Initial results from an ongoing Phase 2 open-label study investigating DISC-3405, a novel anti-TMPRSS6 monoclonal antibody, in participants with polycythemia vera (RESTORE-PV)

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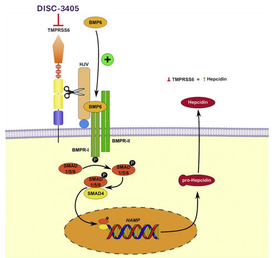
INTRODUCTION

- **Polycythemia Vera (PV) Burden:** PV is a Janus kinase (JAK) 2-driven myeloproliferative neoplasm characterized by pathologic erythrocytosis. Key treatment goals include maintaining hematocrit (HCT) below 45% to reduce thromboembolic complications.[1-2]
- **Standard of Care Limitations:** Standard of care includes phlebotomy (PHL) and cytoreductive therapies (CRT), which can be burdensome and negatively impact quality of life (QoL). Frequent PHL can lead to iron deficiency, contributing to fatigue and exacerbating symptom burden.[3]
- **Mechanism of Action:** DISC-3405 is an investigational, novel humanized immunoglobulin G (IgG)1 monoclonal antibody (mAb) that targets transmembrane serine protease 6 (TMPRSS6; matriptase-2) to stimulate endogenous production of hepcidin, the master regulator of iron homeostasis, while also reducing iron and hematocrit (Figure 1).[4] DISC-3405 is the first anti-TMPRSS6 mAb trialed in PV and is administered subcutaneously.

Figure 1. DISC-3405 Mechanism of Action



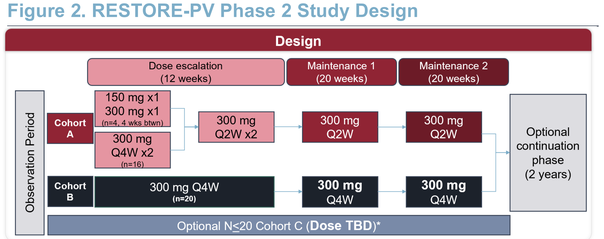
Modified from Béliveau, 2019[5]
BMP = bone morphogenetic protein; BMPR = bone morphogenetic protein receptor; HAMP = hepcidin antimicrobial peptide; HJV = hemojuvelin; P = phosphorylated; TMPRSS6 = transmembrane serine protease 6; SMAD = small mothers against decapentaplegic

METHODS AND STUDY DESIGN

Study Design and Enrollment Status

- RESTORE-PV is a Phase 2, multicenter, open-label, 52-week study (NCT06985147) across 14 sites in the United States (Figure 2).

Figure 2. RESTORE-PV Phase 2 Study Design



QXW = every X weeks
*Optional Cohort C can be explored as an expansion of Cohorts A and B or to explore additional dose levels and dose regimens

- As of the July 13, 2026, data cutoff, all 20 participants in Cohort A have been dosed, and all 20 participants in Cohort B are enrolled, with 18 of 20 dosed. PHL burden and other screening and baseline characteristics are shown in Figure 3 and Table 1. Baseline values represent Day 1 pre-dose values.

RESULTS

Table 1. Demographics and Baseline Characteristics

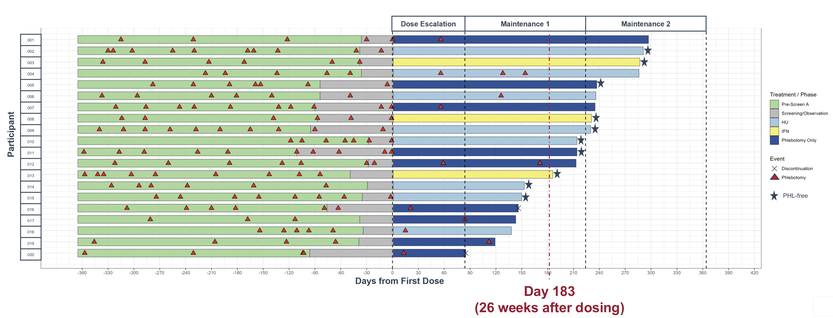
Variable	Cohort A (N=20)	Cohort B (N=20)
Age, years; mean (SD)	58.6 (13.3)	60.1 (11.4)
Sex, male; n (%)	16 (80.0)	8 (40.0)
Race	95% White 5% Black	95% White 5% Asian
Disease duration, years; mean (SD)	5.8 (5.7)	5.6 (3.7)
Risk High Low	 65% 35%	 60% 40%
JAK2 mutation V617F Exon 12	 95% 5%	 100% 0%
CRT use* None (PHL only) HU IFN	 45% 40% 15%	 50% 45% 15%
Baseline PHL rate, 26 weeks prior to dosing; mean (SD)	3.7 (1.4), 0.14/week (0.05)	3.9 (2.1), 0.15/week (0.08) *N=18*
Baseline ferritin, ng/mL; mean (SD)	14.2 (7.9)	15.7 (9.3) *N=18*
Time on study since Day 1, days; mean (SD)	205.5 (62.2)	65.0 (30.3) *N=18*

