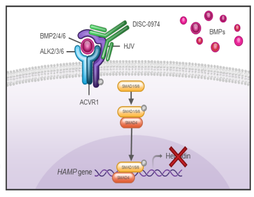
A Phase 1b/2 Study of DISC-0974, an Anti-Hemojuvelin Antibody, in Patients with Myelofibrosis and Anemia

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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, reducing 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

- 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)
- +/- JAK inhibitor or hydroxyurea use is allowed

Phase 1b study design

Screening (28 Days)	Treatment Period (6 Cycles q28 Days)	Follow-Up (Days)	Continuation (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)
Other	3 (8.6)
JAK2 mutation present	23 (65.7)
Concomitant JAK inhibitor, n (%)	13 (37.1)
Ruxolitinib	10 (77.0)
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)

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.

RESULTS *(Continued)*

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

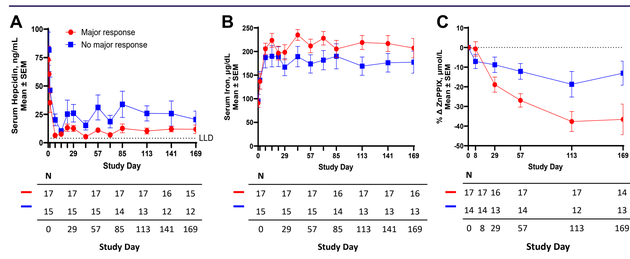
Table 3. Summary of Hematologic Response

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.

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

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

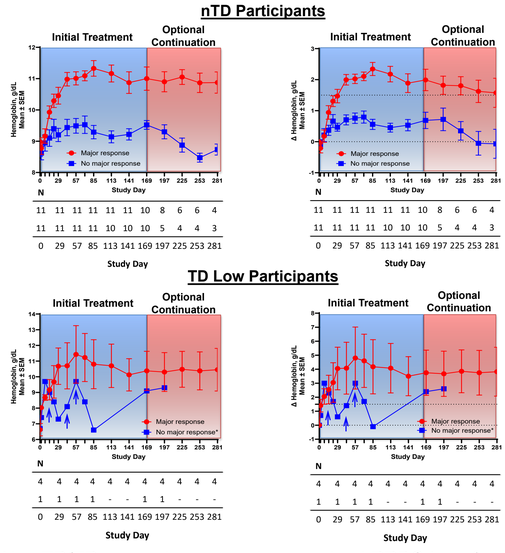


- Responders treated with DISC-0974 also experienced a **43% and 29% reduction from baseline at Day 113 in erythropoietin and ferritin**, respectively

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

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



- 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 doses
- Reduction in hepcidin and ZnPPIX and iron mobilization support **mechanism of target engagement**
- **Hematologic improvement is durable** through continuation phase of study

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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