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(Virtual)

Pharmacokinetics and Safety of Cefepime-Taniborbactam (formerly Cefepime/VNRX-5133) in Subjects with Renal Impairment

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Background

- Multidrug-resistant (MDR) Gram-negative pathogens remain a growing threat to the effective treatment of patients with serious and life-threatening infections (CDC 2019).
- Taniborbactam (fomerly VNRX-5133) is a novel, non-β-lactam, β-lactamase inhibitor, which when combined with cefepime, has activity against serine- (Class A, C, D) and metallo- (Class B) β-lactamases including epidemiologically important carbapenemases (e.g. NDM, VIM) (Hamrick 2020).
- Cefepime-taniborbactam is being developed to address the unmet medical need for difficult to treat MDR Gram-negative resistant pathogens including ESBL-producing organisms, carbapenem-resistant *Enterobacterales* and *Pseudomonas aeruginosa*. Initial development is focused on the treatment of complicated urinary tract infections.
- Prior studies have demonstrated that taniborbactam demonstrated a dose proportional PK profile following single (62.5-1500 mg) and multiple doses (250-750 q8h for 10 days) and that taniborbactam is primarily eliminated unchanged in urine (Geibel 2018). Therefore, cefepime and taniborbactam are likely to require dose adjustment in patients with renal impairment and end-stage renal disease (ESRD).

Objectives

- To evaluate the safety and PK of taniborbactam when co-administered with cefepime in subjects with mild, moderate, or severe renal impairment, and subjects with ESRD requiring dialysis compared to age-, gender-, and weight-matched subjects with normal renal function.

Methods

Study Design
- Phase 1, open-label, single dose safety and PK study of taniborbactam and cefepime in subjects with normal renal function, renal impairment, and ESRD on hemodialysis.
- Subjects with normal renal function and renal impairment received a single dose of co-administered cefepime and taniborbactam.
- ESRD subjects were co-administered cefepime and taniborbactam prior to dialysis (Period 1) and following dialysis (Period 2) separated by a 9-day washout period.

Study Treatments
- Cefepime 2g and taniborbactam 500mg were co-administered as a 2-hour IV infusion.

Study Subjects
- Age 18-80 years with a BMI of 18.5-40.0 kg/m2 with a minimum weight of 45 kg.
- Healthy subjects (Group 1):
  - No clinically relevant clinical findings based on medical history, physical examination, vital signs, lab tests, and ECG.
  - eCL_{CR} ≥ 90 mL/min by Cockcroft-Gault equation.
  - Matches to one or more subjects with renal impairment by gender, age (±10 years), and weight (±10 kg).
- Renal Impairment / ESRD subjects
  - Stable (no significant change in eGFR in previous 30 days) pre-existing renal impairment / ESRD.
  - Mild (Group 2), moderate (Group 3), and severe (Group 4) renal impairment based on MDRD calculated eGFR (60-89, 30-59, and <30 mL/min/1.73m^2, respectively), and subjects with ESRD on chronic intermittent hemodialysis (Group 5).
  - Stable comorbidities and concomitant medications for 14 days at the time of study entry.

Study Assessments
- Blood samples for cefepime and taniborbactam plasma concentration determination were collected prior to infusion and up to 96 hours (Group 1-4) and up to 72 hours (Group 5, Period 1 and 2) following co-administration of cefepime and taniborbactam.
- Urine samples were collected for up to 96 hours (Group 1-4) and up to 48 hours (Group 5, Period 1 and 2) except if anuric.
- Safety assessments included adverse events (AEs), vital signs, clinical laboratory evaluations, electrocardiograms, and physical examinations.

Pharmacokinetic Analysis
- Plasma concentrations of study drugs were determined using validated methods (LC-MS/MS).
- Pharmacokinetic parameters were calculated from individual concentration-time profiles using noncompartmental analysis (NCA) methods.
- PK parameters were summarized by renal group (normal, mild, moderate, severe, and dialysis) and treatment period (dialysis subjects only).

Results

- 33 subjects were enrolled, and all subjects completed the study
- Baseline characteristics **(Table 1)**: Most subjects were male (66.7%), white (57.6%), black or African Americans (39.4%), and not Hispanic or Latino (97%). Median age and BMI were 55.0 years and 29.5 kg/m^2, respectively.

Table 1 Baseline Characteristics

Characteristic	Normal (Group 1) N=8	Mild (Group 2 N=6	Moderate (Group 3) N=6	Severe (Group 4) N=6	ESRD (Group 5) N=7
Median Age (Range), years	45.5 (38-72)	57.5 (48-70)	64.5 (44-71)	63.0 (42-71)	53.0 (27-56)
Male, n (%)	6 (75.0)	3 (50.0)	3 (50.0)	3 (50.0)	7 (100)
Race, n (%)					
White	4 (50.0)	5 (83.3)	5 (83.3)	5 (83.3)	0
African American	3 (37.5)	1 (16.7)	1 (16.7)	1 (16.7)	7 (100)
Other	1 (12.5)	0	0	0	0
Median BMI (Range), kg/m^2	30.85 (22.8-38.9)	29.55 (26.5-35.5)	26.45 (25.0-33.6)	30.50 (20.6-34.1)	27.70 (22.8-33.9)
Mean eGFR (SD), mL/min/1.73m2*	101.81 (24.77)	74.78 (8.86)	38.78 (7.11)	22.22 (8.83)	NA

