

A Phase 1, Multicenter, Open-Label, Parallel-Group Study to Assess the Safety and Pharmacokinetics of Oral Epetraborole Tablets in Adult Subjects with Varying Degrees of Renal Function

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Abstract

Background: Epetraborole (EBO) is an orally available bacterial leucyl transfer RNA synthetase (LeuRS) inhibitor with potent activity against nontuberculous mycobacteria in clinical development for treatment-refractory MAC lung disease. The objective of the study was to evaluate the pharmacokinetics (PK) of EBO in adult subjects with varying degrees of renal impairment (RI) and end stage renal disease (ESRD) with intermittent hemodialysis (IHD).

Methods: Open-label, single-dose EBO 500 mg PO was given to subjects in 5 cohorts (normal renal function, mild, moderate, and severe RI, and ESRD); ESRD subjects received a second 500 mg dose on Day 5 approximately 1 hour before receiving IHD. Concentrations of EBO and its major metabolite (M3) in plasma, urine and dialysate were measured by validated LC-MS/MS methods. Plasma PK parameters were determined using non-compartmental methods and compared between cohorts using analysis of variance (ANOVA). Standard clinical and laboratory evaluations and treatment-emergent adverse events (TEAEs) were assessed.

Results: 40 subjects were enrolled (8/cohort). Subjects with RI did not exhibit quantitatively distinct EBO plasma PK profiles compared to those with normal renal function; AUC values were 1.1-1.4 higher in subjects with RI, and the mean ratios of maximum observed concentration C_{max} values did not exceed 1.16. The elimination half-life ($t_{1/2}$) increased slightly from 9.3 to 11.0 h in ESRD subjects, and clearance decreased by about 30%. Renal elimination was not a major route of excretion (~15% of dose over 72 h) for EBO, with mean renal clearance ranging from 4.24 L/h to 1.04 L/h. Metabolite M3 AUC increased 4-fold in subjects with severe RI, and 1% increased from 20 to 32 h. EBO was well-tolerated; 7 subjects (17.5%) experienced at least 1 TEAE (11 events), all mild in severity except 1 moderately-severe TEAE of worsening anemia. There were no severe or serious TEAEs.

Conclusion: Minimal increases in plasma EBO exposures and similar $t_{1/2}$ values were observed in subjects with varying degrees of RI including ESRD-IHD. Single 500 mg doses of EBO were well tolerated in each RI cohort. Overall, these data suggest that no dose adjustment of EBO is needed in subjects with any degree of RI.

Introduction

EBO is a boron-containing, oral inhibitor of bacterial LeuRS, an essential enzyme in protein synthesis, being developed for the treatment of treatment-refractory *Mycobacterium avium* complex (MAC) lung disease and acute melioidosis. EBO is primarily metabolized to M3 which is microbiologically inactive and excreted predominantly in urine. As patients with MAC lung disease and melioidosis may have impaired renal function, the effect of renal impairment on both EBO and M3 was evaluated.

Objective

Assess the PK of EBO and M3 in adult subjects with normal renal function, subjects with various degrees of RI, and subjects with ESRD receiving IHD.

Methods

Study Design and Population

This was a Phase 1 multicenter, open-label, non-randomized, parallel group study conducted at 3 sites in the United States. A total of 40 subjects were enrolled in 1 of 5 cohorts (Table 1) based on estimated glomerular filtration rate (eGFR), which was calculated using the chronic kidney disease epidemiology collaboration (CKD-EPI) formula.

Methods

Study Design and Population Continued

A single EBO 500 mg dose (2 x 250 mg tablets) was administered orally following an overnight fast on Day 1 for Cohorts 1 to 4. Subjects in Cohort 5 were administered a single oral EBO 500 mg dose following a fast of at least 6 hr and within 2 hr after completion of the subject's regularly scheduled IHD on Day 1, and a single oral EBO 500 mg dose following an overnight fast and approximately 1 hr (± 15 minutes) prior to the subject's regularly scheduled IHD on Day 5.

