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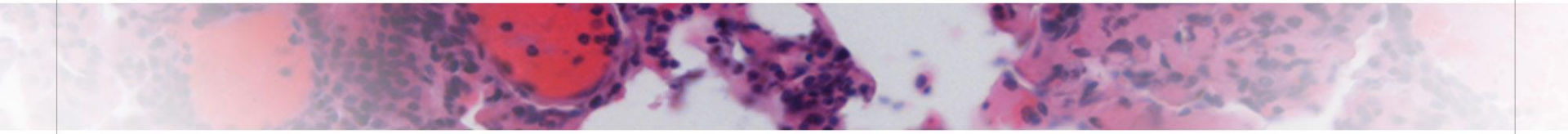


A Phase 1b Study of DISC-0974, an Anti-Hemojuvelin Antibody, in Patients with Myelofibrosis and Anemia

Naseema Gangat[1], James Foran[2], Anna Halpern[3,4], Raajit Rampal[5], Prithviraj Bose[6], Elizabeth Hexner[7], Moshe Talpaz[8], Laura Michaelis[9], Prioty Islam[5], Ronan Swords[10], Sima Bhatt[11], Akshay Buch[11], Olivia Pelletier[11], William Savage[11], Ayalew Tefferi[1]

1. Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN
2. Division of Hematology, Department of Medicine, Mayo Clinic, Jacksonville, FL
3. Department of Medicine, University of Washington, Seattle, WA
4. Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, WA
5. Memorial Sloan Kettering Cancer Center, New York, NY
6. MD Anderson Cancer Center, Houston, TX
7. University of Pennsylvania, Philadelphia, PA
8. University of Michigan, Ann Arbor, MI
9. Medical College of Wisconsin, Milwaukee, WI
10. Oregon Health and Science University, Portland, OR
11. Disc Medicine, Watertown, MA

Hepcidin is a Key Driver of Myelofibrosis-Related Anemia

Anemia of MF

Etiology of Anemia

- High hepcidin from inflammation
- Inflammatory cytokine expression
- Ineffective erythropoiesis
- JAK inhibitors may worsen anemia

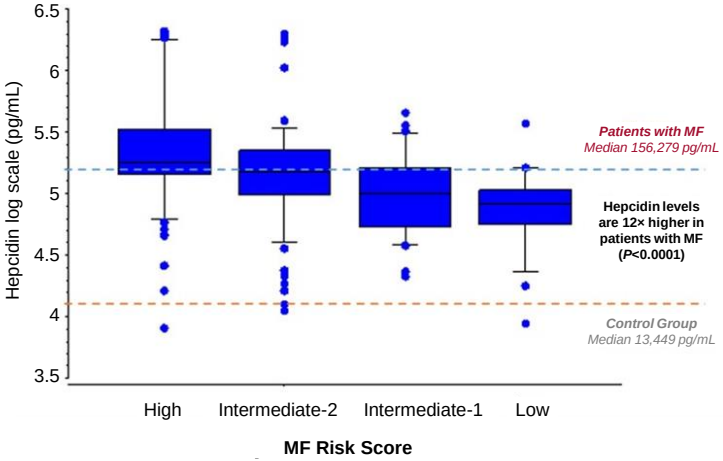
Estimated # of Patients

- 25,000 patients (US)
- ~87% have anemia

Unmet Medical Needs

- Anemia may limit optimal JAK inhibitor treatment
- No approved therapy specifically for anemia treatment
- Agents targeting TGF-β-BMP-SMAD pathway under investigation

Hepcidin Levels are Elevated in MF
~12× higher than control and associated with severity of anemia and transfusion burden

