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A Phase 1, Open-Label, Single Dose Study to Evaluate the Pharmacokinetics (PK), Safety, and Tolerability of Epetraborole Tablets and the Impact of Alcohol Dehydrogenase Genotype on the PK of Epetraborole and Metabolite M3 in Healthy Japanese Adult Subjects

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Abstract

Background: Epetraborole (EBO), an orally available bacterial leucyl transfer RNA synthetase (LeuRS) inhibitor with potent activity against nontuberculous mycobacteria is under clinical development for treatment-refractory *Mycobacterium avium* complex (MAC) lung disease. Nonclinical studies suggest that metabolism of EBO to its metabolite, M3 may involve oxidation by alcohol dehydrogenase (ADH). The goal of this study was to evaluate the impact of ADH genotype on the pharmacokinetics (PK) of EBO and M3 in healthy Japanese subjects.

Methods: In this open-label trial, a single oral 500 mg EBO dose was administered to subjects in 3 cohorts defined by ADH1B genotype (*1/*1, *1/*2, or *2/*2). EBO and M3 plasma concentrations were measured by a validated LC-MS/MS method, and plasma EBO and M3 PK were determined using non-compartmental methods. Standard clinical and laboratory evaluations and treatment-emergent adverse events (TEAEs) were assessed.

Results: 18 subjects were enrolled (6/cohort). EBO was rapidly absorbed, with M3 subsequently appearing in plasma. After reaching C_{max}, EBO and M3 concentrations declined with a geometric mean $t_{1/2}$ of 10.7 to 11.4 h and 26.7 to 33.1 h, respectively. EBO exposures (C_{max} and AUC) were similar between Cohort 1 and Cohort 2, while exposures were 1.2- to 1.4-fold higher in Cohort 3; however, exposure of M3 was similar across all cohorts. Compared to Cohort 1, EBO:M3 ratios for Cohort 3 were generally similar for C_{max} and were approximately 20% lower for AUC. No apparent differences in $t_{1/2}$ were observed across cohorts for either EBO or M3. No TEAEs or clinically significant changes in clinical laboratory parameters, vital signs, physical examinations, or electrocardiogram (ECGs) were reported in this study.

Conclusion: Administration of EBO in Japanese subjects with varying ADH1B genotypes had no meaningful effect on EBO or M3 plasma exposure. The slightly increased EBO exposures associated with the 500 mg dosage in subjects with ADH1B *2/*2 genotype were within the range of tolerable exposures. Oral EBO was well tolerated in this study; no TEAEs were reported. These data suggest that no dose adjustment of EBO is needed in Japanese subjects, or between subjects with different ADH1B genotypes.

Introduction

- EBO is a boron-containing, oral inhibitor of LeuRS, an essential enzyme in protein synthesis, and is being developed for the treatment of treatment-refractory MAC lung disease and acute melioidosis.
- Nonclinical studies suggested that the polymorphic enzyme ADH is responsible for the formation of the primary EBO metabolite, M3. It is well known that variants of ADH have effects on multiple substrates, and various genotypes of the ADH1B subtype may affect metabolism of those substrates, including ethanol. East Asian populations commonly have ADH1B genotypes that result in more rapid ethanol metabolism; for example, 81-100% of the Japanese population have at least 1 ADH1B *2 allele that may confer rapid ethanol metabolism (Suzuki, 2004; Eng, 2007). It is unknown whether certain ADH1B genotypes are associated with rapid EBO metabolism (analogous to ethanol metabolism), thus potentially impacting EBO PK.

Introduction (continued)

- As Asian patients with MAC lung disease are being enrolled in EBO clinical studies, this Phase 1 study was designed to evaluate EBO PK in healthy Japanese subjects with different ADH1B genotypes to assess what impact this may have on EBO exposures.

Ojectives

The goals of this study were:

1. To assess the PK of EBO in Japanese subjects and to assess the impact of ADH genotype on the PK of EBO and its primary metabolite, M3.
2. To demonstrate that EBO exposure in Japanese subjects was similar to other populations studied previously.

Methods

Study Design and Population

- This was a Phase 1, open label single dose study conducted in healthy adult Japanese subjects.
- All subjects were evaluated to determine their ADH1B genotype (*1/*1, *1/*2, or *2/*2). The ADH1B *1/*1 genotype is considered wild-type and referenced as having normal ethanol metabolism. The ADH1B *1/*2 genotype is considered to have a moderate increase in ADH activity while the ADH1B *2/*2 genotype is considered to have an even greater increase in ADH activity resulting in increased rate of ethanol metabolism (Eng, 2007). Once ADH1B genotyping test results were available, 6 subjects each with ADH1B *1/*1, *1/*2, or *2/*2 were allocated into Cohort 1, 2, or 3, respectively, for a total of 18 subjects.
- A single EBO 500 mg (2 x 250 mg tablets) dose was administered orally following an overnight fast of at least 8 hours. Subjects were required to fast for a minimum of 2 hours following study drug administration.

