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Tebipenem Pivoxil Hydrobromide: Safety and Tolerability Profile of the First Oral Carbapenem for Complicated Urinary Tract Infection and Acute Pyelonephritis

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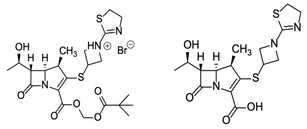
Introduction

- Tebipenem pivoxil hydrobromide (TBP-PI-HBr) is an oral carbapenem prodrug that is converted to TBP, the active moiety in body.[1,2]
- TBP is active against multi-drug resistant (MDR) pathogens, including ESBL-producing Enterobacterales and gram-negative pathogens resistant to other antibiotic classes including fluoroquinolones.[3-6]
- TBP-PI-HBr has the potential to address the unmet medical need for an oral carbapenem to treat serious infections due to MDR gram-negative pathogens in adults and children and is being development for the treatment of complicated UTI and acute pyelonephritis (AP).
- The clinical development program for TBP-PI-HBr included a randomized, double-blind, double-dummy, Phase 3 study that compared oral TBP-PI-HBr and intravenous (IV) ertapenem in patients with cUTI/AP [7] and a series of Phase 1 clinical pharmacology studies to confirm the PK and safety of TBP-PI-HBr in healthy subjects.[8-14]

Figure 1. Chemical structure of tebipenem and TBP-PI-HBR



Tebipenem Pivoxil HBr (orally bioavailable prodrug)

Tebipenem (active moiety)

Objective

- Examine the safety and tolerability of TBP-PI-HBr from results of the Phase 3 study in patients with cUTI/AP and from Phase 1 clinical pharmacology studies.

Methods

- The development program for TBP-PI-HBr included 7 Phase 1 clinical studies (Table 1).
- Except for Study SPR994-101 all studies evaluated TBP-PI-HBr 600 mg in single or repeat dose oral administration.
- Patients in the Phase 3 study were randomized to oral TBP-PI-HBr 600 mg q8h or IV ertapenem 1g q24h.
- Safety data from the Phase 3 study in patients with cUTI/AP are presented in detail, supported by data from Phase 1 studies (Table 1).

Table 1. Summary of TBP-PI-HBr Exposure in Completed Clinical Studies

Phase	Study ID	Study Type	Total Enrolled	Total Exposed to TBP-PI-HBr
1	SPR994-101	First in human SAD/MAD and food effect [8]	124	87*
1	SPR994-102	Single dose renal impairment and end-stage renal disease [9]	39	39
1	SPR994-103	Effect on intestinal microbiota [10]	30	15
1	SPR994-104	Thorough QT study [11]	24	24
1	SPR994-105	Single-dose bioequivalence and food effect study [12]	36	36
1	SPR994-106	Single-dose absorption, metabolism, excretion [13]	8	8
1	SPR994-107	Single-dose gastric drug:drug interaction [14]	20	20
3	SPR994-301	Pivotal cUTI/AP (ADAPT-PO) [7]	1,372	685
Total			1,653	914

*Of the 87 subjects, 36 received the immediate-release formulation and 51 received other time-released formulations, 75 received a single dose and 12 received repeat doses q8h over 14 days.

Results

Phase 3 Study

- Overall, 25.7% of patients with TBP-PI-HBr and 25.6% with ertapenem experienced at least one TEAE (Table 2).
- The majority of TEAEs were mild or moderate in severity.
- Severe TEAEs were uncommon, occurring in 1.5% and 1.3% of TBP PI HBr and ertapenem patients, respectively.
- Drug-related TEAEs occurred in 9.3% of patients in the TBP PI HBr group and 6.1% in the ertapenem group.

Table 2. Treatment-Emergent Adverse Events in Phase 3 cUTI Study (Safety Population)

Adverse Event Category	TBP-PI-HBr (N=685) n (%)	Ertapenem (N=687) n (%)	Overall n (%)
TEAE	176 (25.7)	176 (25.6)	352 (25.7)
Diarrhea	39 (5.7)	30 (4.4)	69 (5.0)
Headache	26 (3.8)	26 (3.8)	52 (3.8)
Nausea	10 (1.5)	6 (0.9)	16 (1.2)
Severe TEAE	10 (1.5)	9 (1.3)	19 (1.4)
Serious AE	9 (1.3)	12 (1.7)	21 (1.5)
Drug-related TEAE	64 (9.3)	42 (6.1)	106 (7.7)
Drug-related serious AE	0	2 (0.3)	2 (0.1)
TEAE leading to premature discontinuation of study drug	1 (0.1)	8 (1.2)	9 (0.7)
TEAE leading to early withdrawal from study	1 (0.1)	1 (0.1)	2 (0.1)
TEAE leading to death	0	0	0

- TEAEs were balanced between treatment groups. Only three TEAEs (diarrhea, headache, and nausea) were observed in >1% of patients in either treatment group.
- Drug related TEAEs occurred in <10% in each group; most were mild and self-limited; the only drug-related TEAE reported in over 1% of patients in either group was diarrhea (reported for 4.1% of TBP PI HBr patients and 2.5% of ertapenem patients);
- Three *C. difficile*-associated TEAEs occurred in the ertapenem group; two were serious AEs (one possibly and one probably related to the study drug), and one was a non-serious TEAE (possibly related to study drug).
- One patient who received TBP-PI-HBr and 8 who received ertapenem experienced a TEAE leading to premature discontinuation of study drug; the AE: retroperitoneal abscess reported for the TBP-PI-HBr patient was considered unrelated.
- Two patients withdrew from the study due to the TEAEs: *Klebsiella pneumoniae* sepsis in a TBP-PI-HBr patient and paravertebral cyst with ertapenem, both unrelated to drug.