HU = hydroxyurea; IFN = interferon
* IFN includes: Cohort A – n=3 for ropeginterferon-alfa-2b-njft; Cohort B – n=1 for ropeginterferon-alfa-2b-njft, n=2 peginterferon alfa-2a; n=2 patients in Cohort B on both HU and IFN
Only N=18 shown for baseline results in Cohort B as 2 participants in Cohort B were still in Observation Period at the time of data cut
Data cutoff July 13, 2026

Phlebotomy Burden Reduction and Efficacy

- **Sustained Phlebotomy Reduction:** DISC-3405 significantly reduced PHL events in Cohort A participants (Figure 3).
- **26-Week Completers in Cohort A (N=13):**
  - Mean total PHL events significantly decreased from 4.0 (0.4) pre-dosing to 0.6 (0.3) post-Day 1 through 26 weeks, representing a mean difference of -3.4 (SE = 0.5; 95% CI: -4.5 to -2.3; p<0.0001) (Figure 4).
  - 61.5% (8/13) of participants remained entirely PHL-free post-baseline through 26 weeks.
  - Of those who completed Maintenance 1 (n=9), 77.8% (7/9) of participants remained PHL-free during the Maintenance 1 Period

Figure 3. DISC-3405 Reduced PHL Events in Cohort A Participants



N=2 patients voluntarily withdrew, not due to adverse events
N=2 patients met PHL eligibility at 1 time point each but did not receive PHL, and those episodes of PHL eligibility are not represented on the swim-lane plot
Data cutoff July 13, 2026

Pharmacokinetic-Pharmacodynamic-HCT Control Continuum

- **Predictable Exposure (PK):** Subcutaneous administration of DISC-3405 results in predictable, dose-proportional PK with an extended terminal half-life and no treatment-emergent anti-drug antibodies (Figure 5A).
- **Direct Target Engagement and Hepcidin Activation (PD):** Inhibition of TMPRSS6 elevates endogenous hepcidin levels, leading to reduced serum iron levels (Figure 5B), and increased ferritin, suggesting redistribution of iron (Figure 5C).
- **Hematocrit Control and Phlebotomy Exemption:** Restricting iron availability limits excessive erythropoiesis, maintaining mean hematocrit stably <45% (Figure 5D).

Figure 5. DISC-3405, Hepcidin, Serum Iron, Ferritin, and HCT Response Over Time

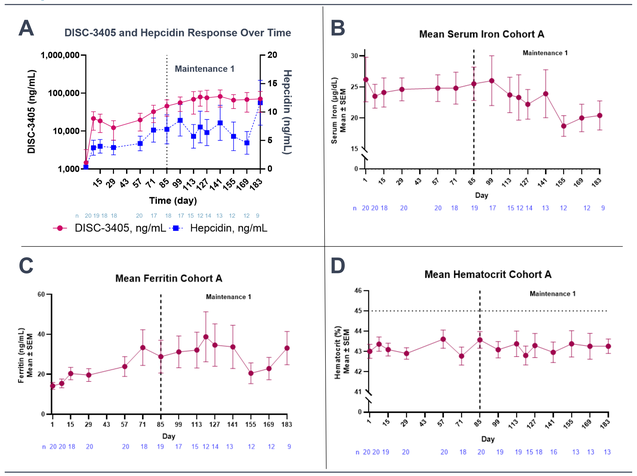
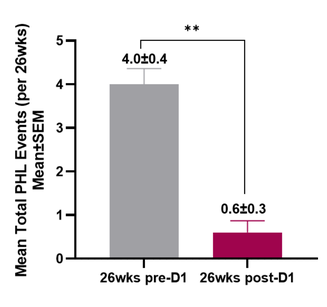


Figure 4. Total PHL Events: 26 Weeks Pre- vs Post-Treatment Initiation (D1)