Table 1. eGFR Enrollment Criteria by Study Cohort

Cohort	eGFR
Cohort 1 (normal renal function)	eGFR ≥90 mL/min/1.73 m ²
Cohort 2 (mild renal impairment)	eGFR ≥60 and <90 mL/min/1.73 m ²
Cohort 3 (moderate renal impairment)	eGFR ≥30 and <60 mL/min/1.73 m ²
Cohort 4 (severe renal impairment)	eGFR <30 mL/min/1.73 m ²
Cohort 5* (end stage renal disease)	eGFR <15 mL/min/1.73 m ²

*Subjects must have been stable and received IHD for at least 3 weeks at least 3 months prior to screening. Cohorts 3-5 were enrolled in parallel. After enrollment of cohorts 3 and 4, matched controls (BMI <20%, age <10 yrs), sex 1:1 to 1) were enrolled in Cohort 1.

eGFR (mL/min/1.73 m²): 142 (interquartile range), 10 (interquartile range), 10 (interquartile range), 10 (interquartile range), 10 (interquartile range)

n = 8 (1 female) for 0.3 (male); n = 2 (1 female) for 0.3 (male)

PK Sampling

Cohorts 1-4: 13 blood samples for PK assessment were collected at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72 hr after the administration of study drug. Urine samples were collected over a period of 72 hr post dose.

Cohort 5: Blood samples for subjects in cohort 5 on both day 1 and 5, were collected at the same timepoints as those in cohorts 1-4; however, an additional sample was obtained following the end of dialysis on day 5. On Day 5, blood samples for PK assessments were collected from both the inflow (pre-dialysis/arterial) and outflow (post-dialysis/venous) lines pre-dialysis and at specified timepoints until 3 hr after initiation of IHD or at the end of IHD (whichever was later). On Day 5, dialysate was also collected over the full dialysis period.

Concentrations of EBO and M3 in plasma, urine and dialysate were measured by validated LC-MS/MS methods.

PK parameters of EBO and metabolite M3 were determined using noncompartmental methods using Phoenix WinNonlin® version 8.0.

Results

Table 2. Demographics and Baseline Characteristics

	Cohort 1 (N=8)	Cohort 2 (N=8)	Cohort 3 (N=8)	Cohort 4 (N=8)	Cohort 5 (N=8)
Age (years), Mean (SD)	65.1 (3.83)	62.9 (6.08)	71.5 (6.26)	68.4 (11.38)	55.3 (7.05)
Sex, Male/Female	5/3	3/5	4/4	7/1	8/0
Race (n (%))					
Black or African American	3 (37.5)	3 (37.5)	0	0	6 (75.0)
White	5 (62.5)	5 (62.5)	8 (100.0)	8 (100.0)	2 (25.0)
Weight (kg), Mean (SD)	81.31 (7.44)	75.88 (15.294)	88.65 (16.212)	90.99 (14.036)	88.80 (15.109)
BMI (kg/m ²), Mean (SD)	28.98 (2.219)	27.68 (4.329)	31.25 (4.609)	31.53 (3.378)	28.98 (3.954)
eGFR (mL/min/1.73m ²), Mean (SD)	98.4 (4.03)	71.3 (10.65)	47.9 (12.23)	20.0 (5.86)	NA

Pharmacokinetics

- Subjects with various degrees of RI and on dialysis did not exhibit quantitatively distinct EBO PK profiles when comparing to AUCs in subjects with normal renal function.
- EBO concentrations declined in a log-linear fashion with a geometric mean $t_{1/2}$ of approximately 8.83 to 10.96 hrs across the spectrum of renal impairment
- Renal elimination of EBO did not play a major role as a route of excretion of EBO with ~15% of administered dose recovered in urine over 72 hr
- Increases in plasma exposures (AUCs) M3 were observed in subjects with decreasing renal function (cohorts 2-4) ranging from 1.25-4.46-fold higher as compared to those with normal renal function (Cohort 1)
- M3 $t_{1/2}$ increased from Cohorts 1 to 4 with geometric mean $t_{1/2}$ of 19.76 hr (Cohort 1) to 32.11 hr (Cohort 4)
- A standard 4-hr hemodialysis session was able to remove about 11% of the administered EBO dose.

Figure 1. Semi-log Mean Concentration versus Time Profile of EBO and M3.

