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Pharmacokinetic-Pharmacodynamic Target Attainment Analyses to Support Epetraborole Dose Selection for the Treatment of Patients with *Mycobacterium avium* Complex Lung Disease

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INTRODUCTION

- Epetraborole (previously known as GSK2251052 and AN3365) is an orally available benzoxaborole, a boron-heterocyclic antimicrobial class that inhibits leucyl transfer RNA synthetase (LeuRS). LeuRS is an essential enzyme for protein synthesis whose inhibition stops bacterial growth [1, 2].
- Epetraborole has potent activity against nontuberculous mycobacteria [2, 3, 4]. Epetraborole has been found to concentrate in alveolar macrophages [5] and is under clinical development for the treatment of *Mycobacterium avium* complex (MAC) lung disease.
- Safety data gathered from five Phase 1 and two Phase 2 studies in which subjects or patients received single or multiple intravenous (IV) or oral (PO) epetraborole doses ranging from 200 to 4000 mg demonstrated that these doses were generally well-tolerated [6].
- To support the selection of PO epetraborole dosing regimens for the clinical development in MAC lung disease, the following analyses were carried out:
  - Pharmacokinetic-pharmacodynamic (PK-PD) analyses using data for MAC isolates studied in a chronic murine MAC lung infection model [7]; and
  - PK-PD target attainment analyses using non-clinical PK-PD targets for efficacy from the above-described analyses, a previously developed population pharmacokinetic (PK) model [8], and simulation.

METHODS

- Hill-type models were used to characterize the relationship between the ratio of epetraborole free-drug plasma area under the concentration-time curve (AUC) to minimum inhibitory concentration (MIC) (AUC:MIC ratio) and change in $\log_{10}$ colony-forming units (CFU) from baseline at 8 weeks for 5 MAC isolates (epetraborole MIC range 2-8 mg/L) in a chronic murine MAC lung infection model [7].
  - Change in $\log_{10}$ CFU was calculated by comparing CFUs after 56 days of epetraborole dosing (10 to 300 mg/kg/day) to CFUs of untreated controls prior to dosing.
  - Data from PK studies in C57BL/6 mice treated with epetraborole PO doses ranging from 10 to 400 mg/kg [7] were used to carry out non-compartmental PK analyses and determine AUC by epetraborole dose. Free-drug plasma AUC values were calculated using a murine protein binding estimate of 7.6% [1].
- Simulations were carried out using a previously developed population PK model for epetraborole based on data from Phase 1 and 2 studies. The final population PK model was a three-compartment model with linear elimination [8].
  - PK parameters were calculated for 10,000 simulated patients with MAC lung disease. Weight, a covariate in the population PK model, was randomly assigned with replacement using a weight distribution from a target population of nontuberculous mycobacteria patients [9].
  - Given that the population PK model for epetraborole was largely derived from healthy volunteers, the variability in PK parameter estimates was more narrow than would be expected in the target patient population. Thus, the interindividual variability was increased to 30% when the observed interindividual variability was less than 30%.
  - Using the population PK model and the resultant individual PK parameters, total-drug plasma concentration-time profiles at steady-state after administration of epetraborole 250 and 500 mg PO every 24 hours (q24h) for 21 days were generated for simulated patients in a fasted state.
  - Free-drug plasma AUC values were calculated using a human protein binding estimate of 0% [6].
- Percent probabilities of PK-PD target attainment were assessed using median, randomly assigned, and the highest of the free-drug plasma AUC:MIC ratio targets from the Hill-type models developed using the above-described *in vivo* study data.

RESULTS

- **Figure 1** shows the relationship between epetraborole free-drug plasma AUC:MIC ratio and change in $\log_{10}$ CFU from baseline at 8 weeks based on Hill-type models for individual MAC isolates evaluated. **Table 1** summarizes the epetraborole free-drug plasma AUC:MIC ratio targets for each isolate based on the associated Hill-type model.
- The Hill-type models fit to the individual isolate data yielded no discernable outliers.

Figure 1. Non-clinical PK-PD relationships for epetraborole efficacy based on data by MAC isolates [7]

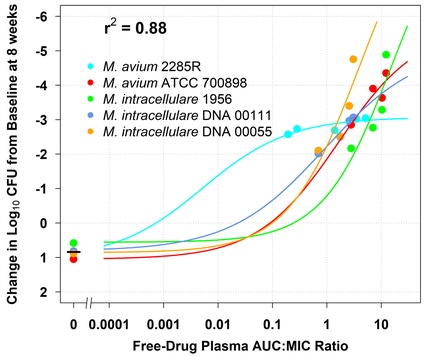


Table 1. Summary of epetraborole non-clinical free-drug plasma AUC:MIC ratio targets for efficacy by MAC isolate

MAC isolate	MIC (mg/L)	Free-drug plasma AUC:MIC ratio targets by bacterial reduction endpoint[a]			
		Net bacterial stasis	$\log_{10}$ CFU reductions from baseline		
			1-$\log_{10}$ CFU	2-$\log_{10}$ CFU	3-$\log_{10}$ CFU
M. avium 2285R	4	0.0007	0.0051	0.0351	8.509
M. avium ATCC 700898	2	0.0901	0.391	1.154	3.191
M. intracellulare 1956	2	0.243	1.274	3.131	6.196
M. intracellulare DNA 00111	8	0.0230	0.176	0.739	2.929
M. intracellulare DNA 00055	8	0.0984	0.370	0.847	1.632
Pooled		0.0071	0.0587	0.295	1.805
Median		0.0901	0.370	0.847	3.191
Mean		0.0911	0.443	1.181	4.491
Minimum		0.0007	0.0051	0.0351	1.632
Maximum		0.243	1.274	3.131	8.509

a. Reductions in $\log_{10}$ CFU on Day 84 were relative to baseline, which was represented by control data collected on Day 27.