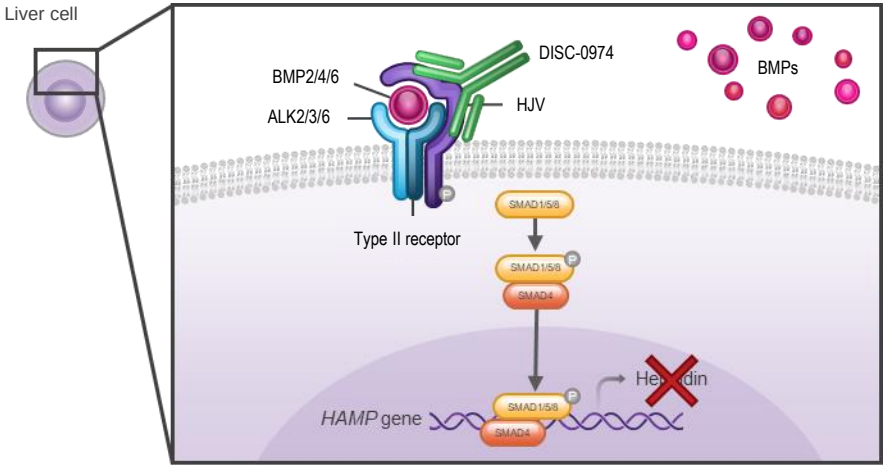


Source: Pardanani et al, Am J Hematol, 2013

DISC-0974 Targets Hemojuvelin (HJV) to Suppress Hepcidin

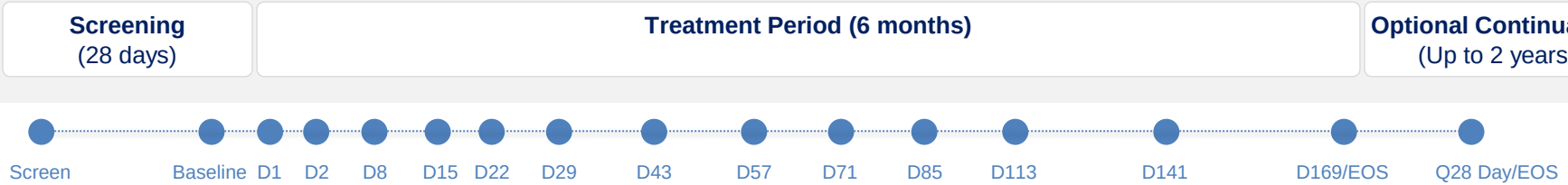
Inhibiting HJV Prevents Hepcidin Expression and Increases Iron

- **DISC-0974** is a first-in-class monoclonal antibody that binds to HJV and blocks BMP signaling
  - ↓ Hepcidin production
  - ↑ Iron absorption
  - ↑ Mobilization of stored iron into circulation
  - ↑ Hgb levels



DISC-0974 Phase 1b Study Overview

Enrollment Data as of October 17, 2024



	14 mg	28 mg	50 mg	75 mg	100 mg	Overall
Treated, N	1	7	12	9	6	35
Completed study, N (%)	1 (100)	6 (86)	12 (100)	8 (89)	5 (83)	32 (91)
Subjects with early withdrawal (N)*	0	1	0	0	1	2
Participating in continuation, N (%)	0	2 (29)	10 (83)	8 (89)	4 (67)	24 (69)

*Reason for early withdrawal: Physician decision due to inadequate response (n=2)

Study Endpoints

Primary: Safety and tolerability; **Secondary:** Hematologic response, pharmacodynamic markers of mechanism engagement

DISC-0974 Key Criteria

Eligibility Criteria

- Age ≥18 years, with primary, post-essential thrombocythemia, or post-polycythemia vera MF
- Intermediate-2 or high-risk disease
- Hemoglobin <10 g/dL on ≥3 assessments over 84 days or TD
- Washout prior to screening for androgens, EPO, cladribine, immunomodulators, and IFNα is required
- Concomitant stable JAK inhibitor or hydroxyurea use is allowed
- Participants with anemia due to infection, bleeding, or iron or vitamin B12 deficiency are excluded

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

Criteria adapted from Tefferi et al, Blood, 2024; *during 84 days prior to screening·

