# EPETRABOROLE DEMONSTRATES AN EXPOSURE-DEPENDENT EFFECT ON ERYTHROPOIESIS IN HEALTHY SUBJECTS

AN2 Therapeutics

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## INTRODUCTION

Epetraborole (EBO), a boron-containing small molecule, specifically reduces erythropoiesis in nonhuman primates, healthy human subjects, and non-polycythemia vera (PV) patients, suggesting its potential utility for oral treatment of PV. The objective of the current analysis is to describe pharmacokinetics (PK), tolerability, safety, and hematological effects of oral EBO administered at 250, 500, 750, or 1000 mg every 24 hours (q24h) or 500 or 1000 mg every 48 hours (q48h) for up to 28 days.

## METHODS

**DESIGN:** Double-blind, placebo-controlled, dose-ranging Phase 1b study (EBO-101). Healthy males or females, aged 18 to 65 years, randomized to receive EBO (n=39) or placebo (n=12) for up to 28 days.

Subjects were enrolled sequentially into 7 cohorts:

- Cohort 1 (6 active : 2 placebo): 250 mg q24h
- Cohort 2 (6 active : 3 placebo): 500 mg q48h
- Cohort 3 (6 active : 2 placebo): 500 mg q24h
- Cohort 4 (6 active : 2 placebo): 750 mg q24h
- Cohort 5 (6 active : 2 placebo): 1000 mg q48h
- Cohort 6* (1 active : 1 placebo): 1000 mg q24h
- Cohort 7 (8 active fed/fasted): 500 mg single dose

* Randomization in Cohort 6 was terminated prematurely due to COVID-19 pandemic restrictions

**MAIN OUTCOME MEASURES:** EBO/metabolite M3 plasma concentrations, treatment-emergent adverse events (TEAEs), and clinical laboratory tests including hematological parameters. Plasma concentrations of EBO were measured by validated LC-MS/MS. Plasma PK parameters were determined using non-compartmental methods.

## RESULTS

Of 51 subjects randomized, 48 (94.1%) completed the study and 47 (92.2%) completed administration of EBO or placebo. Of the 39 subjects administered EBO, 3 (7.7%) subjects did not complete treatment due to TEAEs. Of the 12 subjects administered placebo, 1 (8.3%) subject did not complete treatment due to a family issue.

### PK Summary for q24h Dose Cohorts 1, 3, and 4:

EBO reached $C_{max}$ rapidly with a median $T_{max}$ of 1 to 1.5 hours without any meaningful accumulation after repeat dosing. Half-life was ~10.5 hours. $AUC_{0\text{-}24}$ and $C_{max}$ generally increased in a linear dose-proportional manner (**Table 1**).

**Table 1: Summary Statistics of EBO PK Parameters at Day 28 for q24h Dose Cohorts 1, 3, and 4 (PK Population; Study EBO-101)**

| Dose Cohort | EBO Dose Regimen | N | $AUC_{0\text{-}24}$ (hr·ng/mL)[a] | $C_{max,ss}$ (ng/mL)[a] | $t_{½}$ (h)[a] | $T_{max,ss}$ (h)[b] |
|---|---|---|---|---|---|---|
| 1 | 250 mg q24h | 5 | 7100 ± 792 | 1390 ± 278 | 10.6 ± 0.966 | 1.50 (1.00 to 1.50) |
| 3 | 500 mg q24h | 6 | 13700 ± 2380 | 2850 ± 275 | 10.2 ± 1.12 | 1.00 (0.50 to 1.50) |
| 4 | 750 mg q24h | 6 | 24400 ± 6240 | 5280 ± 1430 | 10.3 ± 1.47 | 1.00 (0.50 to 1.50) |

$AUC_{0\text{-}24}$ = area under the concentration-time curve, from time 0 to 24 hours; $C_{max,ss}$ = maximum steady state concentration; h = hour; N = number of subjects in cohort; q24h = every 24 hours; $t_{½}$ = elimination half-life; $T_{max,ss}$ = time to reach maximum concentration following drug administration at steady state.
Note: Cohorts 2 and 5 are excluded from the table as they were q48h dosing. Cohort 6 is excluded as there was only 1 participant enrolled before the cohort was terminated prematurely due to COVID-19 pandemic restrictions. Cohort 7 is excluded from the table as it was a single-dose cohort.
[a] Data presented as the arithmetic mean ± standard deviation.
[b] Data presented as the median (range).