RESULTS

- **Table 2** summarizes percent probabilities of PK-PD target attainment by MIC based on free-drug plasma AUC:MIC ratio targets associated with 1- and 2-$\log_{10}$ CFU reductions from baseline. These data are shown graphically in **Figure 2**.

Epetraborole 250 mg q24h

- Percent probabilities of PK-PD target attainment based on free-drug plasma AUC:MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction were ≥ 90% at an MIC value of 4 mg/L for all targets and at an MIC value of 8 mg/L for the median target only.
- Percent probabilities of PK-PD target attainment based on free-drug plasma AUC:MIC ratio targets associated with a 2-$\log_{10}$ CFU reduction were ≥ 90% at an MIC of 2 mg/L for median and randomly assigned targets and at an MIC value of 4 mg/mL for the median target only.

Epetraborole 500 mg q24h

- Percent probabilities of PK-PD target attainment based on free-drug plasma AUC:MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction were ≥ 90% at an MIC value of 8 mg/L for all targets and at an MIC value of 16 mg/mL for the median target only.
- Percent probabilities of PK-PD target attainment based on free-drug plasma AUC:MIC ratio targets associated with a 2-$\log_{10}$ CFU reduction were ≥ 90% at an MIC value of 4 mg/L for median and randomly assigned targets and at an MIC value of 8 mg/mL for the median target only.

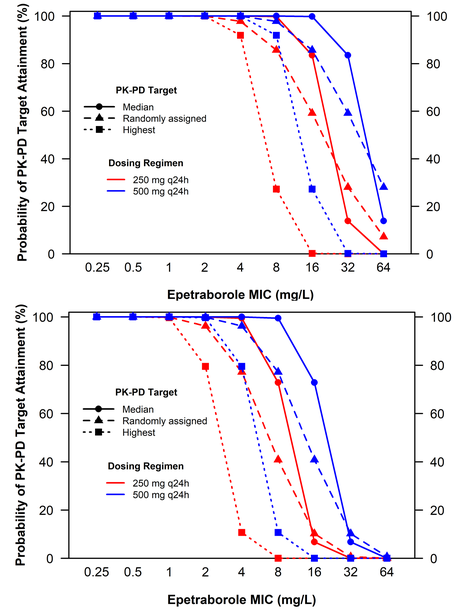
- Percent probabilities of PK-PD target attainment were interpreted in the context of the *in vitro* activity of epetraborole against 51 clinical MAC isolates, which showed that the MIC values at which 50 and 90% of isolates were inhibited was 2 and 8 mg/L, respectively [6].

Table 2. Percent probabilities of PK-PD target attainment by MIC at steady-state based on the assessment of epetraborole free-drug plasma AUC:MIC ratio targets associated with 1- and 2-$\log_{10}$ CFU reductions from baseline for MAC isolates among simulated patients by epetraborole dosing regimen

Endpoints for PK-PD target	MIC (mg/L)	Percent probability of PK-PD target attainment by MIC by epetraborole dosing regimen and approach[a]					
		Epetraborole 250 mg q24h			Epetraborole 500 mg q24h		
		Median of all PK-PD targets	Randomly assigned based on all PK-PD targets	Highest PK-PD target	Median of all PK-PD targets	Randomly assigned based on all PK-PD targets	Highest PK-PD target
1-$\log_{10}$ CFU reduction from baseline	0.25	100	100	100	100	100	100
	0.5	100	100	100	100	100	100
	1	100	100	100	100	100	100
	2	100	100	99.9	100	100	100
	4	100	97.8	91.9	100	100	99.9
	8	99.8	85.6	27.2	100	97.8	91.9
	16	83.5	59.2	0.2	99.8	85.6	27.2
	32	13.9	28.0	0	83.5	59.2	0.2
	64	0	7.2	0	13.9	28.0	0
2-$\log_{10}$ CFU reduction from baseline	0.25	100	100	100	100	100	100
	0.5	100	100	100	100	100	100
	1	100	99.9	99.7	100	100	100
	2	100	96.2	79.5	100	99.9	99.7
	4	99.5	77.2	10.7	100	96.2	79.5
	8	72.8	40.8	0	99.5	77.2	10.7
	16	6.8	10.2	0	72.8	40.8	0
	32	0	0.6	0	6.8	10.2	0
	64	0	0	0	0	0.6	0

Note: Shaded cells indicate percent probabilities of PK-PD target attainment ≥ 90%.
a. The median and highest PK-PD targets were based on data for all MAC isolates shown in **Table 1**. The randomly assigned PK-PD targets were based on data for all MAC isolates shown in **Table 1** excluding the data for *M. avium* 2285R.

Figure 2. Percent probabilities of PK-PD target attainment by MIC at steady-state based on the assessment of epetraborole free-drug plasma AUC:MIC ratio targets associated with 1- and 2-$\log_{10}$ CFU reductions from baseline (Panels A and B, respectively) for MAC isolates among simulated patients by epetraborole dosing regimen



CONCLUSIONS

The high percent probabilities of PK-PD target attainment associated with plasma exposures after the administration of epetraborole 250 or 500 mg PO q24h support the advancement of these dosing regimens as part of combination therapy into clinical studies in patients with MAC lung disease.

ACKNOWLEDGEMENTS
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