** $p < 0.0001$ (paired t-test)
Mean (SE) Difference = -3.4 (0.5) (95% CI: -4.5 to -2.3) N=1 patient met PHL eligibility at 1 time point but did not receive PHL; Counting PHL+1 PHL eligibility event, the post-D1 26 weeks mean (SE) rate is 0.7 (0.3), with mean (SE) difference of -3.3 (0.6) and 95% CI -4.5 to -2.1; p<0.0001

Safety

- **DISC-3405 was well tolerated without dose-limiting toxicities**
  - The majority (82.4%) of adverse events (AEs) were Grade 1
  - No related serious AEs
  - No treatment-emergent AEs (TEAEs) leading to discontinuation
  - All Injection site reactions were Grade 1
  - 1 Grade 2 Anemia AE in Cohort B that resolved with dose reduction
  - No clinically significant changes in vital signs, physical examinations, or electrocardiograms

Table 2. Treatment-Emergent Adverse Events in ≥2 Participants

Adverse Event Preferred Term	Cohort A (N=20)	Cohort B (N=18)	Total (N=38)
Any TEAE, n (%)*	16 (80.0)	11 (61.1)	27 (71.1)
Serious AE*	1 (5.0)	1 (5.6)	2 (5.3)
Related TEAE^Δ	4 (20.0)	6 (33.3)	10 (26.3)
Abdominal pain	6 (30)	1 (5.6)	7 (18.4)
Injection site reaction†	**3 (15.0)**	**2 (11.1)**	**5 (13.2)**
Early satiety	4 (20.0)	0	4 (10.5)
Bone pain	3 (15.0)	0	3 (7.9)
Disturbance in attention	3 (15.0)	0	3 (7.9)
Dizziness	3 (15.0)	0	3 (7.9)
Contusion	2 (10.0)	1 (5.6)	3 (7.9)
Headache	1 (5.0)	2 (11.1)	3 (7.9)
Pyrexia	2 (10.0)	0	2 (5.3)
Hyperhidrosis	2 (10.0)	0	2 (5.3)
Decreased appetite	2 (10.0)	0	2 (5.3)
Muscular weakness	1 (5.0)	1 (5.6)	2 (5.3)
Constipation	1 (5.0)	1 (5.6)	2 (5.3)
Flank pain	1 (5.0)	1 (5.6)	2 (5.3)
Fatigue	1 (5.0)	1 (5.6)	2 (5.3)
Night sweats	0	2 (11.1)	2 (5.3)
Hot flush	0	2 (11.1)	2 (5.3)
Blurred vision	0	2 (11.1)	2 (5.3)

*Includes 1 unrelated Basal cell carcinoma diagnosed at Day 22 (Cohort A) in a participant who was symptomatic prior to study enrollment, 2 unrelated SAEs (headache, cholecystitis); ^Includes Possibly Related, Probably Related, Definitely Related AEs: Cohort A – Grade 1 Injection site reaction (n=3), Grade 2 Rash (n=1), Grade 1 Fatigue (n=1); Cohort B – Grade 1 Injection site reaction (n=2), Grade 1 Abdominal Pain (n=1), Grade 1 Headache (n=1), Grade 1 Stomatitis (n=1), Grade 2 Anemia (n=1), Grade 1 Sinus tachycardia (n=1), Grade 1 Peripheral sensory neuropathy (n=1); †Injection site reaction: includes injection site pain (n=3 Cohort A) and injection site reaction (n=2 Cohort B); only 1/5 was recurrent.
Data cutoff July 13, 2026

CONCLUSIONS

- DISC-3405 is the first monoclonal antibody targeting TMPRSS6 that has demonstrated phlebotomy reduction in patients with PV.
- DISC-3405 led to predictable PK and no evidence of anti-drug antibodies.
- DISC-3405 predictably increased hepcidin, lowered serum iron, and stabilized HCT, which led to initial improvement in symptom burden.
- DISC-3405 appears to be safe and well-tolerated: adverse events consistent with underlying disease; low rate of injection site reactions, which were mild and self-limited.
- These data support further development of DISC-3405 as a treatment for people living with PV.

References

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Acknowledgements

We would like to thank the patients and caregivers who are taking part in this important study.

Contact

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DISC-3405 is an investigational agent and is not approved for use as therapy in any jurisdiction worldwide.

Presented at the Society of Hematology Oncology Annual Meeting, September 9-12, 2026, Houston TX