222

Clinical and microbiological outcomes for Enterobacterales uropathogens in the Phase 3 ADAPT-PO Study of oral tebipenem pivoxil hydrobromide

Ian A. Critchley[1], Paul B. Eckburg[1], Lori Muir[1], Aaron Dane[2], Gary Moore[3], David Melnick[1], Angela K. Talley[1]

[1]Spero Therapeutics, Cambridge, MA; [2]Danestat Consulting, Macclesfield, UK; [3]Moore Computing Services, Inc., Little Rock, AR

Ian A. Critchley, PhD
Spero Therapeutics
675 Massachusetts Ave
14th Floor
Cambridge, MA 02139
E-mail: icritchley@sperotherapeutics.com

Background

Enterobacterales are frequently implicated in complicated urinary tract infection, including acute pyelonephritis (cUTI/AP) with *Escherichia coli* being the most prevalent pathogen. Extended-spectrum β-lactamase (ESBL)-producing organisms are increasing in prevalence and often co-resistant to existing oral antibiotics such as the fluoroquinolones and trimethoprim-sulfamethoxazole (TMP-SMX). Intravenous (IV) carbapenems retain antibacterial activity against most resistant Enterobacterales but require patients to be hospitalized highlighting the unmet need for new oral options with the same spectrum and potency to prevent unnecessary hospitalizations.

Tebipenem pivoxil hydrobromide (TBP-PI-HBr) is a novel oral carbapenem that was compared with IV ertapenem in the treatment of cUTI/AP in the ADAPT-PO Phase 3 clinical trial. The goal of the analyses conducted in this study was to assess the clinical response and by-pathogen microbiological responses for Enterobacterales pathogens, including those with resistant phenotypes. Published topline results of the ADAPT-PO trial showed TBP-PI-HBr was non-inferior to IV ertapenem using the sponsor pre-specified analysis.[1]

Methods

ADAPT-PO was a Phase 3 multinational, double-blind trial evaluating orally administered TBP-PI-HBr vs. IV ertapenem in 1372 hospitalized patients with cUTI/AP. Patients were randomized 1:1 to oral TBP-PI-HBr (600 mg q8h) or IV ertapenem (1 g q24h) for 7-10 days. The primary analysis population was the micro-ITT that included randomized patients with confirmed diagnosis of cUTI or AP with positive urine culture of 1 or 2 uropathogens at ≥10^5 CFU/mL. All urine and/or blood isolates were shipped to a central laboratory for identification confirmation and susceptibility testing. Clinical cure was complete resolution or significant improvement in signs and symptoms of cUTI or AP that were present at baseline and no new symptoms such that no further therapy was needed. Microbiological eradication was a reduction of baseline uropathogens(s) to <10^3 CFU/mL and negative blood culture if blood culture was positive for growth at baseline. Urine cultures were collected at baseline, Day 5, EOT, TOC and LFU. Analysis of resistant phenotypes included ESBL (ceftazidime MIC ≥2 µg/mL or ceftriaxone MIC ≥2 µg/mL if ceftazidime result was not available), fluoroquinolone non-susceptible (levofloxacin MIC ≥1 µg/mL) and TMP-SMX-resistant (TMP-SMX MIC ≥4 µg/mL). Clinical response and microbiological responses at the test-of-cure (TOC) for patients with Enterobacterales including resistant phenotypes were assessed in the microbiological intent-to-treat population (micro-ITT population) using the sponsor pre-specified analyses set forth in the protocol and statistical analysis plan.

Results

Figure 1. Baseline pathogens from urine and/or blood (micro-ITT Population)

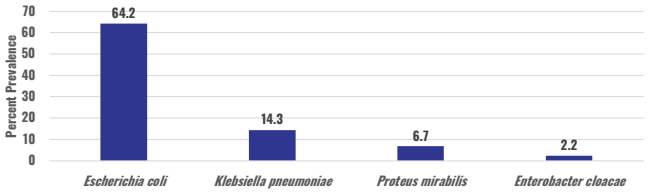

Table 1. Baseline Enterobacterales pathogens with resistant phenotypes identified from urine and/or blood (micro-ITT Population) Isolates from patients in both treatment groups resistant phenotype (%)

Urine and/or blood pathogen	Prevalence of resistant phenotype (%)		
	ESBL+	Levofloxacin-NS	TMP-SMX-R
All Enterobacterales	23.5	38.4	41.8
E. coli	17.4	29.9	37.6
K. pneumoniae	55.6	71	58.9
P. mirabilis	13.8	60.3	62.1
E. cloacae	63.2	52.6	63.2

Table 2. Minimum inhibitory concentration of study drug received by baseline pathogen (micro-ITT Population)

