days – Optional)

Ascending dose: subcutaneous (SC) at 14, 28, 50, 75, and 100 mg
(BOIN design with accelerated titration)

Key endpoints: safety and tolerability (primary), PD markers of mechanisms of engagement, **hematologic response**

Baseline Transfusion	Major Hematologic Response	Minor Hematologic Response	Overall
nTD (Hgb <10 and 0 units transfused)*	Mean Hgb ↑1.5 g/dL ≥12 weeks	Mean Hgb ↑1 g/dL ≥12 weeks	Major + Minor
TD Low (1-2 units transfused)*	Transfusion independence ≥16 weeks (rolling window) and Hgb ≥7 g/dL	≥50% reduction in transfusions from baseline over rolling 12-week window	
TD High (3-12 units transfused)*	Transfusion independence ≥12 weeks (rolling window) and Hgb ≥7 g/dL	≥50% reduction in transfusions from baseline over rolling 12-week window	

Criteria adapted from Tefferi et al, Blood, 2024[3]; * During 84 days prior to screening

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

RESULTS *(Data as of October 17, 2024)*

Table 1. Baseline and Demographics

	Overall (n=35)
Age, median (range), years	71 (31, 89)
Male, n (%)	23 (65.7)
Race, n (%)	
White	28 (80)
Black or African American	4 (11.4)
Asian	1 (2.9)
American Indian or Alaska Native	1 (2.9)
Other	1 (2.9)
JAK2 mutation present	23 (65.7)
Concomitant medication, n (%)	
JAK inhibitor	13 (37.1)
Ruxolitinib	10 (77.0)
Hydroxyurea	4 (11.4)
Transfusion requirement*, n (%)	
nTD (Hgb <10 g/dL and 0 units transfused)	23 (65.7)
TD low (1-2 units transfused)	5 (14.3)
TD high (3-12 units transfused)	7 (20.0)
Baseline hepcidin	
Median (range), ng/mL	68.9 (8.7, 374.7)
Mean (SD), ng/mL	85.8 (71.0)
Baseline Hgb, median (range), g/dL	8.4 (5.5, 10.0)

*During 84 days prior to screening

Table 2. Summary of Safety

Preferred term	28 mg (n=7)	50 mg (n=12)	75 mg (n=9)	100 mg (n=6)	Overall (n=35)
Any TEAE	6 (85.7)	12 (100)	8 (88.9)	6 (100)	32 (94.1)
Related AE	4 (57.1)	6 (50)	5 (55.6)	1 (16.7)	16 (47.1)
SAE	1 (14.3)	2 (16.7)	0	1 (16.7)	4 (11.8)
Common TEAEs in ≥5 participants					
Diarrhea	3 (42.9)	5 (41.7)	5 (55.6)	1 (16.7)	14 (41.2)
Nausea	2 (28.6)	2 (16.7)	2 (22.2)	2 (33.3)	8 (23.5)
Vomiting	1 (14.3)	2 (16.7)	0	3 (50.0)	6 (17.6)
Constipation	0	4 (33.3)	1 (11.1)	0	5 (14.7)
Fatigue	3 (42.9)	3 (25.0)	1 (11.1)	3 (50.0)	10 (29.4)
Lymphocyte count decreased	1 (14.3)	2 (16.7)	2 (22.2)	1 (16.7)	6 (17.6)
Dizziness	0	2 (16.7)	2 (22.2)	3 (50.0)	7 (20.6)
Headache	1 (14.3)	1 (8.3)	1 (11.1)	2 (33.3)	5 (14.7)
Dyspnea	0	1 (8.3)	2 (22.2)	2 (33.3)	5 (14.7)
Hyperhidrosis	1 (14.3)	1 (8.3)	1 (11.1)	2 (33.3)	5 (14.7)
Anemia	5 (71.4)	4 (33.3)	0	0	9 (26.5)
Hypertension	0	3 (25.0)	3 (33.3)	0	6 (17.6)

Abbreviations: TEAE=treatment emergent adverse event; SAE=serious adverse event
No TEAEs were reported at the 14 mg dose level. Related AEs occurring in ≥2 participants: diarrhea (n=6); SAEs: arthralgia, cellulitis related to cat scratch, cellulitis related to cat bite, and kidney infection; ≥Grade 3 AEs were considered not related to study drug and included: anemia, lymphocyte count decreased, platelets decreased, cellulitis, kidney infection (same as SAE), muscular weakness, and headache.

Hematologic response is achieved regardless of baseline transfusion or concomitant JAK inhibitor

Table 3. Summary of Hematologic Response

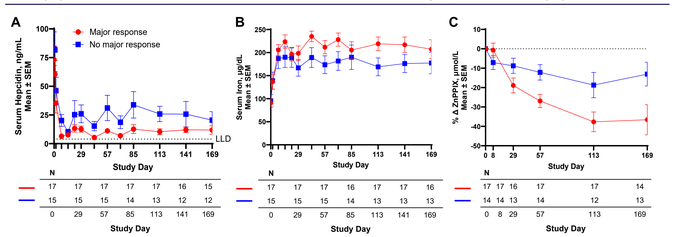
Participants (%) achieving hematologic response	All participants*			Participants on concomitant ruxolitinib		
	nTD (n=22)	TD Low (n=5)	TD High (n=5)**	nTD (n=6)	TD Low (n=0)	TD High (n=4)
Overall response	59%	100%	60%	83%	---	50%
Major response	50%	80%	40%	83%	---	25%

