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Pharmacokinetics (PK) of Delafloxacin (DLX), Vancomycin (VAN), and Linezolid (LNZ) in a Phase 2 Exploratory Study in Subjects with Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

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Abstract

Background
DLX, an investigational fluoroquinolone, has activity against Gram-positive organisms including methicillin-resistant *S. aureus* (MRSA), and against fluoroquinolone-susceptible Gram-negative organisms.

Methods
A stratified, randomized, double blind, Phase 2, multicenter study was conducted to evaluate the efficacy, safety, and PK of intravenous infusion (IV) DLX compared with IV LNZ and IV VAN for the treatment of ABSSSI. Subjects were randomly assigned in a 1:1:1 ratio to DLX 300 mg every 12 hr, LNZ 600 mg every 12 hr, or VAN 15 mg/kg or 1000-1250 mg every 12 hr. Subjects were treated for 5 to 14 days based on investigator judgment. Plasma samples for PK were collected from all subjects on Day 3 ± 1 of treatment at predose, and 1, 2, 3, 5, and 12 hr after the start of infusion. Plasma samples were analyzed for DLX, LNZ, and VAN using validated LC MS/MS methods. PK parameters were calculated from plasma concentrations using noncompartmental methods.

Results
The following table presents mean (CV) pharmacokinetic parameters for DLX, LNZ, and VAN.

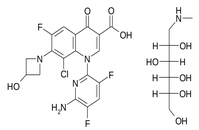
	AUClast (hr*µg/mL)	AUCinf (hr*µg/mL)	Cmax (µg/mL)	C12hr (µg/mL)
DLX	21.9 (46.9%)	23.4 (50.1%)	7.00 (47.6%)	--
LNZ	95.2 (45.8%)	106 (44.6%)	15.7 (30.9%)	--
VAN	216 (38.8%)	--	44.5 (40.2%)	9.88 (51.6%)

Conclusion
The exposures of DLX, LNZ, and VAN were determined after multiple intravenous infusions in subjects in a Phase 2 study on the treatment of ABSSSI. Exposures to each drug were in the expected range. DLX exposures were similar to those observed in previous clinical experience with this dosing regimen, which was shown to be efficacious, and support 300 mg twice daily as a dose for Phase 3 studies.

Introduction

Delafloxacin (DLX, RX-3341) is an investigational fluoroquinolone that is active against Gram-positive and –negative bacteria, including methicillin- and quinolone-resistant strains of *Staphylococcus aureus* (MRSA, QRSA). In general, the in vitro antibacterial activity of DLX is more potent than that of levofloxacin (LVX) against most quinolone-susceptible pathogens. DLX is more active than LVX against most gram-positive pathogens and, notably, is 64-fold more active than LVX against MRSA isolates, including LVX-nonsusceptible isolates. In addition, DLX has good activity against gram-negative organisms that are susceptible to LVX (1-3). DLX has demonstrated good clinical efficacy in previous Phase 2 trials in complicated skin and skin structure, community-acquired pneumonia, and bronchitis infections. A Phase 2 US study was conducted in 2011 to evaluate the safety and efficacy of DLX compared to linezolid and vancomycin in patients with acute bacterial skin and skin structure infections.

Figure 1. Structure of DLX Meglumine



Methods

Study Design
This was a stratified, randomized, double blind, Phase 2, multicenter study of IV delafloxacin compared with IV linezolid and IV vancomycin for the treatment of ABSSSI, defined as cellulitis/erysipelas, wound infection, major cutaneous abscess, or burn infection, of a minimum surface area of 75 cm^2. Subjects who met entry criteria were randomly assigned in a 1:1:1 ratio to DLX 300 mg every 12 hours, LNZ 600 mg every 12 hours, or VAN 15 mg/kg (based on actual body weight) or according to local standard of care, up to 1250 mg every 12 hours. Both DLX and LNZ were delivered as 1-hour IV infusions in a volume of 300 mL. VAN was delivered as a 2-hour IV infusion in two 300 mL bags. Treatment was given for 5 to 14 days based on the investigator's judgment.

Pharmacokinetic Sampling
Blood samples for pharmacokinetic analysis were obtained from all subjects on Day 3 (±1 day) of treatment within 2 hours before the first study drug administration, and at 1 hour, 2 hours, 3 hours, 5 hours, and 12 hours (ie, immediately prior to second dose) after the start of the first infusion. All time points had a ±10 minute window. PK samples were collected into K_2EDTA tubes.

Bioanalysis
Delafloxacin, linezolid, and vancomycin in plasma were quantitated using validated LC-MS/MS methods.

Plasma samples for delafloxacin analysis were processed by liquid-liquid extraction using 50:50 ethyl acetate:hexane. The processed samples were analyzed by an LC-MS/MS method with a calibration range of 5 to 2500 ng/mL. Plasma samples for linezolid analysis were processed by protein precipitation with 3: acetonitrile:methanol. The processed samples were analyzed by an LC-MS/MS method with a calibration range of 50 to 20,000 ng/mL. Plasma samples for vancomycin analysis were processed by solid phase extraction with STRATA-X-C extraction plates. The processed samples were analyzed by an LC-MS/MS method with a calibration range of 10 to 5000 ng/mL.

Noncompartmental Pharmacokinetic Analysis
Plasma concentration data for delafloxacin, linezolid, and vancomycin were analyzed by noncompartmental methods using SAS, Version 9.2. Pharmacokinetic parameters determined included Cmax, Tmax, Cmin, AUClast, AUCinf, T1/2, CL and Vz. Actual sample times were used. Certain samples and profiles were identified as pharmacokinetically implausible and excluded from calculations of means.

