TRIAL IN PROGRESS: Phase 2 Study of Oral Epetraborole for Treatment of Phlebotomy-Dependent PV

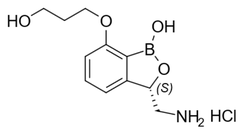
AN2 Therapeutics

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INTRODUCTION



- First-line treatment of polycythemia vera (PV) is therapeutic phlebotomy, which is burdensome for PV patients and decreases their quality of life
- Epetraborole (EBO) is a novel, oral, boron-containing small molecule that selectively modulates erythropoiesis, while sparing other hematopoietic lineages
- The effect of EBO on erythropoiesis was observed in nonhuman primates, healthy volunteers and non-PV patients (SOHO, 2026a-d)
  - EBO produced decreases in Hct, Hgb, MCV, MCH, and MCHC; an EBO exposure-Hgb response was evident in PK-PD analyses
  - Mean WBC counts and mean platelet counts generally remained within the normal range
  - Hematological values recovered to or towards baseline levels after cessation of EBO dosing
- These data support further evaluation of oral EBO as a treatment for phlebotomy-dependent PV

DESIGN

This Phase 2 trial will evaluate the efficacy, safety, tolerability, PK, and PD of oral EBO treatment in adults with phlebotomy-dependent high- or low-risk PV.

PK sampling, assessment of hematological parameters, and collection of patient-reported outcomes will be performed.

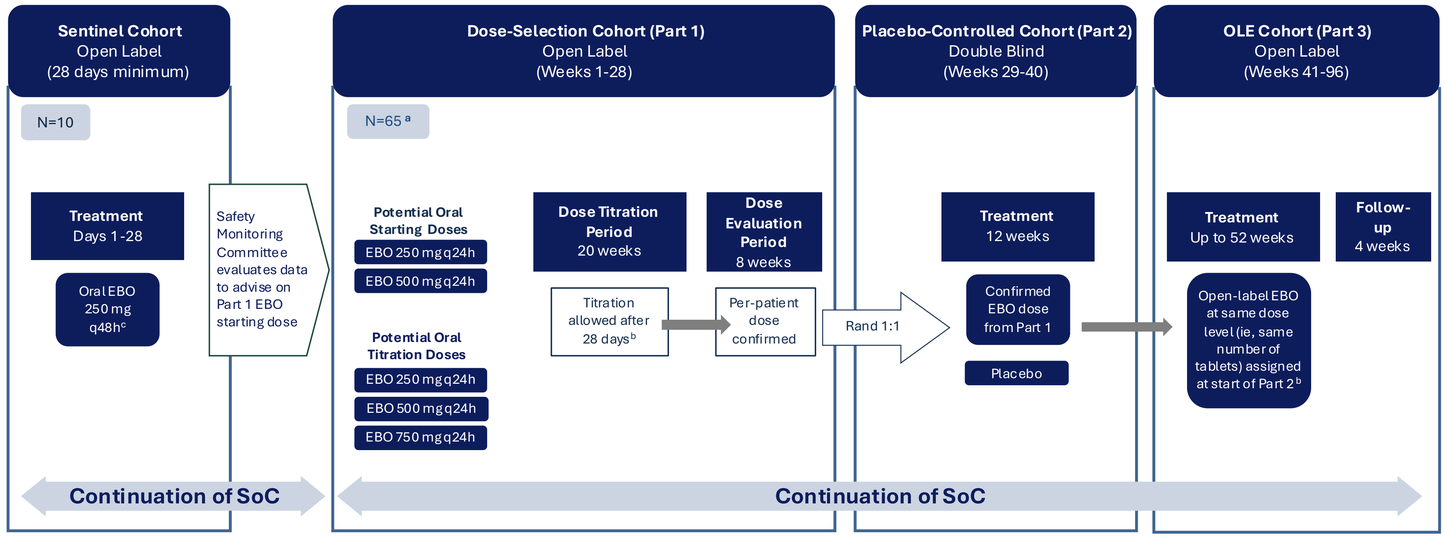
The trial is designed to confirm the safety profile of oral EBO in the PV patient population and to identify 1 or more oral EBO doses for the treatment of phlebotomy-dependent PV.

The trial comprises 4 parts (**Figure 1**). Major inclusion/exclusion criteria are shown in **Table 1.** Major objectives and statistical analysis are summarized in **Table 2.**

Primary Hypothesis

Among participants achieving an efficacious oral EBO dose in the open-label Part 1, the proportion maintaining phlebotomy-free Hct control during 12 weeks of randomized treatment in Part 2 will be superior to the proportion randomized to placebo.