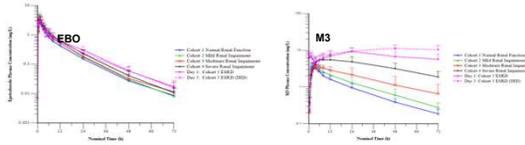


Table 3. Plasma PK EBO and M3 Parameters (geometric mean (CV%)), except where noted

EBO PK Parameter (Unit)	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5 Day 1	Cohort 5 Day 5
N	8	8	8	8	8	8
C_{max} (mg/L)	2.91 (39.0)	3.33 (45.5)	3.39 (37.1)	3.23 (35.1)	3.25 (19.8)	2.91 (21.3)
Fold-Change C_{max}	--	1.14	1.16	1.11	1.12	1.00
T_{max} (hr) median (min, max)	1.00 (1.00, 1.50)	1.00 (0.50, 3.00)	1.00 (1.00, 2.00)	1.50 (1.00, 4.00)	1.01 (1.00, 2.00)	1.00 (0.50, 1.50)
AUC ₀₋₇₂ (hr*mg/L)	17.1 (33.0)	19.6 (38.9)	21.2 (22.5)	23.9 (24.2)	24.5 (25.9)	21.7 (25.3)
AUC _{0-∞} (hr*mg/L)	17.2 (33.0)	19.7 (39.1)	21.4 (23.0)	24.1 (24.0)	24.7 (26.2)	22.0 (25.5)
$t_{1/2}$ (hr)	9.34 (22.8)	8.83 (19.4)	9.24 (26.7)	9.98 (19.1)	10.96 (10.5)	11.93 (12.3)
Fold-Change	--	1.1	1.2	1.4	1.4	1.3
AUC _{0-∞}	391 (34.7)	323 (41.0)	311 (26.4)	299 (27.8)	320 (19.6)	392 (22.3)
CL/F (L/hr)	29.0 (33.0)	25.4 (39.1)	23.3 (23.0)	20.8 (24.0)	20.2 (26.2)	22.8 (25.5)
CL _r (L/hr)	4.24 (0.917)	3.63 (1.21)	2.33 (0.770)	1.04 (0.415)	NC	8.08 (2.03)*
Fe (%)	14.73 (3.94)	13.65 (2.41)	9.66 (2.66)	5.01 (1.71)	NC	10.96 (2.13)*
M3 PK Parameter (Unit)	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5 Day 1	Cohort 5 Day 5
N	8	8	8	8	8	8
C_{max} (mg/L)	3.60 (22.0)	3.34 (22.1)	3.71 (16.1)	5.72 (27.8)	9.45 (27.8)	11.2 (28.3)
Fold-Change C_{max}	--	0.93	1.03	1.59	2.63	3.11
T_{max} (hr) median (min, max)	3.00 (2.00, 4.00)	4.00 (3.00, 8.00)	4.00 (2.00, 24.00)	7.00 (6.00, 24.22)	24.04 (24.00, 48.13)	48.13 (47.87, 72.43)
AUC ₀₋₇₂ (hr*mg/L)	63.6 (25.8)	77.9 (32.8)	115 (35.9)	256 (32.0)	461 (35.1)	663 (25.5)
AUC _{0-∞} (hr*mg/L)	68.8 (21.8)	86.3 (32.5)	119 (24.3)*	307 (27.7)*	NC	NC
Fold-Change	--	1.25	1.73	4.46	7.25*	10.42*
AUC _{0-∞}	19.76 (7.2)	22.13 (10.1)	23.09 (14.3)*	32.11 (22.4)*	NC	NC
$t_{1/2}$ (hr)	1.17 (27.5)	0.95 (30.1)	1.03 (38.6)	1.67 (30.6)	2.75 (23.4)	3.63 (37.6)
M/P (AUC)	3.77 (18.1)	4.14 (22.5)	5.47 (18.7)*	13.04 (24.0)*	17.79 (32.8)*	28.86 (32.0)*
Ae (mg)	240 (59.2)	312 (36.6)	282 (48.9)	259 (78.0)	NC	134 (32.8)*
CL _r (L/hr)	3.69 (0.568)	4.18 (1.36)	2.62 (0.965)	1.05 (0.482)	NC	6.45 (1.34)*

* Represents excretion in dialysate. NC: not calculated.