*based on MDRD equation; NA = not applicable

Pharmacokinetics
- Mean concentration-time profiles for taniborbactam and cefepime are shown in **Figures 1 and 2** respectively. With decreasing renal function, exposure of both cefepime and taniborbactam increased.
- Cefepime and taniborbactam plasma concentrations declined more slowly with decreasing renal function.
- Cefepime and taniborbactam pharmacokinetic parameters are shown in **Table 2**. For both cefepime and taniborbactam, exposures increased, and CL decreased with increasing renal impairment.
- Mean elimination half-life ($t_{1/2}$) increased for both cefepime and taniborbactam with decreasing renal function.
- Concentrations of both drugs declined faster during the on-dialysis session than during the off-dialysis session.
- The mean (SD) hemodialysis extraction ratio was 47.4% (7.7%) and 49.7% (7.1%) for cefepime and taniborbactam respectively.

Safety
- A total of 7 subjects experienced 8 treatment-emergent AEs (**Table 3**).
- All AEs were mild except jaw pain (moderate) and no discontinuation due to AEs occurred.
- No safety concerns were identified in vital signs, clinical laboratory evaluations, electrocardiograms, and physical examinations.

Figure 1 Taniborbactam Concentration-Time Profile (A) Renal Impairment Groups, (B) Dialysis Group, On and Off Dialysis

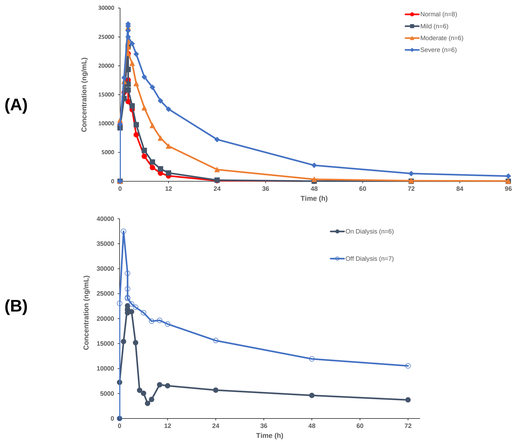

Figure 2 Cefepime Concentration-Time Profiles (A) Renal Impairment Groups, (B) Dialysis Group, On and Off Dialysis

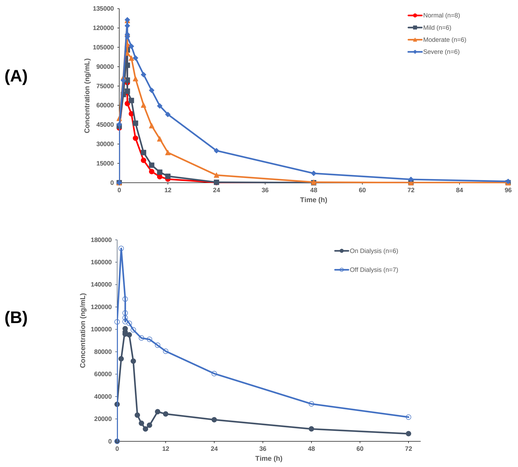

Table 2 Pharmacokinetics Parameters

Renal Function Group (eGFR range [mL/min/1.73m^2])*	Taniborbactam AUC$_{(0\text{-inf})}$ (h*μg/mL) Mean (SD)	Taniborbactam CL (L/h) Mean (SD)	Cefepime AUC$_{(0\text{-inf})}$ (h*μg/mL) Mean (SD)	Cefepime CL (L/h) Mean (SD)
Normal (≥ 90)	84.1 (9.7)	5.83 (0.66)	345.8 (45.9)	5.69 (0.75)
Mild (60-89)	97.9 (11.1)	4.99 (0.70)	419.5 (37.7)	4.64 (0.54)
Moderate (30-59)	229.8 (50.2)	2.17 (0.55)	927.9 (182.1)	2.13 (0.48)
Severe (<30)	557.5 (462.6)	1.30 (0.73)	1,891.4 (1330.1)	1.41 (0.74)

* based on MDRD equation

Table 3 Treatment Emergent Adverse Events

	Normal (Group 1) N=8	Mild (Group 2 N=6	Moderate (Group 3) N=6	Severe (Group 4) N=6	ESRD (Group 5) N=7
Abdominal Pain	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
C. difficile Infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Diarrhea	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)
Dizziness	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Drug Withdrawal Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)
Migraine	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Pain in Jaw	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)

Conclusions

- Co-administration of cefepime and taniborbactam was safe and well-tolerated; there was no trend in the incidence, type, or severity of treatment-emergent AEs with declining renal function.
- Cefepime and taniborbactam are primarily excreted unchanged in urine.
- Cefepime and taniborbactam clearance (CL) is similarly reduced with varying degrees of renal impairment.
- Dialysis removes a high fraction of both drugs.
- Dose adjustments recommended for cefepime are appropriate for taniborbactam (cefepime USPI).

References

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