Table 3. Summary of Elevated Liver Laboratory Values – Phase 3 cUTI Study (Safety Population)

Patients with Post-Baseline Liver Enzyme Elevations by Category:	TBP-PI-HBr n (%)	Ertapenem n (%)
ALT		
>3x ULN	15/684 (2.2)	9/686 (1.3)
>5x ULN	4/684 (0.6)	3/686 (0.4)
>10x ULN	2/684 (0.3)	0/686 (0.0)
AST		
>3x ULN	8/684 (1.2)	6/686 (0.9)
>5x ULN	4/684 (0.6)	2/686 (0.3)
>10x ULN	1/684 (0.1)	0/686 (0.0)
AST and ALT		
>3x ULN	7/683 (1.0)	4/686 (0.6)
>5x ULN	2/683 (0.3)	2/686 (0.3)
>10x ULN	0/683 (0.0)	0/686 (0.0)
Total Bilirubin		
>2x ULN	1/678 (0.1)	1/679 (0.1)
Laboratory Criteria for Hy's Law		
>3x ULN and Total Bilirubin >2x ULN	0/676 (0.0)	0/679 (0.0)

- The incidence of liver enzyme elevations >3x, 5x, and 10x upper limit of normal (ULN) were low in both treatment groups, and no patient met criteria for potential Hy's Law (Table 3).
- TEAEs possibly indicative of hematological disorders were reported in 7 (1.0%) patients with TBP-PI-HBr and 8 (1.2%) with ertapenem (included anemia, neutropenia, leukopenia, hemoglobin decreased, and thrombocytopenia).
- Four (0.6%) patients in each group reported TEAEs of blood creatinine increased (3 patients in the TBP-PI-HBr group and 2 patients in the ertapenem group) and renal failure (1 TBP-PI-HBr and 2 ertapenem patients).
- Overall, 33 (4.8%) TBP-PI-HBr and 39 (5.7%) ertapenem patients had a change in QTcF from baseline >60 ms.

- Enteric colonization with carbapenem-resistant Enterobacterales (CRE) was assessed for all organisms isolated from rectal swabs collected at baseline and TOC.
  - Enteric colonization (post-baseline CRE isolated from a rectal swab at the test of cure visit in patients who were negative for CRE at baseline) was low in both treatment groups.
  - 96.3% of TBP-PI-HBr patients and 95.3% of ertapenem patients who were CRE-negative at baseline remained negative at TOC.

Phase 1 Clinical Pharmacology Studies

- In the pooled Phase 1 studies, 25.6% of subjects experienced at least one TEAE, mostly mild or moderate in severity (Table 4).

Table 4. Treatment-Emergent Adverse Events in Phase 1 Clinical Pharmacology Studies (Safety Population)

	Number (%) of Subjects						
Adverse Event Category	TBP-PI-HBR <600 mg (N=42)	TBP-PI-HBR 600 mg (N=108)	TBP-PI-HBR >600 mg (N=36)	TBP-PI-HBR All Healthy (N=162)	TBP-PI-HBR Renally Impaired (N=32)	Placebo (N=49)	Overall (N=219)
TEAE	11 (26.2)	27 (25.0)	6 (16.7)	43 (26.5)	3 (9.4)	10 (20.4)	56 (25.6)
Drug-related TEAE[a]	6 (14.3)	13 (12.0)	4 (11.1)	23 (14.2)	1 (3.1)	3 (6.1)	27 (12.3)
TEAE of Severe or Worse[b]	0	0	1 (2.8)	1 (0.6)	0	1 (2.0)	2 (0.9)
Serious TEAE	0	0	0	0	0	0	0
Drug-related SAE[a]	0	0	0	0	0	0	0
TEAE leading to treatment discontinuation	0	0	0	0	0	1 (2.0)	1 (0.5)
TEAE leading to death	0	0	0	0	0	0	0

[a] Includes events with a possible or probable relationship to study drug.
[b] Includes events with severity denoted as fatal, life-threatening or disabling, or severe.
Subjects in studies with a crossover design were counted more than once in each dosing category. "Overall" group combines renally impaired subjects and all healthy subjects who received placebo and/or TBP-PI-HBr. Renally impaired subjects all received TBP-PI-HBr 600 mg. A TEAE is defined as an adverse event that started or worsened

- The most common TEAEs with TBP-PI-HBr were diarrhea and headache.
- Severe TEAEs were uncommon (0.9%), occurring in one TBP-PI-HBr subject (syncope; >600 mg dose) and one placebo subject (ALT increased).
- No subject in any of the Phase 1 studies experienced a serious AE.
- TEAEs leading to treatment discontinuation were uncommon (<1% overall).
- No subject in Phase 1 studies experienced a maximum QTcF change from baseline of >500 ms and >60 ms.

Summary and Conclusions

- In a phase 3 non-inferiority trial conducted in hospitalized patients with cUTI/AP, oral TBP PI HBr and IV ertapenem were well-tolerated.
- TEAEs were observed in approximately 26% of patients in both treatment arms; the majority were mild in severity and non-treatment-limiting.
- No increase in post-treatment enteric colonization with CRE occurred with TBP-PI-HBr.

- In pooled Phase 1 studies, the incidence of TEAEs was 25.6% and was similar across TBP-PI-HBr doses.
- No additional safety signals were observed.
- If approved, TBP-PI-HBr may provide an oral treatment option for patients with serious bacterial infections, including cUTI/AP with a safety/tolerability consistent with the carbapenem class.

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