Results

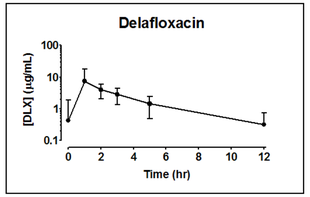
Table 1. Mean Plasma Concentrations for Delafloxacin, Linezolid and Vancomycin

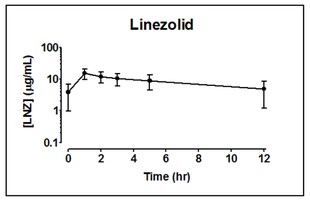
Delafloxacin						
Time (hr)	Mean	Std Dev	Geometric Mean	Min	Median	Max
0	0.42	1.44	0.20	0.03	0.20	11.8
1	6.30	3.89	N/A	0.00	6.43	23.2
2	3.98	1.91	3.54	0.42	3.53	9.81
3	2.85	1.54	2.46	0.11	2.51	8.65
5	1.44	0.97	1.11	0.03	1.30	5.54
12	0.33	0.42	0.21	0.03	0.21	2.84

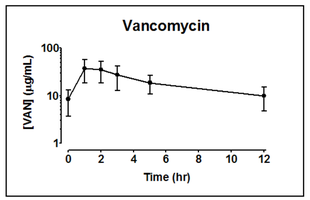
Linezolid						
Time (hr)	Mean	Std Dev	Geometric Mean	Min	Median	Max
0	3.86	2.91	N/A	0.00	3.20	12.9
1	15.2	5.48	13.9	2.02	14.9	27.9
2	12.0	4.53	11.1	1.92	11.3	24.8
3	10.5	4.38	9.56	2.05	9.80	23.9
5	8.90	4.36	7.63	0.24	7.94	20.2
12	4.82	3.59	3.47	0.08	3.83	18.8

Vancomycin						
Time (hr)	Mean	Std Dev	Geometric Mean	Min	Median	Max
0	8.50	4.82	7.32	0.95	7.29	25.6
1	37.6	18.9	33.2	4.19	34.7	132
2	35.3	16.8	N/A	0.00	33.5	91.9
3	27.2	14.3	24.0	2.25	24.8	111
5	18.7	7.85	17.0	2.49	17.6	49.1
12	9.88	5.10	8.72	2.36	8.59	28.5

Figure 2. Mean (±Std Dev) Plasma Concentrations for Delafloxacin, Linezolid and Vancomycin







Results

Table 2. Mean Plasma Pharmacokinetic Parameters for Delafloxacin, Linezolid and Vancomycin

Delafloxacin								
	AUCinf (hr*ug/mL)	AUClast (hr*ug/mL)	Cmax (ug/mL)	Cmin (ug/mL)	Tmax (hr)	T1/2 (hr)	Clearance (L/hr)	Vz (L)
N	57	70	70	70	70	57	57	57
Mean	23.4	21.9	7.00	0.20	1.20	2.40	15.5	52.0
Std Dev	11.7	10.3	3.34	0.26	0.41	0.52	7.01	24.7
CV%	50.1	46.9	47.6	119.3	33.8	21.8	45.3	47.6
Min	7.50	7.2	1.90	0.00	0.80	1.30	3.67	20.5
Median	21.4	20.4	6.80	0.20	1.00	2.40	14.0	46.6
Max	81.8	72.4	23.2	1.7	3.00	3.90	40.1	158

Linezolid								
	AUCinf (hr*ug/mL)	AUClast (hr*ug/mL)	Cmax (ug/mL)	Cmin (ug/mL)	Tmax (hr)	T1/2 (hr)	Clearance (L/hr)	Vz (L)
N	42	62	62	62	62	42	42	42
Mean	106	95.2	15.7	3.70	1.20	4.80	7.14	43.1
Std Dev	47.3	43.6	4.86	2.88	0.63	1.59	4.01	12.8
CV%	44.7	45.8	30.9	78.6	50.2	33.0	56.2	29.8
Min	30.4	23.7	6.20	0.00	0.60	2.10	2.80	23.0
Median	98.8	87.6	15.5	2.70	1.00	4.90	6.07	40.1
Max	214	214	27.9	12.9	5.00	7.40	19.8	79.6

Vancomycin								
	AUCinf (hr*ug/mL)	AUClast (hr*ug/mL)	Cmax (ug/mL)	Cmin (ug/mL)	Tmax (hr)	T1/2 (hr)	Clearance (L/hr)	Vz (L)
N	35	88	88	88	88	35	35	35
Mean	267	216	44.5	8.10	1.80	5.00	5.83	40.6
Std Dev	88.6	84.0	17.9	4.50	1.01	0.92	1.83	9.70
CV%	33.2	38.9	40.2	55.2	56.2	18.3	31.4	23.9
Min	124	36.0	5.60	1.00	-1.40	3.30	3.26	26.0
Median	247	193	41.5	7.00	1.90	5.00	5.43	38.9
Max	485	472	132	25.1	6.00	6.70	10.1	62.9

Conclusions

- Delafloxacin exposures were similar to those observed in previous clinical experience with this dosing regimen, which was shown to be efficacious, and support 300 mg twice daily as a dose for Phase 3 studies.
- Intersubject variability in delafloxacin exposure was moderate.
- Linezolid and vancomycin exposures were within their expected ranges.

References

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