Safety, tolerability and pharmacokinetics of WCK 4282 (FEP-TAZ) in healthy adult subjects

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INTRODUCTION AND PURPOSE

- WCK 4282 (FEP-TAZ) is an injectable combination of cefepime (FEP) and tazobactam (TAZ). The increased proportion of tazobactam in FEP-TAZ is likely to translate into clinically relevant synergy against AmpC and Klebsiella pneumoniae carbapenemase (KPC) strains in addition to Class A ESBL strains, as demonstrated in in-vitro studies. FEP-TAZ is being developed as a new therapeutic option mainly for the treatment of Gram-negative infections prevalent in hospital settings such as complicated urinary tract infections, nosocomial pneumonia and complicated intra-abdominal infections.
- This phase 1 clinical study was conducted to assess safety and tolerability, as well as pharmacokinetics (PK) of multiple escalating doses of intravenous WCK 4282 in healthy adult human subjects in Netherlands.

METHODS

Cohort	Number of subjects	FEP-TAZ dosage	Infusion time	Treatment duration
1	8: FEP-TAZ 2: placebo	1g FEP + 1g TAZ every 8 hours (q8h)	60 min.	7 days
2	8: FEP-TAZ 2: placebo	2g FEP + 2g TAZ every 12 hours (q12h)	90 min.	7 days
3	8: FEP-TAZ 2: placebo	2g FEP + 2g TAZ every 8 hours (q8h)	90 min.	7 days

- Physical examinations, vital signs, 12-lead ECGs, clinical safety laboratory parameters, concomitant medicantions and adverse events (including local tolerability at the injection site) were monitored throughout the study.
- PK parameters were determined for both FEP and TAZ from serial plasma and urine samples collected over a 48-hour interval on the first and last dosing days. The measured PK parameters included C_{max}, C_{last}, C_{8h} (cohorts 1 and 3 only), C_{12h} (cohort 2 only), t_{max}, t_{last}, k_{el}, t1/2, AUC_{0-t}, AUC_{0-24}, AU_{C0-inf}, %AUC, CL, Vz and Ae_{urine}.
- Concentration-time data were presented individually and using descriptive statistics by treatment. Dose proportionality was explored using a regression (power) model relating log-transformed C_{max} and AUC parameters to the log-transformed dose. Ae_{urine} was analysed descriptively.

RESULTS

STUDY SUBJECTS

Gender	Mean age	Race	Mean BMI
Males: 17 (56.7%) Females: 13 (43.3%)	31.7 years (SD=15.3)	Caucasian: 24 (80%) Asian: 2 (6.7%) African American: 1 (3.3%) Other: 3 (10%)	23.17 kg/m^2 (SD = 2.53)

Twenty-seven (90%) subjects completed the study as per protocol.

CLINICAL SAFETY

- In total, 28 subjects reported 115 treatment emergent AEs. The AEs reported were generally mild in intensity and resolved during the study. No severe events and clinically significant changes in vital signs and ECGs were reported

Safety result	Placebo q8h or q12h (N=6)	FEP-TAZ 1g+1g q8h (N=8)	FEP-TAZ 2g+2g q12h (N=8)	FEP-TAZ 2g+2g q8h (N=8)
All TEAEs	13 events in 5 (83.3%) subjects	39 events in 8 (100%) subjects	22 events in 7 (87.5%) subjects	41 events in 8 (100%) subjects
Serious AEs	-	1* in 1 (12.5%) subject	-	-
AEs probably/ likely related	-	-	-	1** in 1 (12.5%) subj.
Discontinuated subjects	1 (16.7%) AE: fever	-	1 (12.5%) AE: skin rash	1 (12.5%) Consent withdrawal

* bone fracture after discharge from study unit; not related
**increased WBC (mild)

PHARMACOKINETICS

- Descriptive statistics of AUC_{0-24} (µg*hr/mL) on Day 7 for FEP and TAZ:

Day 7 / Final Dose[1]				
Analyte	Cohort	N	Geometric mean	Range
FEP	1	8	513.9	467.0 - 631.6
	2	7	748.2	589.2 - 1058.6
	3	6	1123.9	868.9 - 1297.0
TAZ	1	8	95.3	78.1 - 113.8
	2	7	170.4	125.9 - 215.1
	3	6	259.3	149.0 - 338.4

[1] Final dose = third dose for Cohorts 1 and 3, and second dose for Cohort 2

PHARMACOKINETICS

- Descriptive statistics of plasma PK parameters of FEP:

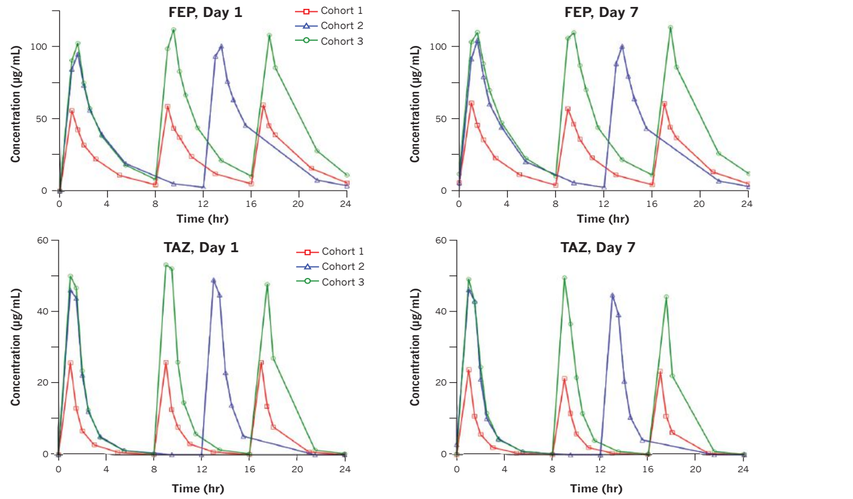
		Day 1 / Dose 1			Day 7 / Final Dose[3]		
Cohort	Parameter	N	Geometric mean	Range [2]	N	Geometric mean	Range [2]
1	AUC [1] (µg*hr/mL)	8	164.1	137.6 - 221.7	8	181.1	156.8 - 231.4
	C_{max} (µg/mL)	8	55.670	43.411 - 64.296	8	60.431	52.644 - 81.047
	T_{max}	8	-	1.09	8	-	1.08
	$t_{½}$(hr)	8	2.08	1.79 - 2.53	8	2.13	1.59 - 2.45
2	AUC[1] (µg*hr/mL)	8	334.0	249.8 - 406.8	7	389.1	307.5 - 556.7
	C_{max} (µg/mL)	8	95.361	75.338 - 110.339	7	99.531	83.554 - 125.744
	t_{max}(hr)	8	-	1.58	7	-	1.60
	$t_{½}$ (hr)	8	2.15	1.67 - 2.62	7	2.28	1.80 - 2.63
3	AUC[1] (µg*hr/mL)	8	329.3	246.2 - 379.3	6	381.3	276.2 - 432.7
	C_{max} (µg/mL)	8	102.354	78.868 - 116.946	6	112.608	85.335 - 121.142
	T_{max} (hr)	8	-	1.58	6	-	1.58
	t½ (hr)	8	1.91	1.63 - 2.16	6	2.12	1.75 - 2.54

- Descriptive statistics of plasma PK parameters of TAZ:

		Day 1 / Dose 1			Day 7 / Final Dose [3]		
Cohort	Parameter	N	Geometric Mean	Range [2]	N	Geometric Mean	Range [2]
1	AUC[1] (µg*hr/mL)	8	35.3	25.8 - 48.1	8	33.6	27.5 - 41.4
	C_{max} (µg/mL)	8	25.304	19.793 - 32.015	8	23.026	19.536 - 28.114
	T_{max}	8	-	1.09 (1.08 - 1.10)	8	-	1.08 (1.08 - 1.08)
	$t_{½}$(hr)	8	0.925	0.732 - 1.242	7	0.778	0.693 - 0.834
2	AUC[1] (µg*hr/mL)	8	87.0	64.7 - 107.4	7	83.9	62.7 - 105.8
	C_{max} (µg/mL)	8	46.263	34.477 - 56.816	7	44.047	33.470 - 54.129
	t_{max}(hr)	8	-	1.00 (1.00 - 1.58)	7	-	1.00 (1.00 - 1.02)
	$t_{½}$ (hr)	8	0.994	0.793 - 2.16	7	0.613	0.502 - 0.763
3	AUC[1] (µg*hr/mL)	8	91.8	52.7 - 118.0	6	86.2	45.0 - 114.1
	C_{max} (µg/mL)	8	49.041	32.593 - 60.646	6	42.148	22.012 - 58.327
	T_{max} (hr)	8	-	1.00 (1.00 - 1.00)	6	-	1.58 (1.57 - 1.60)
	$t_{½}$ (hr)	8	1.05	0.804 - 1.20	4	0.877	0.845 - 0.928

[1]AUC = AUC_{0-inf} (Day 1) or AUC_{0-tau} (Day 7); [2]Median (range) presented for t_{max}.; [3]Final dose = third dose for Cohorts 1 and 3, and second dose for Cohort 2

- C_{max} of FEP and TAZ were typically reached at the end of infusion in all cohorts. The trough concentrations of FEP and TAZ were all below or near to the lower limit of quantitation (LLOQ). AUCs were comparable for TAZ at Day 1 and Day 7 whereas AUCs for FEP were approximately 10-16% higher on Day 7 compared on Day 1.
- Arithmetic mean concentration vs. time curves on Day 1 and Day 7 (normal scale):



- In the dose proportionality assessments for C_{max}, Day 1 data were compared to Day 7 in cohorts 1 and 3 (q8h regimens). The 95% confidence interval (CI) on β for both days contained the value of 1.00 for FEP and TAZ, supporting dose proportionality of both FEP and TAZ Day 1 AUC_{0-inf} and Day 7 AUC_{0-tau}.
- In the dose proportionality assessments for AUC, Day 1 data were compared to Day 7 in cohort 1 (1+1g dose) and combined results of cohorts 2 and 3 (2+2 dose). The 95% CI on β for both days contained the value of 1.00, supporting dose proportionality of FEP. The geometric mean Day 7 AUC_{0-tau} and Day 1 AUC_{0-inf} values appear to be comparable for TAZ; however, the lower 95% confidence interval limits were 1.046 for Day 1 and 1.023 for Day 7, respectively. This may be due to slightly more rapid TAZ clearance rate observed with cohort 1 (mean TAZ CL: 25.2 to 34.9 L/hr, 21.3 to 24.5 L/hr, and 20.1 to 25.0 L/hr,in cohorts 1, 2, and 3, respectively).

CONCLUSIONS

- **Overall, multiple escalating doses of intravenous FEP-TAZ were safe and well tolerated by healthy adult human subjects.**
- **There was no significant accumulation of FEP and TAZ following intravenous administration of FEP-TAZ q12h or q8h for 7 days.**

DISCLOSURES

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