

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

\*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 m<sup>2</sup>): 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

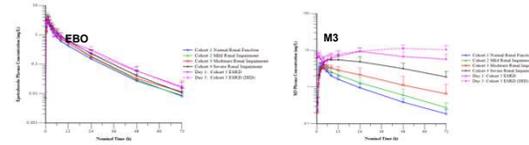
**Table 2. Demographics and Baseline Characteristics**

	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 <sup>2</sup> ), 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 <sup>2</sup> ), 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 <sub>0-72</sub> (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 <sub>0-∞</sub> (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 <sub>0-∞</sub>	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 <sub>r</sub> (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 <sub>0-72</sub> (hr*mg/L)	63.6 (25.8)	77.9 (32.8)	115 (35.9)	256 (32.0)	461 (35.1)	663 (25.5)
AUC <sub>0-∞</sub> (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 <sub>0-∞</sub>	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 <sub>0-∞</sub>	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 <sub>r</sub> (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, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 850, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, 861, 862, 863, 864, 865, 866, 867, 868, 869, 870, 871, 872, 873, 874, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 897, 898, 899, 900, 901, 902, 903, 904, 905, 906, 907, 908, 909, 910, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 923, 924, 925, 926, 927, 928, 929, 930, 931, 932, 933, 934, 935, 936, 937, 938, 939, 940, 941, 942, 943, 944, 945, 946, 947, 948, 949, 950, 951, 952, 953, 954, 955, 956,