*Includes participants dosed at 28-100 mg
**2 TD high participants were considered not evaluable due to incomplete data entry at time of data cut
2 (of 10) participants receiving ruxolitinib escalated JAK inhibitor dosing during treatment period

Pharmacodynamics, Hgb response, and underlying biology of DISC-0974 in Major Responders is further investigated in Figures 1 and 2

Treatment with DISC-0974 leads to sustained reduction in hepcidin, ZnPPIX, and to iron mobilization

Figure 1. Mean / mean % CFB ± SEM over time in serum hepcidin (A), serum iron (B), and ZnPPIX, a measure of iron-restricted Hgb production (C)

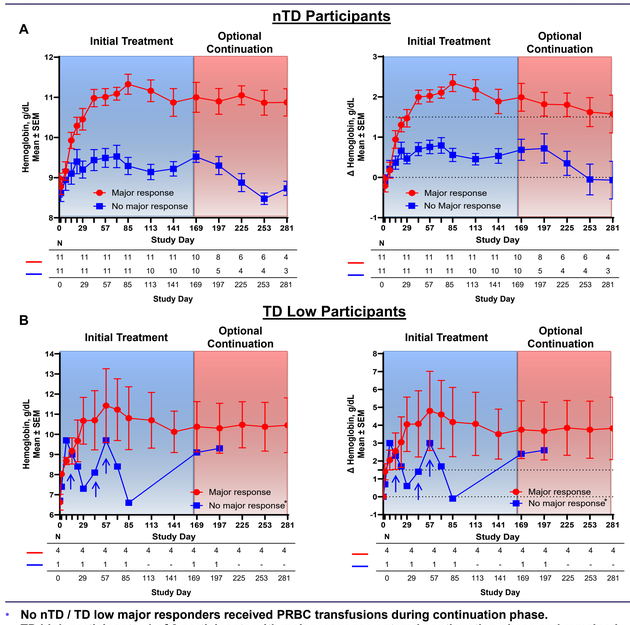


- Major responders treated with DISC-0974 also experienced a **43% and 29% reduction from baseline at Day 113 in erythropoietin and ferritin**, respectively

Abbreviations: CFB=change from baseline; LLD=lower limit of detection; SEM=standard error of mean; ZnPPIX=zinc protoporphyrin IX
Includes participants dosed at 28-100 mg. Excludes 2 TD High participants considered not evaluable due to incomplete data entry at time of data cut and 1 TD low participant starting on Day 113 due to drug held.
No major response: participants achieving either minor or no hematologic response.

Anemia response is durable in continuation phase for major responders

Figure 2. Mean / mean CFB ± SEM Hgb for nTD (A) and TD Low (B) participants



- **No nTD / TD low major responders received PRBC transfusions during continuation phase.**
- **TD high participants: 1 of 2 participants with major response entered continuation phase and remained transfusion independent (TI) at Day 225 with follow-up ongoing.**

↑ **Indicates Study Day of PRBC transfusions received during study treatment**. Abbreviations: CFB=change from baseline; SEM=standard error of mean. Includes participants dosed at 28-100 mg. No major response includes participants achieving either minor or no hematologic response. *Participant did not receive DISC-0974 on Days 113 and 141.

CONCLUSIONS

- DISC-0974 was **safe and well tolerated** at all evaluated dose levels
- Reduction in hepcidin and ZnPPIX along with iron mobilization support **mechanism of target engagement**
- 50% of nTD participants achieved **sustained mean Hgb increases of ≥1.5 g/dL**
- 80% of TD Low participants achieved **TI-16 weeks**
- 40% of TD High participants achieved **TI-12 weeks**
- **Hematologic improvement is durable** through continuation phase of study

RALLY-MF PHASE 2 STUDY DESIGN

NOW ENROLLING

- N=~90
- Hgb <10 g/dL on ≥3 assessments over 12 weeks, or 1 or more packed red blood cell (PRBC) units transfused in 12 weeks
- Severity: DIPSS intermediate-1 to High
- +/- JAK inhibitor permitted

Screening (28 Days) → Treatment Period (6 Cycles q28 Days) → Follow-Up (28 Days) → Continuation Treatment (q28 Days – Optional)

Dosing: 50 mg, SC, q28 days

Open-label, 3 cohorts

- **nTD** (N=30): 0 RBC units transfused over 84 days prior to Screening
- **TD Low** (N=30): 1-2 RBC units transfused over 84 days prior to Screening
- **TD High** (N=30): 3-12 RBC units transfused over 84 days prior to Screening

Exploratory cohort

- momelotinib / pacritinib nTD, TD Low, or TD High; N=10

Flexibility to add exploratory cohorts

Key endpoints:

- Anemia response defined by cohort (TI, transfusion burden reduction, Hgb change)
- Iron, hepcidin, hematologic parameters
- FACIT fatigue score

References

1. Pardanani A, et al. Am J Hematol. 2013;88(4):312-316.
2. Novikov N, et al. Blood. 2022;140(Suppl 1):5339-5340.
3. Tefferi A, et al. Blood. 2024;144(17):1813-1820.

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