### Hematologic Findings:

- Dose-related decreased reticulocyte counts were followed by gradual decreases in hemoglobin (Hgb) (nadir ~Days 8 and 28, respectively). Mean maximal Hgb decreases were -9.8% (EBO 250 mg q24h), -13.5% (500 mg q24h), and -15.7% (750 mg q24h); Hgb decreases reversed post dosing, with compensatory reticulocytosis during/after EBO administration (**Figure 1**)
- Decreases in hematocrit (Hct) paralleled those seen for Hgb (**Figure 1**)
- Dose-related platelet increases occurred but remained within normal limits (WNL) and were considered physiological; no platelet increase was clinically significant or a TEAE; white blood cell (WBC) counts remained WNL (**Figure 1**)
- Mean Day 28 erythropoietin, serum iron, ferritin, and transferrin-iron saturation (TSAT) levels were mildly and variably increased but generally remained WNL, with normalization at Follow-Up Visit (**Figures 2 + 3**)

**Figure 1: Placebo-Adjusted Change from Baseline in Mean Hematology Values vs Time for Dose Cohorts 1-6 (Safety Population; Study EBO-101)**

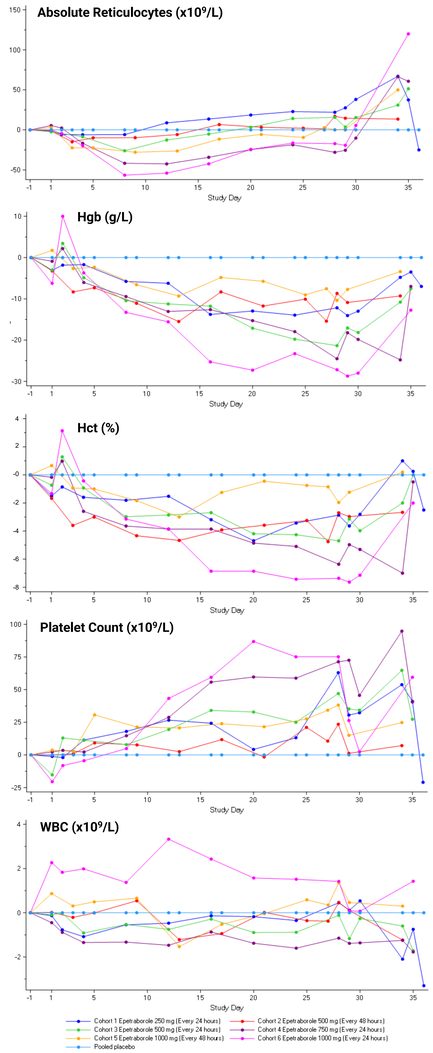



**Figure 2: Placebo-Adjusted Change from Baseline in Mean Erythropoietin Values vs Time for Dose Cohorts 1-6 (Safety Population; Study EBO-101)**

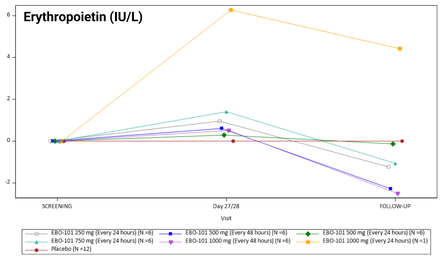
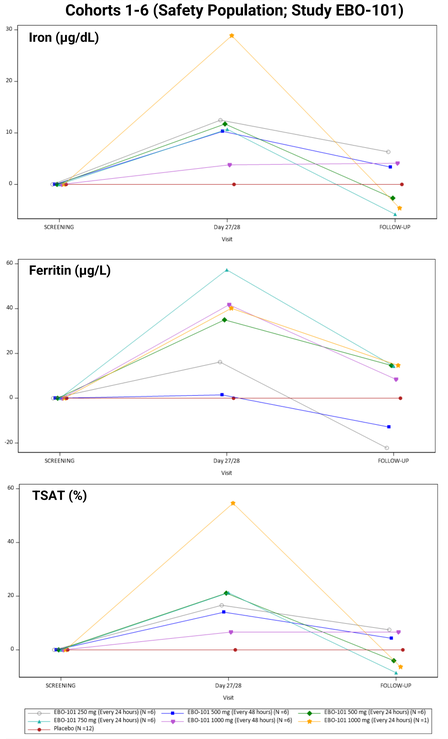



