Anti-Hemojuvelin Monoclonal Antibody Provided Further Improvement in Anemia in Combination with ESA and/or Luspatercept (RAP-536) in Mice

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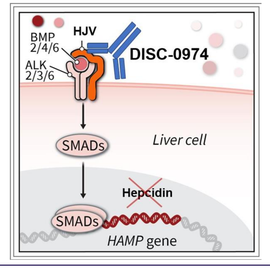
INTRODUCTION

Myelofibrosis (MF) is a hematologic malignancy characterized by excessive proliferation of myeloid cells and release of pro-inflammatory cytokines, leading to bone marrow dysfunction.[1] Anemia is a hallmark of MF. Erythropoiesis-stimulating agents (ESAs) and luspatercept are used off-label to manage anemia associated with MF. Despite some success, limited efficacy and/or response duration as well as potential side effects warrant the need for additional treatment options for patients with MF and anemia.[2]

DISC-0974 is a humanized anti-hemojuvelin (HJV) monoclonal antibody. It was designed to disrupt the interaction between HJV and the bone morphogenetic protein (BMP) receptor complex, leading to decreased hepcidin expression and increased iron availability for enhanced erythropoiesis (Figure 1).[3] DISC-0974 is currently in clinical studies to treat anemia in patients with MF (NCT05320198) and chronic kidney disease (NCT05745883).

Figure 1. DISC-0974 mechanism of action



ALK = activin receptor-like kinase; BMP = bone morphogenetic protein; HJV = hemojuvelin; SMAD = suppressor of mothers against decapentaplegic

The aim of this study was to evaluate whether DBIO-100, a murine analog of DISC-0974, could provide additional benefits in hematologic improvements when used in combination with ESAs or luspatercept.

METHODS

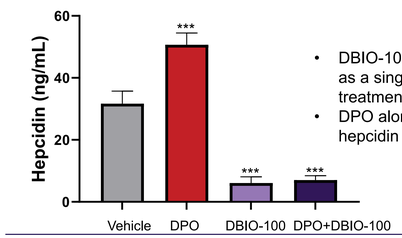
In the DBIO-100/ESA combo study, wild-type C57BL/6J male mice were randomized to receive vehicle, darbepoetin alfa (DPO; 3 ug/kg via subcutaneous [SC] route), DBIO-100 (20 mg/kg via intravenous [IV] route), or a combination of DBIO-100/DPO once a week for 3 weeks.

In the DBIO-100/luspatercept (RAP-536) combo study, wild-type C57BL/6J male mice were randomized to receive vehicle, RAP-536 (3 mg/kg via IV route), DBIO-100 (20 mg/kg via IV route), or a combination of DBIO-100/DBIO-147 once a week for 3 weeks.

RESULTS

DBIO-100/ESA combination study

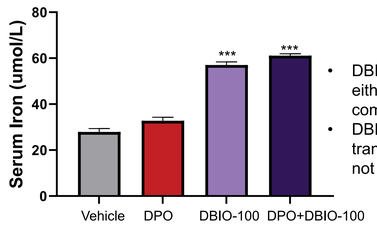
Figure 2. Serum hepcidin



- DBIO-100 lowered serum hepcidin as a single agent or in combination treatment with DPO
- DPO alone increased serum hepcidin level

***$p < 0.001$ *vs* Vehicle; one-way ANOVA

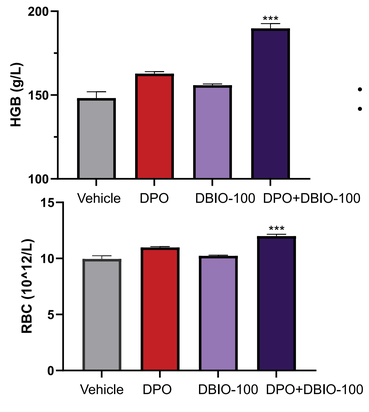
Figure 3. Serum iron



- DBIO-100 increased serum iron either as a single agent or in combination treatment with DPO
- DBIO-100 also increased transferrin saturation (TSAT; data not shown)

***$p < 0.001$ *vs* DPO; t-test

Figure 4. HGB and RBC

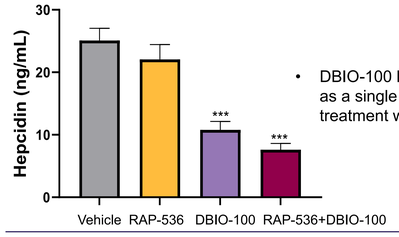


- DPO increased HGB and RBC
- DBIO-100 further improved HGB and RBC when used in combination with DPO

***$p < 0.001$ *vs* DPO; t-test

DBIO-100/RAP-536 combination study

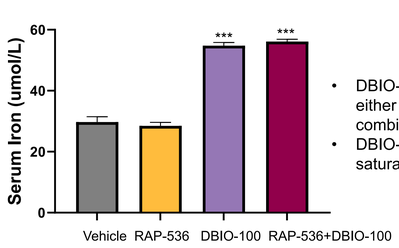
Figure 5. Serum hepcidin



- DBIO-100 lowered serum hepcidin as a single agent or in combination treatment with RAP-536

***$p < 0.001$ *vs* Vehicle; one-way ANOVA

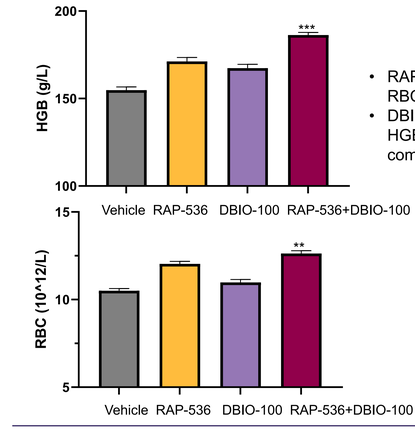
Figure 6. Serum iron



- DBIO-100 increased serum iron either as a single agent or in combination treatment with RAP-536
- DBIO-100 also increased transferrin saturation (TSAT; data not shown)

***$p < 0.001$ *vs* RAP-536; t-test

Figure 7. HGB and RBC



- RAP-536 increased HGB and RBC
- DBIO-100 further improved HGB and RBC when used in combination with RAP-536

**$p < 0.01$, ***$p < 0.001$ *vs* RAP-536; t-test

- Vehicle
- DPO (3 ug/kg)
- DBIO-100 (20 mg/kg)
- DPO (3 ug/kg) + DBIO-100
- Vehicle
- RAP-536 (3 mg/kg)
- DBIO-100 (20 mg/kg)
- RAP-536 (3 mg/kg) + DBIO-100

Abbreviations: ANOVA = analysis of variance; DPO = darbepoetin alfa; HGB = hemoglobin; RBC = red blood cells; TSAT = transferrin saturation

CONCLUSIONS

- DBIO-100, an anti-HJV monoclonal antibody, lowered hepcidin levels, enhanced iron availability, and boosted erythropoiesis in vivo—consistent with its proposed mechanism of action.
- When combined with DPO or RAP-536, DBIO-100 led to additional hematologic benefits beyond those agents alone. Therefore, targeting HJV to promote iron mobilization yielded additive improvements when used with either ESAs (DPO) or luspatercept.
- These findings support the potential of anti-HJV therapy to enhance anemia treatment in patients with myelofibrosis when used alongside ESAs or luspatercept.

References

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3. Novikov N, Buch A, Yang H, et al. First-in-human phase 1 study evaluating the safety, pharmacokinetics, and pharmacodynamics of DISC-0974, an anti-hemojuvelin antibody, in healthy participants. J Clin Pharmacol. 2024;64(8):953-962.

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