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Pharmacokinetics of WCK 2349 in Patients with Complicated Skin & Soft Tissue Infections (cSSTIs) Caused by Gram Positive Bacteria Including MRSA

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Background & Objective

- The global spread of methicillin resistant *Staphylococcus aureus* (MRSA) in hospital and, more recently, in community is an unmet medical need [1,2].
- WCK 2349, a novel fluoroquinolone, is being developed by Wockhardt as an oral anti- MRSA agent
- Objective: To evaluate the pharmacokinetics (PK) of WCK 2349 after multiple oral dosing in selected subjects with cSSTIs caused by Gram positive bacteria including MRSA

Data & Methodology

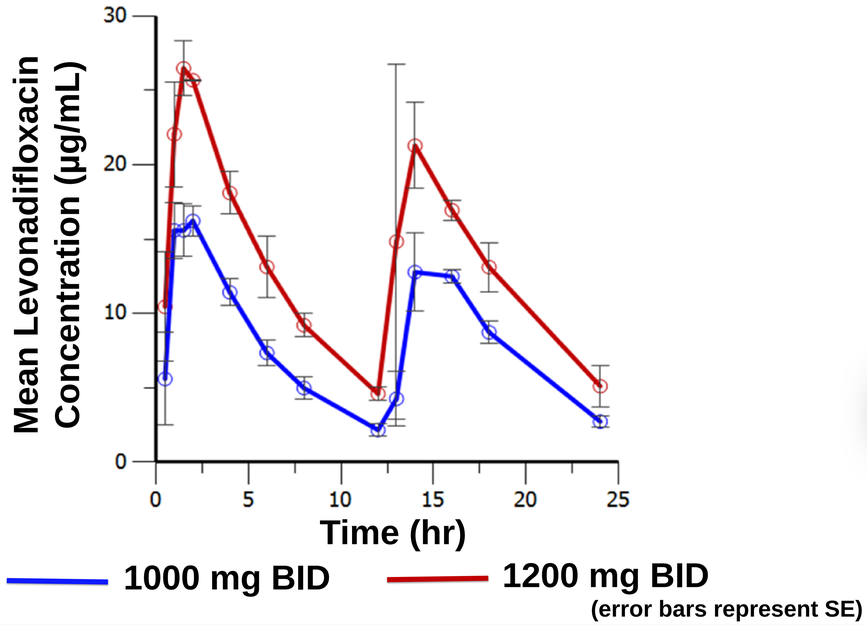
- A phase II open label, parallel, randomized, multi-center clinical trial to evaluate safety and efficacy of oral WCK 2349 (1000 mg BID and 1200 mg BID) in the treatment of cSSTIs caused by gram positive bacteria, including MRSA was conducted in 60 subjects
- The PK data was available from 5 subjects administered 1000 mg BID and 2 subjects administered 1200 mg BID
- Fourteen venous samples were collected in each subject i.e. 30 minutes prior to dosing and then 0.5, 1, 1.5, 2, 4, 6, 8,12, 13, 14, 16, 18 and 24 hours after the 8th dose (98 observations)
- WCK 2349 converts to levonadifloxacin as the active drug *in vivo*
- Non compartmental analysis was conducted in Phoenix WinNonlin version 6.4 to characterize PK of oral WCK 2349

Results

Table 1: Mean PK Parameters of Levonadifloxacin

Parameter	Units	Dose Level			
		1000.00 mg (n=5)		1200.00 mg (n=2)	
		Mean	SD	Mean	SD
C_{max}	µg/mL	17.80	3.67	27.07	1.90
C_{min}	µg/mL	2.38	0.95	4.61	0.59
T_{max}	hr	1.50	0.50	1.75	0.35
$AUC_{(0-24)}$	µg·hr/mL	190.58	41.98	311.84	3.72
$AUC_{(0-12)}$	µg·hr/mL	98.23	22.66	159.84	7.99
$AUC_{(12-24)}$	µg·hr/mL	92.35	20.21	152.00	4.27
λ_z	1/hr	0.19	0.04	0.15	0.04
$t_{1/2}$	hr	3.74	0.69	4.73	1.23
Clearance/F	L/hr	10.84	3.59	7.52	0.38
Volume of distribution/F	L	56.01	6.95	50.96	10.78
Accumulation Ratio		1.13	0.05	1.21	0.11

Figure 1: Mean Levonadifloxacin concentration-time profiles



Conclusions

- Levonadifloxacin appears rapidly in plasma with a T_{max} of 1.5-1.75 hrs
- More than dose proportional pharmacokinetics was observed. The maximum mean plasma concentrations (C_{max}) of levonadifloxacin increased from 17.8 µg/mL for 1000 mg to 27.1 µg/mL for 1200 mg. A 20% increase in dose resulted in a 59% increase in mean C_{max}. Similarly, $AUC_{(0-12)}$ increased by 63% with a dose increase from 1000 to 1200 mg BID
- Apparent volume of distribution is similar at two dose levels while the apparent clearance decreased from 10.8 to 7.5 L/h with increase in dose
- Limited PK data (N=2) available for 1200 mg BID dose level. Therefore, the results should be interpreted with caution
- The terminal half-life was short, 3.7 to 4.7 h. Terminal elimination half-life ($t_{1/2}$) is similar between the two doses
- The accumulation with a BID dosing regimen was minimal (13 to 21%) due to short half-life
- Both doses were well tolerated

References

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2. Harris, S. R. et al. Evolution of MRSA during hospital transmission and intercontinental spread. Science ***327,*** *469–474 (2010).*