Pharmacological Evaluation of a First-in-Class Hemoglobin Elevating Agent (HbEA) AND017 in a Hbb^{d3th} β-Thalassemia Mouse Model

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INTRODUCTION

β-Thalassemia[1] is prevalent in tropical and subtropical regions like Mediterranean, Middle East, Indian subcontinent and Southeast Asia including southern provinces in China; the disease poses serious health, medical and economic burdens to the affected families and societies.

Treatments[1] include blood transfusion plus iron chelation, hematopoietic stem cell transplantation, and recently FDA approved gene therapies and luspatercept; however, none of them can be widely applicable; safe and effective oral, small molecule drugs even non curative ones would still provide economically viable alternatives.

Recently, we discovered a new type of highly efficacious hemoglobin elevating agents (HbEA) via traditional medicinal chemistry approach to identifying novel small molecules to treat anemia in CKD with the aim of overcoming safety concerns of known HIF PH inhibitor drugs and Epogen. Ultimately, we discovered AND017, a first-in-class HbEA, was uniquely safe and effective in several animal models of anemia or blood disorders.

In this study, we evaluated AND017 in mice of Hbb^{d3th} β-thalassemia model[2].

METHOD

Homozygous Hbb$^{d3th/d3th}$ mice[2] were bred from Hbb$^{d3th/d3th}$ male mice and Hbb$^{d3th/+}$ female mice. Their genotypes were identified by PCR analysis and double confirmed prior to dosing.

Twenty-two Hbb$^{d3th/d3th}$ mice (female/F: 14; male/M: 8; 9-15 weeks old) were randomly divided into 4 groups: G1 and G2 (2M+3F, each), G3 and G4 (2M+4F, each). Mice in G1 to G4 were orally dosed once daily with vehicle or AND017 (5, 10, and 15 mg/kg) respectively for 42 days. (**Figure 1**)

Body weight, behavior and activity including food and water consumption were observed, monitored, and recorded daily. RBC, HGB, and HCT were measured and calculated by hematology system on days 0, 15, 29, and 43 respectively. Blood smears were prepared and examined microscopically. The level of statistical significance was set at 5% or $P < 0.05$; the data were compared between groups at the same time point or within the same groups at different time points.

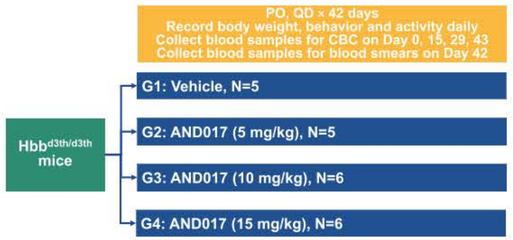

Figure 1. Study design

RESULTS

Hbb$^{d3th/d3th}$ mice had similar symptoms to human β-thalassemia patients, such as lower body weight, hypochromic, microcytic anemia with anisocytosis, poikilocytosis etc.

During the dosing period, only one mouse in the vehicle group and no mice in the AND017 groups died; the body weights of mice in the middle/high-dose AND017 groups increased to a greater extent than those of mice in the low-dose AND017 group or vehicle group. AND017 significantly improved hematological parameters on Hbb$^{d3th/d3th}$ mice in a dose dependent manner. Mice treated with 15 mg/kg AND017 for 42 days had increased Hb levels (+26% over pre-dose; +22% over vehicle), RBC numbers (+22% over pre-dose; +14% over vehicle) and HCT (+31% over pre-dose; +27% over vehicle). (**Figure 2**)

Microscopic examination of blood smears showed the erythrocyte staining was enhanced, and the number of abnormal RBCs (stained blue) decreases notably upon treatment with AND017 dose dependently, indicating marked improvement in the morphology of RBCs. (**Figure 3**)