Organism	N	TBP MIC (µg/mL)			N	ETP MIC (µg/mL)		
		Range	MIC_{50}	MIC_{90}		Range	MIC_{50}	MIC_{90}
All Enterobacterales	416	≤0.004 - 2	0.015	0.12	402	≤0.002 - >8	0.008	0.12
E. coli	286	≤0.004 - 0.12	0.015	0.03	270	≤0.002 - 2	0.008	0.03
K. pneumoniae	53	0.015 - 1	0.03	0.25	71	0.008 - >8	0.06	2
P. mirabilis	35	0.015 - 2	0.12	0.25	23	0.008 - 0.25	0.015	0.03
E. cloacae	11	0.015 - 0.5	0.03	0.12	8	0.015 - 2	0.25	NA

Figure 2. Clinical response at TOC for TBP-PI-HBr and ETP for Enterobacterales pathogens (micro-ITT Population)

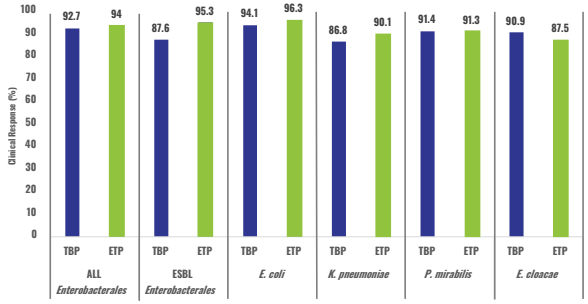

Table 3. By-pathogen microbiological response at TOC for resistant phenotypes for TBP and ETP (micro-ITT Population)

Baseline pathogen	By-pathogen microbiological response at TOC by baseline pathogen	
	TBP-PI-HBr n/N (%)	Ertapenem n/N (%)
All Enterobacterales	**249/417 (59.7)**	**265/402 (65.9)**
ESBL	58/106 (54.7)	53/86 (61.6)
Levofloxacin-NS	89/165 (53.9)	91/149 (61.6)
TMP-SMX-R	99/172 (57.6)	109/170 (64.1)
Escherichia coli	**180/287 (62.7)**	**176/270 (65.2)**
ESBL	36/60 (60.0)	25/37 (67.6)
Levofloxacin-NS	52/96 (54.2)	40/70 (57.1)
TMP-SMX-R	66/108 (61.1)	63/101 (62.4)
Klebsiella pneumoniae	**24/53 (45.3)**	**45/71 (63.4)**
ESBL	13/29 (44.8)	22/40 (55.0)
Levofloxacin-NS	16/34 (47.1)	33/54 (61.1)
TMP-SMX-R	14/27 (51.9)	29/46 (63.0)
Proteus mirabilis	**17/35 (48.6)**	**16/23 (69.6)**
ESBL	2/7 (28.6)	3/6 (50.0)
Levofloxacin-NS	11/22 (50.0)	9/13 (69.2)
TMP-SMX-R	11/25 (44.0)	8/11 (72.7)
Enterobacter cloacae	**6/11 (54.5)**	**4/8 (50.0)**
ESBL	4/6 (66.7)	3/6 (50.0)
Levofloxacin-NS	4/5 (80.0)	3/5 (60.0)
TMP-SMX-R	5/8 (62.5)	3/4 (75.0)

Summary and Conclusions

- Overall, 90.2% of patients in the micro-ITT Population were infected with Enterobacterales with *E. coli* being the most prevalent (64.2%), followed by *K. pneumoniae* (14.3%), *P. mirabilis* (6.7%) and *E. cloacae* (2.2%). (**Figure 1**)
- Among all Enterobacterales, ESBL-positive, fluoroquinolone non-susceptible (NS) and TMP-SMX-resistant phenotypes accounted for 23.5%, 38.4% and 41.8% of Enterobacterales, respectively. (**Table 1**).
- MIC_{90} values for both TBP and ETP against all Enterobacterales from both treatment groups were 0.12 µg/mL. (**Table 2**)
- At TOC, the clinical response rates for TBP and ETP and all Enterobacterales were 92.7% and 94.0%, respectively (Figure 2), and microbiological response was 59.7% and 65.9%, respectively. (**Table 3**). For *E. coli,* clinical response rates were 94.1% in the TBP group and 96.3% in the ETP group (**Figure 2**).
- Clinical response at TOC for TBP and ETP for ESBL positive Enterobacterales was 87.6% and 95.3%, respectively (**Figure 2**).
- Microbiological responses at TOC for key uropathogens and resistant phenotypes are shown in **Table 3**. For all Enterobacterales microbiological responses for TBP and ETP were 59.7% and 65.9%, respectively and for ESBL Enterobacterales were 54.7% and 61.6%, respectively. Similar microbiological response rates were observed for all *E. coli* and resistant phenotypes.
- The discordance between clinical and microbiological response at TOC is an observation consistent with other recent cUTI trials. Given the high (>87%) clinical cure rates, the majority of these cases represent asymptomatic bacteriuria.

References

1. Eckburg PB, et al. Oral tebipenem pivoxil hydrobromide in complicated urinary tract infection N. Engl. J. Med. 2022 386(14):1327-1338. doi: 10.1056/NEJMoa2105462.