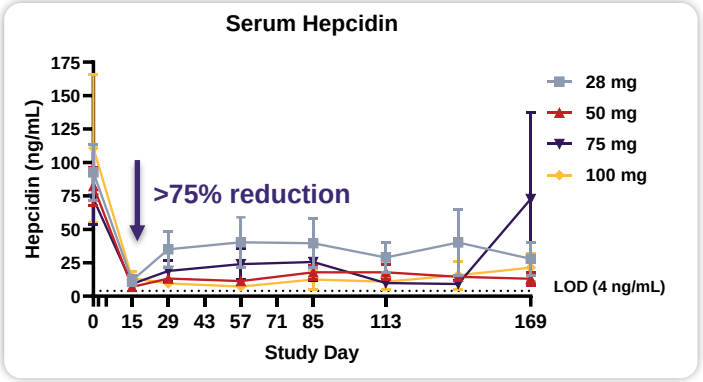
Baseline and Demographics

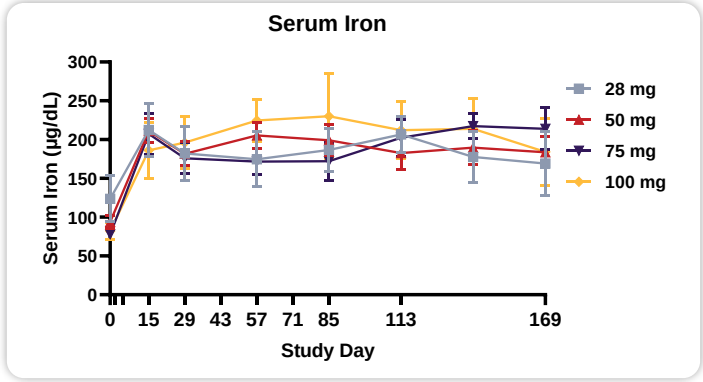
	Overall (n=35)
Age, median (range), years	71 (31, 89)
Male, n (%)	23 (65.7)
Race, n (%)	
White	28 (80)
Black or African American	4 (11.4)
Asian	1 (2.9)
American Indian or Alaska Native	1 (2.9)
Other	1 (2.9)
DIPSS risk level, n (%)	
Intermediate-2	29 (82.9)
High	6 (17.1)
JAK 2 mutation present	23 (65.7)
Concomitant medication, n (%)	
JAK inhibitor	13 (37.1)
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)
Baseline hemoglobin, median (range), g/dL	8.4 (5.5, 10.0)

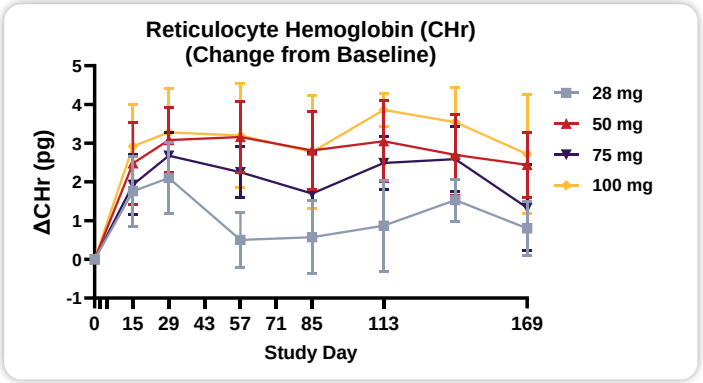
**During 84 days prior to screening*

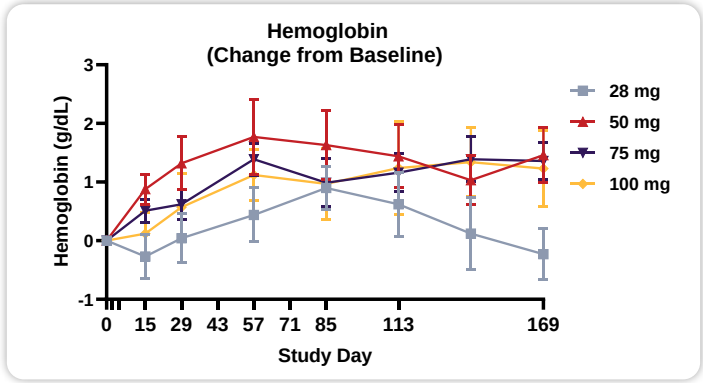
DISC-0974 Pharmacodynamics

Reduction in hepcidin, mobilization of iron, increased reticulocyte hemoglobin, and improvement in hemoglobin





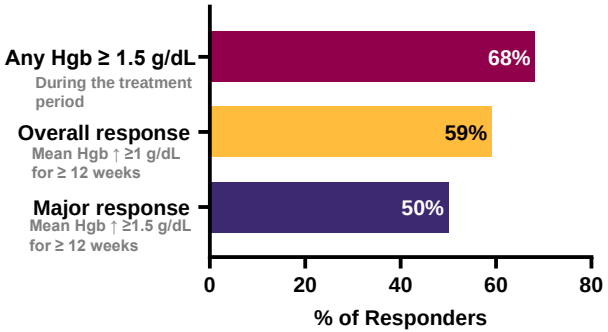


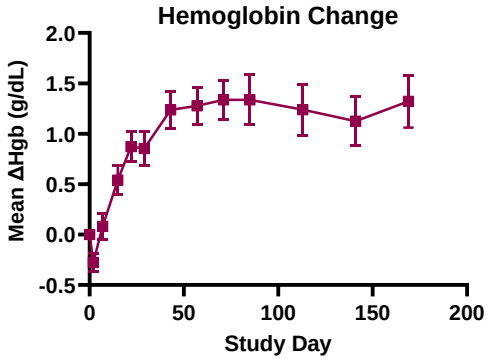


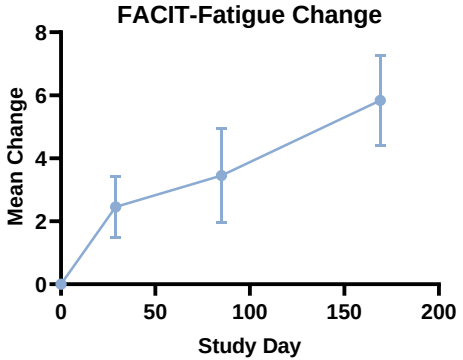
Data presented as mean ± SEM
Includes all participants dosed at 28-100 mg