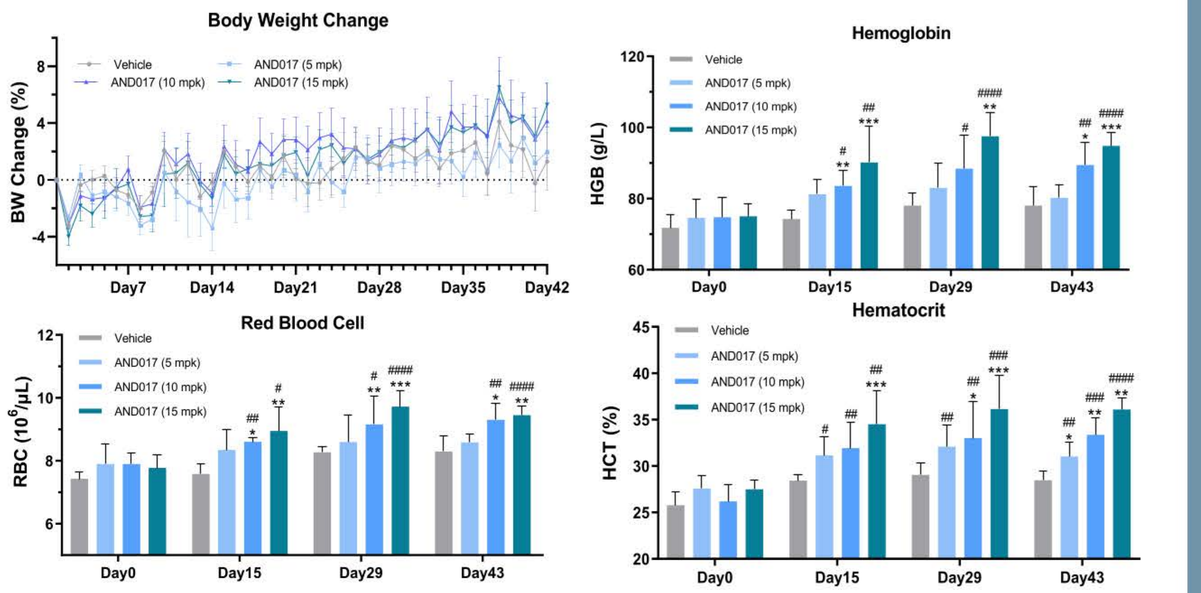

Figure 2. Hemoglobin, red blood cell, hematocrit and body weight change

*Note: Significance: *: across-group comparison; #: in-group comparison; */#, **/##, ***/###, and ****/####: for $p < 0.05$, 0.01, 0.001, and 0.0001 respectively.*

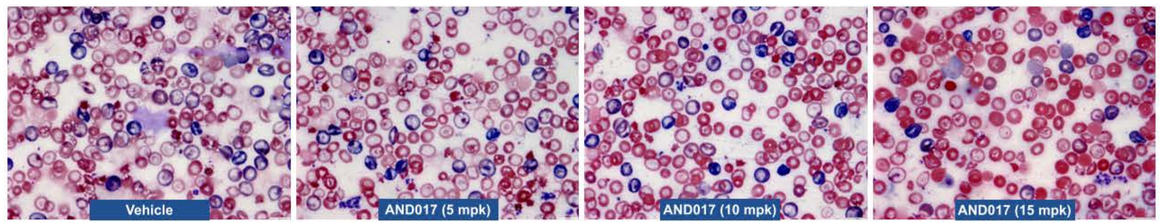

Figure 3. Blood smears

CONCLUSIONS

AND017, a potent first-in-class HbEA, significantly and dose-dependently increased Hb levels, RBC numbers, and HCTs in β-thalassemia mouse model, increased body weight and improved morphology of RBCs, indicating AND017 could be a safe and effective oral treatment for β-thalassemia patients.

REFERENCES

1. A. T. Taher, et al. *NEJM*, 2021, 384 (8), 727-743.
2. L. C. Skow, et al. *Cell*. 1983, 34 (3), 1043-1052.

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