**Figure 3: Placebo-Adjusted Change from Baseline in Mean Serum Iron Metabolism Values vs Time for Dose Cohorts 1-6 (Safety Population; Study EBO-101)**




Note: Cohort 7 is not included in the figures as it was a single-dose cohort

### Safety Findings:

- Oral EBO was generally well tolerated when given for up to 28 days, with a rate of TEAEs comparable to that of placebo; no serious or severe TEAE was reported (**Table 2**)
- Numerically greater rate of gastrointestinal (GI) at EBO doses >500 mg/day compared with doses ≤500 mg/day; most GI events were mild in severity

**Table 2: Incidence of TEAEs (All Dose Cohorts 1-7; Safety Population; Study EBO-101)**

| | Pooled EBO (N=39) n (%) [m] | Pooled Placebo (N=12) n (%) [m] |
|---|---|---|
| **At least 1 TEAE** | 30 (76.9) [153] | 10 (83.3) [50] |
| **Drug-related TEAE** | 11 (28.2) [52] | 5 (41.7) [13] |
| **Serious TEAE** | 0 | 0 |
| **Severe TEAE** | 0 | 0 |
| **TEAE leading to treatment discontinuation [a]** | 3 (7.7) [6] | 0 |
| **TEAE leading to study withdrawal [b]** | 1 (2.6) [1] | 0 |
| **TEAEs in ≥10% of EBO-treated subjects** | | |
| Nausea [c] | 9 (23.1) [9] | 2 (16.7) [2] |
| Vascular access site pain | 9 (23.1) [11] | 3 (25.0) [3] |
| Headache | 7 (17.9) [12] | 3 (25.0) [3] |
| Vessel puncture site bruise | 6 (15.4) [8] | 2 (16.7) [5] |
| Back pain | 5 (12.8) [5] | 0 |
| Decreased appetite [c] | 4 (10.3) [4] | 0 |
| Diarrhea [c] | 4 (10.3) [6] | 1 (8.3) [1] |
| Upper respiratory tract infection | 4 (10.3) [4] | 1 (8.3) [1] |

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; EBO = epetraborole; GGT = gamma-glutamyl transferase; GI = gastrointestinal; m = number of events; n or N = number of subjects; TEAE = treatment-emergent adverse event.
[a] One EBO 250 mg q24h subject with moderate AST increased, moderate ALT increased, mild GGT increased, and mild blood ALP increased; 1 EBO 1000 mg q48h subject with mild nausea; and 1 EBO 500 mg fasting subject with mild unrelated tooth infection.
[b] Mild unrelated tooth infection.
[c] Most GI-related TEAEs were mild in severity.

## CONCLUSIONS

- **EBO exhibited well-behaved PK, was generally well tolerated, and showed dose- and exposure-dependent Hct and Hgb decreases without clinically meaningful platelet/WBC elevations**
- **These PK, safety, and hematological data support further evaluation of EBO for treatment of PV**

**ACKNOWLEDGEMENTS:**
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**DISCLOSURES:**
Baseline characteristics, subject disposition, PK, and safety data were presented at IDWeek 2022 (Washington, D.C. October 19–23; Poster No. 1727). Eckburg PB, Clarke D, Long J, Chanda S, Krause KM, Easom E, Talbot G, Rubino C, Molga A. Tolerability and Pharmacokinetics of Oral Epetraborole at the Predicted Therapeutic Dosage for Mycobacterium avium Complex (MAC) Lung Disease: A Phase 1b Dose-ranging and Food Effect Study.

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

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