Hematologic Response: Non-Transfusion-Dependent Participants[#] (n=22)

68% of nTD participants achieved a Hgb Increase of ≥1.5 g/dL during study period
50% achieved a sustained Hgb response for ≥12 weeks







67% of participants (n=9) receiving concomitant JAKi therapy achieved durable response

nTD participants: Baseline Hgb <10 with 0 units PRBC in the 84 days prior to screening.

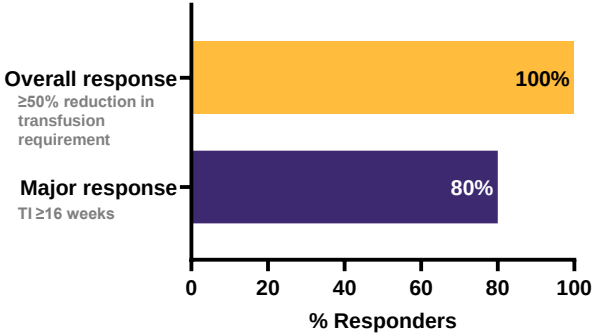
Response	Mean ± SD (days)
Time to first Hgb increase for major response	36 ± 18
Duration of major response during treatment period	150 ± 27

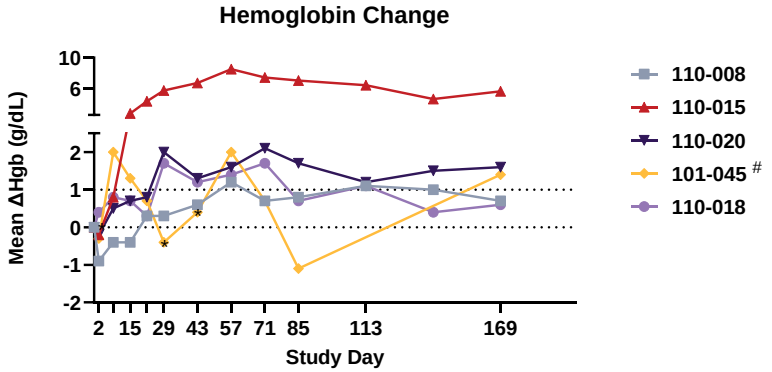
17 of 22 nTD participants have received continuation treatment with median response not reached. Follow-up ongoing (maximum 14.7 months)

participants dosed at 28-100 mg dose levels

Hematologic Response: Transfusion-Dependent-Low Participants (n=5)

100% of TD-low[a] participants achieved a ≥50% reduction in transfusion requirement; 80% of participants achieved TI-16 weeks^





No TD-low participants were receiving concomitant JAKi therapy

[a] *Participants receiving 1-2 units PRBC in the 84 days prior to screening;*
**Indicates transfusion; [#]Indicates patient receiving transfusion during treatment period.*

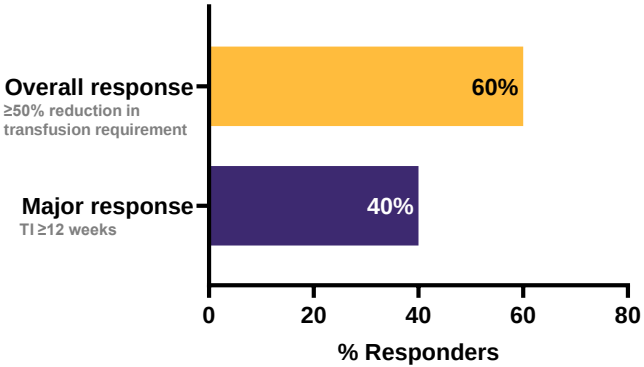
Response	Mean ± SD (days)
TD low duration major of response during treatment period	171 ± 4

