EXPOSURE-RESPONSE ANALYSES OF HEMOGLOBIN CHANGES DURING EPETRABOROLE ADMINISTRATION TO NONHUMAN PRIMATES PREDICT HUMAN EXPOSURE-RESPONSE RELATIONSHIPS

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INTRODUCTION

- Epetraborole (EBO) is a novel, boron-containing small molecule found to specifically decrease erythropoiesis in nonhuman primates (NHPs) [1].
- This effect, limited to the erythroid cell line, suggests a potential role of EBO in treating polycythemia vera (PV) [1].
- PV is a rare blood cancer in which there is an abnormal increase in red blood cells [2].

OBJECTIVES

- Develop an exposure-response model for the relationship between EBO free-drug area under the concentration-time curve (AUC) and maximal hemoglobin (Hgb) decrease.
- Evaluate the translatability of exposure-response relationships from NHPs to predict Hgb changes during EBO administration in humans.

METHODS

Data

- Two toxicity studies in which NHPs were administered EBO once daily for at least 90 days (n=116). NHPs underwent intense pharmacokinetic (PK) sampling over the course of treatment and had hematology sampling prior to treatment, 4 times during treatment, and once during follow-up [3].
  - Study G11163 (N=44): 75, 150, or 300 mg/kg IV
  - Study A14-0009-TX (N=72): 50, 150 or 450 mg/kg PO
- Human Phase 1 studies
  - Study EBO-101: healthy participants received oral EBO administered at 250, 500, 750, or 1000 mg every 24 hours or 500 or 1000 mg every 48 hours for up to 28 days. Participants underwent intensive PK sampling on Days 1 and 28 [4].
  - Study EBO-102: participants with varying degrees of renal impairment received EBO 500 mg PO as a single dose. Participants underwent intensive PK sampling [5].
  - Study EBO-103: healthy participants in Japan received EBO 500 mg PO as a single dose. Participants underwent intensive PK sampling [3].
- Study EBO-301: a Phase 2/3 study of treatment-refractory *Mycobacterium avium* complex lung disease [6].
  - Patients were treated with 500 mg PO once daily (QD).

Exposure-Response Model

- Data from the NHP toxicity studies was used to construct a sigmoidal, Emax model correlating EBO PK exposure with maximum percent change from baseline in Hgb during treatment.
- PK exposure in each NHP was estimated using non-compartmental methods.
- Exposure-response models were fit to the data using R, statistical software.

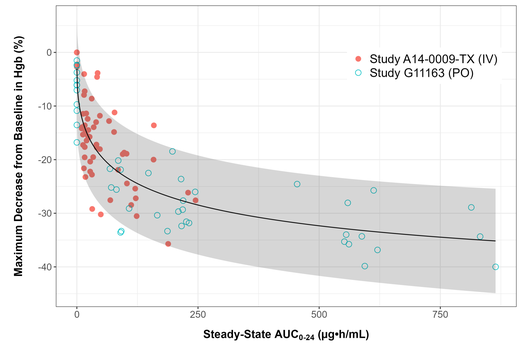
Population PK Model Development and Simulations

- Data from Phase 1 studies was used to develop a population PK model to describe the PK of EBO in humans.
- The model was then qualified using observed EBO concentration-time data from Phase 2/3 participants.
- The population PK model was used to predict EBO PK exposure in a hypothetical population of patients (N=10,000, with characteristics resampled from Study EBO-301).
- Simulated exposures were then input into the exposure-response model to predict the maximum percent change from baseline in Hgb during treatment.
- Summary statistics of the percent change from baseline in Hgb were calculated using observed data from participants randomized to EBO in Study EBO-301.

RESULTS

- In NHPs, a clear exposure-response pattern between EBO exposure (steady-state AUC from zero to 24 hours [$AUC_{0\text{-}24}$]) and maximum drop in Hgb after 90 days of treatment was identified, as shown in **Figure 1**.

Figure 1: Maximum Decrease in Hgb After 90 Days of EBO Treatment in NHP Toxicity Studies



Note: Circles indicate observed data, colored by route of EBO administration. Solid black line is the mean relationship between steady-state $AUC_{0\text{-}24}$ and maximum drop in Hgb. Shaded region shows the 5th and 95th percentiles of the predicted maximum change.

- The most robust fit to the observed human PK data was obtained using a population PK model containing two systemic compartments with oral absorption described using transit compartments. Covariate analyses identified statistically significant relationships between PK parameters and body weight, renal function, and fed status. External qualification analyses indicated that the model was able to robustly capture the Phase 2/3 data.
- The results of the model-based simulations are presented in **Table 1**.
  - Steady-state EBO $AUC_{0\text{-}24}$, simulated using the human population PK model, increases with increasing dose.
  - Predicted mean maximal decrease in Hgb, estimated using the simulated human $AUC_{0\text{-}24}$ and the exposure-response model developed from NHP data, also increases with increasing dose.