Figure 1: EBO-PV-201 Trial Schema



a. Participants from Sentinel Cohort will enroll in Part 1; thus, the total number of participants enrolled in Part 1 will be ~75.
b. EBO dose up/down-titration based on hematologic response, safety parameters, and Investigator judgment.

EBO = epetraborole; OLE = open-label extension; q#h = every # hours; rand = randomization; SoC = standard of care.

METHODS

Sentinel Cohort (Open-label):

10 participants will be enrolled for PK sampling and safety and hematological evaluations. Oral EBO 250 mg q48h will be administered for at least 28 days, up to a maximum of 98 days. The Sentinel Cohort will characterize the dynamics of hematological variables and EBO plasma exposures.

Part 1 (Open-label):

An additional 65 participants will be enrolled in a 28-week dose-selection phase (20-week Dose Titration Period and an 8-week Dose Evaluation Period) to identify 1 or more efficacious oral EBO doses. Possible oral EBO doses to be administered in the titration phase are 250 mg q24h, 500 mg q24h, and 750 mg q24h.

Part 2 (Randomized, blinded, placebo-controlled):

Participants who successfully complete Part 1 will enter a 12-week placebo-controlled phase to confirm the dose(s) selected in Part 1. Participants will be randomized (1:1 ratio; oral EBO or placebo) and stratified by receipt of cytoreductive therapy (yes or no), geographic region, and EBO dose level. Clinical success (primary efficacy endpoint) is defined as phlebotomy-free control of Hct (ie, without either a Hct of ≥45% that is ≥3 percentage points higher than the Hct at Part 2 baseline or a Hct of >48%) through 12 weeks of follow-up.

Part 3 (Open-label):

1-year Open-Label Extension phase assessing long-term safety and durability of efficacy.

Table 1: Major Inclusion and Exclusion Criteria

Inclusion	Exclusion
• Confirmed diagnosis of PV according to ICC (Thiele, 2023), including Hgb/Hct level, EPO level, and documented positive JAK2 V617F (exon 14) or JAK 2 exon 12 mutation	• History of clinically significant arterial or venous thrombosis within 24 weeks before Day 1
• Low-risk PV (age <60 years & no prior thrombotic event) or high-risk PV (age ≥60 years and/or prior thrombotic event)	• History of major bleeding events and/or requirement for blood transfusion due to bleeding in the 6 months before Day 1
• Hct <45% at Screening	• Meets criteria for post-PV myelofibrosis as defined by the International Working Group-Myeloproliferative Neoplasms Research and Treatment (Tefferi, 2023)
• Has records of all phlebotomies performed for at least 28 weeks before Day 1	• Platelets >1000 × 10^9/L, WBC count >25 × 10^9/L; or presence of any blast cells in peripheral blood at Screening
• Phlebotomy-dependent, defined as at least 3 phlebotomies during the 28 weeks prior to Day 1, including a phlebotomy within 8 weeks prior to Screening	• Secondary polycythemia

Table 2: Major Objectives and Statistical Analyses

Phase	Key Objective	Other Objectives	Analyses
Sentinel Cohort	Determine safety, tolerability, and PK profile of the oral EBO starting dose	Assess effect of EBO 250 mg q48h on Hct and other key hematological variables	Descriptive statistics for comparisons over time for key variables
Part 1	Select an oral EBO dose on a by-participant level for evaluation in Part 2	Describe PK/PD relationships for EBO's effect on key hematological parameters	Descriptive statistics for comparisons over time for key variables
Part 2	Assess efficacy of oral EBO based on data generated in the double-blind, PBO-controlled period	Determine effect of withdrawal of EBO treatment on key hematological variables and phlebotomy rates	*Prespecified primary efficacy analysis:* Difference between EBO and PBO groups in proportion of participants achieving clinical success at the end of 12 weeks of randomized trial intervention, using Miettinen-Nurminen test. *
Part 3	Assess effect of oral EBO dose(s) on the durability of Hct control based on data generated in the open-label, uncontrolled treatment period	Assess maintenance of efficacy and safety at the Part 3 dose	Descriptive statistics for comparisons over time for key variables

*A statistically significant outcome at an alpha = 0.10 would be interpreted as favorable and support further trials especially if positive trends were observed in multiple efficacy endpoints.

SUMMARY: **This study will evaluate epetraborole PK, safety, and efficacy in patients with PV**

STATUS: **Regulatory process underway in the United States, Australia, and India**

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CONFLICTS OF INTEREST
GHT and AS are paid consultants to the pharmaceutical industry, including AN2 Therapeutics, Inc.

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