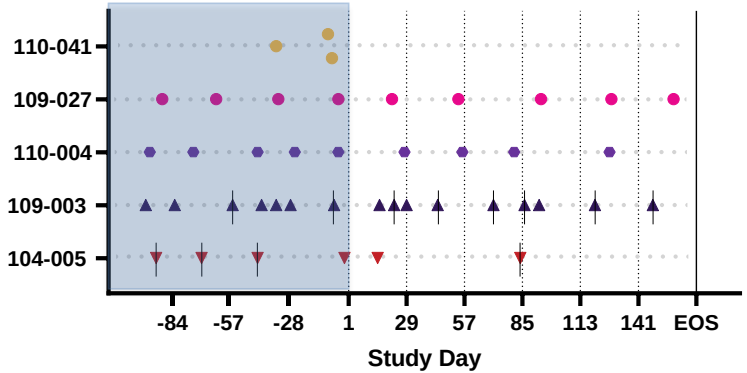
5 of 5 TD-low participants have received continuation treatment with median response not reached. Follow-up ongoing (maximum 16.6 months)

^ with a minimum Hgb of 7 g/dL

Hematologic Response: Transfusion-Dependent-High Participants (n=5)[#]

60% of TD-high[a] participants achieved a ≥50% reduction in transfusion requirement; 40% of participants achieved TI-12 weeks^





50% of participants (n=4) receiving concomitant JAKi therapy achieved ≥ 50% transfusion reduction; 25% achieved TI-12

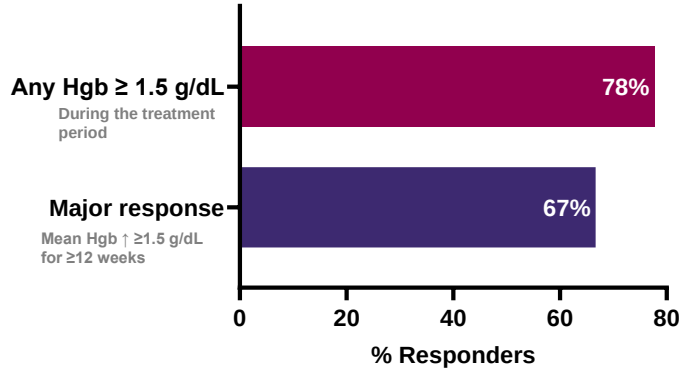
[a] Participants receiving 3-12 units PRBC in the 84 days prior to screening; [#]2 TD-high participants were considered not evaluable due incomplete data entry at time of data cut

Response	Mean ± SD (days)
TD-high duration of major response during treatment period	127 ± 60

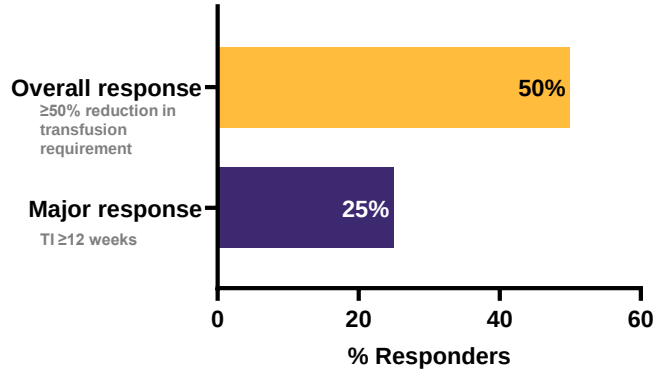
^ with a minimum Hgb of 7 g/dL

Hematologic Response with Concomitant JAKi Therapy (n=13)

nTD Response (n=9)



TD-High Response (n=4)



Overall, 54% of participants receiving concomitant JAKi therapy achieved a major hematologic response

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)

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: anemia, lymphocyte count decreased, platelets decreased, cellulitis, kidney infection (same as SAE), muscular weakness, and headache.

Conclusions

- DISC-0974 was **safe and well tolerated** at all evaluated dose levels
- DISC-0974 resulted in **sustained ↓hepcidin and ↑serum iron** for several weeks after each dose
- Among participants treated at 28 mg to 100 mg:
  - ✓ 50% of nTD participants with durable mean Hgb increases of ≥1.5 g/dL
  - ✓ nTD participants have clinically meaningful improvement in FACIT-fatigue
  - ✓ 80% of TD-low participants achieved TI-16 weeks
  - ✓ 40% of TD-high participants achieved TI-12 weeks
  - ✓ 60% of TD-high participants achieved a 50% reduction in transfusions over a rolling 12-week window
  - ✓ 54% of participants (n=13) receiving concomitant JAKi therapy achieved durable hematologic responses
- **Phase 2 enrollment is ongoing with a 50 mg starting dose**
  - Study will include additional correlatives including cytokine levels and NGS testing