PK Sampling

A total of 15 blood samples were collected for PK assessments at predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 48 h following administration and a single sample between days 8 to 15. All blood samples were analyzed to determine EBO and M3 concentrations using a validated HPLC/MS/MS method with a limit of quantitation of 5 ng/mL for both analytes. A calibration curve ranging from 5.00 to 3000 ng/mL was used to quantify EBO and M3 in the samples. Plasma PK parameters of EBO and M3 were determined using noncompartmental methods in Phoenix WinNonlin® v8.0. Plasma PK parameters determined included C_{max}, T_{max}, $t_{1/2}$, $AUC_{0\text{-}inf}$, and metabolite to parent ratios for C_{max} and AUC.

Results

A total of 18 healthy Japanese subjects were enrolled, with 6 subjects in each of the 3 cohorts. All subjects received study drug and completed the study; Ten subjects were male and 8 were female.

Table 1. Summary of Demographics and Baseline Characteristics

		Cohort 1 (ADH1B *1/*1) (N=6)	Cohort 2 (ADH1B *1/*2) (N=6)	Cohort 3 (ADH1B *2/*2) (N=6)	Overall (N=18)
Age (years) at Pre-Study Genetic Test Period, Mean (SD)		36.8 (14.72)	28.5 (10.91)	33.5 (11.98)	32.9 (12.38)
Sex, n (%)	Female	2 (33.3)	3 (50.0)	3 (50.0)	8 (44.4)
	Male	4 (66.7)	3 (50.0)	3 (50.0)	10 (55.6)
Race, n (%)	Asian	6 (100.0)	6 (100.0)	6 (100.0)	18 (100.0)
	Japanese	6 (100.0)	6 (100.0)	6 (100.0)	18 (100.0)
Childbearing potential (females only), n (%)	Yes	1 (50.0)	3 (100.0)	3 (100.0)	7 (87.5)
	No	1 (50.0)	0	0	1 (12.5)
Weight in kg, Mean (SD)		58.87 (8.438)	63.05 (9.401)	58.08 (7.149)	60.00 (8.186)
Height in cm, Mean (SD)		168.6 (7.56)	167.9 (7.85)	164.0 (11.00)	166.8 (8.65)
Body mass index (kg/m^2), Mean (SD)		20.640 (1.8807)	22.278 (1.9430)	21.557 (0.9799)	21.492 (1.7056)
ADH1B genotype, n (%)	ADH1B *1/*1	6 (100.0)	0	0	6 (33.3)
	ADH1B *1/*2	0	6 (100.0)	0	6 (33.3)
	ADH1B *2/*2	0	0	6 (100.0)	6 (33.3)

Results

Pharmacokinetics

- EBO was rapidly absorbed following administration across all cohorts. The metabolite M3 appeared steadily in plasma and reached C_{max} shortly after that of EBO. Plasma EBO and M3 concentrations declined with a geometric mean $t_{1/2}$ of approximately 10.7 to 11.4 h and 26.7 to 33.1 h, respectively, across all cohorts. (See Figure 1). The respective PK profiles are similar to those reported for healthy subjects (Eckburg et al, ID Week 2022, poster #1727)
- A summary of EBO and M3 PK for each cohort is displayed in Table 2. Exposure of EBO based on C_{max} and AUC was similar among subjects with ADH1B genotypes *1/*1 (Cohort 1) and *1/*2 (Cohort 2). However, EBO C_{max} and AUC were approximately 1.2- to 1.4-fold higher in Cohort 3 subjects with ADH1B *2/*2 genotype compared to Cohorts 1 or 2.
- Exposure of metabolite M3 based on C_{max} and AUC was similar among subjects with ADH1B genotypes *1/*1 (Cohort 1), *1/*2 (Cohort 2), and *2/*2 (Cohort 3).
- There were no apparent differences in $t_{1/2}$ in any cohort for either EBO or M3.
- Metabolite to parent ratios for Cohort 3 (ADH1B *2/*2 genotype) were similar for C_{max} but were approximately 20% lower for $AUC_{0\text{-}inf}$ compared to Cohorts 1 and 2.

Safety

- EBO was well tolerated and no TEAEs were reported. No clinically significant changes in lab parameters, vital signs or ECGs were reported.