* a_e at 7, 8 hr; a_e at 10, 11 hr; a_e at 12, 13 hr; a_e at 14, 15 hr; a_e at 16, 17 hr; a_e at 18, 19 hr; a_e at 20, 21 hr; a_e at 22, 23 hr; a_e at 24, 25 hr; a_e at 26, 27 hr; a_e at 28, 29 hr; a_e at 30, 31 hr; a_e at 32, 33 hr; a_e at 34, 35 hr; a_e at 36, 37 hr; a_e at 38, 39 hr; a_e at 40, 41 hr; a_e at 42, 43 hr; a_e at 44, 45 hr; a_e at 46, 47 hr; a_e at 48, 49 hr; a_e at 50, 51 hr; a_e at 52, 53 hr; a_e at 54, 55 hr; a_e at 56, 57 hr; a_e at 58, 59 hr; a_e at 60, 61 hr; a_e at 62, 63 hr; a_e at 64, 65 hr; a_e at 66, 67 hr; a_e at 68, 69 hr; a_e at 70, 71 hr; a_e at 72, 73 hr; a_e at 74, 75 hr; a_e at 76, 77 hr; a_e at 78, 79 hr; a_e at 80, 81 hr; a_e at 82, 83 hr; a_e at 84, 85 hr; a_e at 86, 87 hr; a_e at 88, 89 hr; a_e at 90, 91 hr; a_e at 92, 93 hr; a_e at 94, 95 hr; a_e at 96, 97 hr; a_e at 98, 99 hr; a_e at 100, 101 hr; a_e at 102, 103 hr; a_e at 104, 105 hr; a_e at 106, 107 hr; a_e at 108, 109 hr; a_e at 110, 111 hr; a_e at 112, 113 hr; a_e at 114, 115 hr; a_e at 116, 117 hr; a_e at 118, 119 hr; a_e at 120, 121 hr; a_e at 122, 123 hr; a_e at 124, 125 hr; a_e at 126, 127 hr; a_e at 128, 129 hr; a_e at 130, 131 hr; a_e at 132, 133 hr; a_e at 134, 135 hr; a_e at 136, 137 hr; a_e at 138, 139 hr; a_e at 140, 141 hr; a_e at 142, 143 hr; a_e at 144, 145 hr; a_e at 146, 147 hr; a_e at 148, 149 hr; a_e at 150, 151 hr; a_e at 152, 153 hr; a_e at 154, 155 hr; a_e at 156, 157 hr; a_e at 158, 159 hr; a_e at 160, 161 hr; a_e at 162, 163 hr; a_e at 164, 165 hr; a_e at 166, 167 hr; a_e at 168, 169 hr; a_e at 170, 171 hr; a_e at 172, 173 hr; a_e at 174, 175 hr; a_e at 176, 177 hr; a_e at 178, 179 hr; a_e at 180, 181 hr; a_e at 182, 183 hr; a_e at 184, 185 hr; a_e at 186, 187 hr; a_e at 188, 189 hr; a_e at 190, 191 hr; a_e at 192, 193 hr; a_e at 194, 195 hr; a_e at 196, 197 hr; a_e at 198, 199 hr; a_e at 200, 201 hr; a_e at 202, 203 hr; a_e at 204, 205 hr; a_e at 206, 207 hr; a_e at 208, 209 hr; a_e at 210, 211 hr; a_e at 212, 213 hr; a_e at 214, 215 hr; a_e at 216, 217 hr; a_e at 218, 219 hr; a_e at 220, 221 hr; a_e at 222, 223 hr; a_e at 224, 225 hr; a_e at 226, 227 hr; a_e at 228, 229 hr; a_e at 230, 231 hr; a_e at 232, 233 hr; a_e at 234, 235 hr; a_e at 236, 237 hr; a_e at 238, 239 hr; a_e at 240, 241 hr; a_e at 242, 243 hr; a_e at 244, 245 hr; a_e at 246, 247 hr; a_e at 248, 249 hr; a_e at 250, 251 hr; a_e at 252, 253 hr; a_e at 254, 255 hr; a_e at 256, 257 hr; a_e at 258, 259 hr; a_e at 260, 261 hr; a_e at 262, 