Table 1: Predicted EBO Steady-State $AUC_{0\text{-}24}$ and Mean Maximal Effect on Hgb in EBO-Treated Patients Using the Human Population PK Model and the Exposure-Response Model from NHP Toxicity Studies

Dose	Percentile of simulated AUC	$AUC_{0\text{-}24}$ at steady-state (µg•h/mL)	Estimated mean maximal change (%) from baseline in Hgb
125 mg	25th	3.565	-8.93
	50th	4.547	-9.58
	75th	5.730	-10.26
	95th	8.039	-11.35
250 mg	25th	7.130	-10.95
	50th	9.094	-11.77
	75th	11.46	-12.62
	95th	16.08	-13.97
500 mg	25th	14.26	-13.48
	50th	18.19	-14.49
	75th	22.92	-15.51
	95th	32.16	-17.12
750 mg	25th	21.39	-15.20
	50th	27.28	-16.32
	75th	34.38	-17.44
	95th	48.24	-19.17
1000 mg	25th	28.52	-16.53
	50th	36.38	-17.73
	75th	45.84	-18.91
	95th	64.31	-20.72

Note: All regimens administered PO QD.

- The summary statistics of percent change in Hgb from baseline to nadir in patients from Study EBO-301 are presented in **Table 2**.
- Consistency was seen between the model-predicted drop in Hgb in NHPs and that which was observed in patients. The predicted mean maximal percentage decrease from baseline predicted from the NHP model at the 50th percentile of simulated AUC for the 500 mg QD dose was -14.5% (**Table 1**), whereas in Study EBO-301, the mean maximal percentage Hgb decrease was -19.0% (range: -38.3% to -4.0%) at the same dose (**Table 2**).
- Patients whose baseline Hgb was less than the lower limit of normal (LLN) had a lesser mean maximal Hgb decrease than patients whose baseline Hgb was ≥ LLN (-16.7% [range: -26.4% to -6.0%] versus -20.0% [range: -38.3% to -4.0%], respectively).

Table 2: Summary Statistics of Percent Change in Hgb from Baseline to Nadir, Stratified by Baseline Category and Gender

Category	N	Mean (%)	Range (%)
All baseline Hgb values			
All patients	103	-18.97	-38.3 to -4.0
Males	28	-17.24	-38.3 to -4.0
Females	75	-19.62	-38.3 to -6.0
Baseline Hgb < LLN			
All patients	32	-16.66	-26.4 to -6.0
Males	15	-17.01	-26.3 to -7.8
Females	17	-16.35	-26.4 to -6.0
Baseline Hgb ≥ LLN			
All patients	71	-20.01	-38.3 to -4.0
Males	13	-17.50	-38.3 to -4.0
Females	58	-20.57	-36.3 to -7.3

Note: LLN was defined as 12.0 g/dL for females and 13.6 g/dL for males. A single outlier with a +23.2% Hgb "nadir" value was excluded; this patient had a baseline Hgb value that was discordant with that obtained at Screening, and the patient only received a very short course of treatment before study drug discontinuation and withdrawal of consent.

CONCLUSIONS

- **Exposure-response analyses of Hgb changes during EBO administration to NHPs were informative for predicting Hgb changes in humans during EBO treatment.**
- **Changes in Hgb after administration of EBO are predicted to be dose-dependent, with increasing EBO doses causing larger decreases in Hgb.**

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

1. AN2 Therapeutics announces plans to advance oral epetraborole into Phase 2 study for polycythemia vera (PV) [press release]. Menlo Park, CA: AN2 Therapeutics, Inc.; March 3, 2026. https://investor.an2therapeutics.com/node/8496/pdf. Accessed August 4, 2026.
2. Harrison CN, Barbui T, Bose P, et al. Polycythaemia vera. Nat Rev Dis Primers. 2025;11(1):26.
3. Data on file, AN2 Therapeutics, Inc.
4. AN2 Therapeutics, Inc. Phase 1 study of epetraborole tablets. ClinicalTrials.gov identifier: NCT04892641. Updated March 21, 2024. Accessed August 5, 2026. https://clinicaltrials.gov/study/NCT04892641
5. AN2 Therapeutics, Inc. A study of epetraborole tablets in subjects with degrees of renal function. ClinicalTrials.gov identifier: NCT05283746. Updated July 15, 2022. Accessed August 5, 2026. https://clinicaltrials.gov/study/NCT05283746
6. AN2 Therapeutics, Inc. Study of epetraborole in patients with treatment-refractory MAC lung disease. ClinicalTrials.gov identifier: NCT05327803. Updated June 10, 2026. Accessed August 5, 2026. https://clinicaltrials.gov/study/NCT05327803

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