Figure 1. Mean EBO and M3 Plasma Concentration-Time Profile

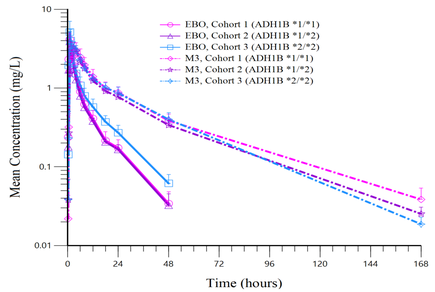


Table 2. EBO and M3 Pharmacokinetic Parameters

Parameter	Cohort 1 (ADH1B *1/*1) (N=6)	Cohort 2 (ADH1B *1/*2) (N=6)	Cohort 3 (ADH1B *2/*2) (N=6)
Epetraborole			
C_{max} (mg/L)[a]	4.21 (13.6)	4.24 (19.3)	5.04 (33.9)
T_{max} (h)[b]	1.00 (1.00, 1.50)	1.00 (1.00, 1.50)	1.00 (1.00, 2.00)
$AUC_{0\text{-}inf}$ (h*mg/L)[a]	20.3 (18.2)	19.1 (7.7)	26.1 (23.8)
$t_{1/2}$ (h)[a]	10.7 (17.6)	10.8 (23.7)	11.4 (15.7)
M3			
C_{max} (mg/L)[a]	3.02 (28.1)	3.13 (20.0)	3.35 (19.2)
T_{max} (h)[b]	3.00 (2.00, 4.00)	3.00 (2.00, 3.00)	2.50 (1.50, 3.00)
$AUC_{0\text{-}inf}$ (h*mg/L)[a]	71.1 (21.6)	63.4 (9.2)	67.3 (14.7)
$t_{1/2}$ (h)[a]	33.1 (9.8)	30.3 (6.4)	26.7 (2.2)
M/P C_{max}[a]	0.677 (30.3)	0.696 (27.1)	0.628 (34.7)
M/P $AUC_{0\text{-}inf}$[a]	3.31 (20.5)	3.14 (9.9)	2.44 (13.0)

Notes: Geometric CV% = 100 * (exp (SD^2)-1)$^{0.5}$, where SD is the SD of the log-transformed data.
Abbreviations: $AUC_{0\text{-}inf}$ = area under the concentration-time curve from time 0 to infinity; C_{max} = maximum observed plasma concentration; CV = coefficient of variation; M/P = metabolite to parent; $t_{1/2}$ = half-life; T_{max} = time to maximum observed plasma concentration.
[a] Data are presented as the geometric mean (geometric CV%); [b]Data are presented as the median (minimum, maximum).

Figure 2. Box Plots of $AUC_{0\text{-}inf}$ (h*mg/L) and C_{max} (mg/L) of EBO by Cohort.

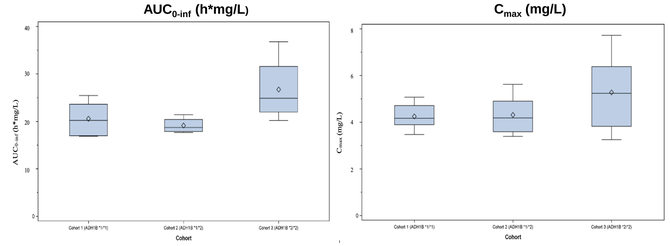
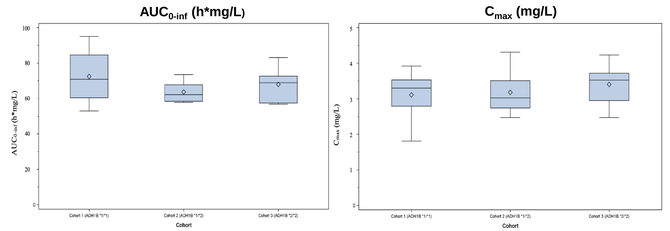


Figure 3. Box Plots of $AUC_{0\text{-}inf}$ (h*mg/L) and C_{max} (mg/L) of M3 by Cohort.



Conclusions

- EBO 500 mg was well tolerated in healthy Japanese adults when administered as a single dose.
- EBO exposure (C_{max} and AUC) in subjects with the ADH1B *2/*2 genotype was slightly higher than in subjects with the ADH1B *1/*1 genotype.
- The slightly increased EBO exposures associated with a 500 mg dose in subjects with ADH1B *2/*2 genotype were within the range of tolerable exposures noted in earlier studies.
- The PK observed in Japanese subjects was similar to that observed in previous studies in healthy volunteers.

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