263 hr; a_e at 264, 265 hr; a_e at 266, 267 hr; a_e at 268, 269 hr; a_e at 270, 271 hr; a_e at 272, 273 hr; a_e at 274, 275 hr; a_e at 276, 277 hr; a_e at 278, 279 hr; a_e at 280, 281 hr; a_e at 282, 283 hr; a_e at 284, 285 hr; a_e at 286, 287 hr; a_e at 288, 289 hr; a_e at 290, 291 hr; a_e at 292, 293 hr; a_e at 294, 295 hr; a_e at 296, 297 hr; a_e at 298, 299 hr; a_e at 300, 301 hr; a_e at 302, 303 hr; a_e at 304, 305 hr; a_e at 306, 307 hr; a_e at 308, 309 hr; a_e at 310, 311 hr; a_e at 312, 313 hr; a_e at 314, 315 hr; a_e at 316, 317 hr; a_e at 318, 319 hr; a_e at 320, 321 hr; a_e at 322, 323 hr; a_e at 324, 325 hr; a_e at 326, 327 hr; a_e at 328, 329 hr; a_e at 330, 331 hr; a_e at 332, 333 hr; a_e at 334, 335 hr; a_e at 336, 337 hr; a_e at 338, 339 hr; a_e at 340, 341 hr; a_e at 342, 343 hr; a_e at 344, 345 hr; a_e at 346, 347 hr; a_e at 348, 349 hr; a_e at 350, 351 hr; a_e at 352, 353 hr; a_e at 354, 355 hr; a_e at 356, 357 hr; a_e at 358, 359 hr; a_e at 360, 361 hr; a_e at 362, 363 hr; a_e at 364, 365 hr; a_e at 366, 367 hr; a_e at 368, 369 hr; a_e at 370, 371 hr; a_e at 372, 373 hr; a_e at 374, 375 hr; a_e at 376, 377 hr; a_e at 378, 379 hr; a_e at 380, 381 hr; a_e at 382, 383 hr; a_e at 384, 385 hr; a_e at 386, 387 hr; a_e at 388, 389 hr; a_e at 390, 391 hr; a_e at 392, 393 hr; a_e at 394, 395 hr; a_e at 396, 397 hr; a_e at 398, 399 hr; a_e at 400, 401 hr; a_e at 402, 403 hr; a_e at 404, 405 hr; a_e at 406, 407 hr; a_e at 408, 409 hr; a_e at 410, 411 hr; a_e at 412, 413 hr; a_e at 414, 415 hr; a_e at 416, 417 hr; a_e at 418, 419 hr; a_e at 420, 421 hr; a_e at 422, 423 hr; a_e at 424, 425 hr; a_e at 426, 427 hr; a_e at 428, 429 hr; a_e at 430, 431 hr; a_e at 432, 433 hr; a_e at 434, 435 hr; a_e at 436, 437 hr; a_e at 438, 439 hr; a_e at 440, 441 hr; a_e at 442, 443 hr; a_e at 444, 445 hr; a_e at 446, 447 hr; a_e at 448, 449 hr; a_e at 450, 451 hr; a_e at 452, 453 hr; a_e at 454, 455 hr; a_e at 456, 457 hr; a_e at 458, 459 hr; a_e at 460, 461 hr; a_e at 462, 463 hr; a_e at 464, 465 hr; a_e at 466, 467 hr; a_e at 468, 469 hr; a_e at 470, 471 hr; a_e at 472, 473 hr; a_e at 474, 475 hr; a_e at 476, 477 hr; a_e at 478, 479 hr; a_e at 480, 481 hr; a_e at 482, 483 hr; a_e at 484, 485 hr; a_e at 486, 487 hr; a_e at 488, 489 hr; a_e at 490, 491 hr; a_e at 492, 493 hr; a_e at 494, 495 hr; a_e at 496, 497 hr; a_e at 498, 499 hr; a_e at 500, 501 hr; a_e at 502, 503 hr; a_e at 504, 505 hr; a_e at 506, 507 hr; a_e at 50