Poster A-18

CHARACTERIZATION OF ORITAVANCIN PHARMACOKINETICS (PK) IN PLASMA AND BLISTER FLUID IN NORMAL HEALTHY VOLUNTEERS

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ABSTRACT

Background: Oritavancin is a novel glycopeptide antibiotic currently being developed for the treatment of complicated skin/skin structure infections (cSSSI), including those caused by multi-drug resistant Gram-positive pathogens. The disposition of oritavancin in skin structures was investigated using a cantharide-induced blister fluid model. **Methods:** 16 healthy male volunteers (8/dose group) received oritavancin 200 mg QD for three days (Grp A) or 800 mg as one single dose (Grp B). Grp A plasma, and exudates from blister samples, were collected on Days 3, 4, 7, 9, and 12, and on Days 3, 4, 7, and 9, respectively. Grp B samples were collected on Days 1, 2, 5, 7, and 10, and on Days 1, 2, 5, and 7, respectively. Drug concentration was determined using a LC/MS/MS assay and noncompartmental PK analysis was performed to generate parameter estimates for each group in both plasma and blister fluid. Differences between treatment groups in $AUC_{blister\ fluid}/AUC_{plasma}$ ratios were evaluated using a *t*-test (α=0.05). **Results:** Mean (SD) PK parameter estimates for plasma and blister fluid in each Grp are presented below (see table). Mean (SD) $AUC_{blister\ fluid}/AUC_{plasma}$ ratios at 24 h were 0.190 (0.052) and 0.182 (0.062) for Grps A and B, respectively ($p = 0.791$). Overall, oritavancin was well tolerated. **Conclusions:** To place these results in a clinical context, the oritavancin MIC_{90} of *S. aureus* is 2 µg/mL. Following administration of both dosing regimens, mean oritavancin concentrations in blister fluid exceed the MIC_{90} of *S. aureus* by approximately 2- to 5.5-fold at 12 h and 1.5- to 3-fold at 24 h. These results support the potential use of oritavancin for the treatment of cSSSI.

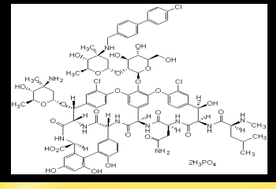
PK Parameters Mean (SD)	Plasma		Blister	
	200 mg QD x 3d	800 mg x 1	200 mg QD x 3d	800 mg x 1
C_{max} (µg/mL)[a]	46.2 (10.7)	137 (28.6)*	5.85 (3.05)	12.2 (4.70)*
t_{max} (h)	1.00	1.50	10.0 (6.05)	9.50 (3.67)
C_{12} (µg/mL)	17.2 (4.42)	36.2 (10.8)	3.90 (1.53)	11.4 (4.90)
C_{24} (µg/mL)	10.3 (2.99)	19.5 (7.17)	3.12 (1.37)	6.28 (3.31)
AUC_{0-24} (µg*h/mL)[a]	457 (99.4)	1111 (316)*	90.7 (35.7)	208 (76.7)*
AUC_{0-t} (µg*h/mL)[a]	1146 (277)	2267 (762)*	NC	NC

[a]PK parameter was tested for a difference between treatment groups
*statistically significant ($p < 0.005$)
NC – not calculated

INTRODUCTION

- **Oritavancin**
  - novel semi-synthetic glycopeptide antibiotic currently being developed for the treatment of complicated skin and skin structure infections (cSSSI)
  - bactericidal against clinically relevant gram-positive pathogens including those resistant to available antibiotics (*S. aureus* and *Enterococcus* spp., including methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci (VRE) strains)
- **Pharmacokinetics**
  - highly lipophilic due to its physicochemical properties
  - displays triexponential disposition
    - α-, β- (mainly tissue distribution), and γ- (mainly slow elimination) phases
  - no evidence of metabolism in animals
  - linear pharmacokinetics within the dose range of 0.5 to 9.0 mg/kg (35 to 600 mg)
  - approximately 86 to 90% bound to human plasma proteins
  - approximately 5% and 1% of the dose is excreted in urine and feces, respectively, after two weeks following a single dose

Figure 1. Structure of Oritavancin



OBJECTIVES

- Characterize the pharmacokinetics of oritavancin in both plasma and skin blister fluid using a cantharidin-induced skin blister model
- Provide support for the dose selection for cSSSI in the Phase III trials

METHODS

Prior to oritavancin administration, seven cantharide blisters were induced on the forearm of each subject
--0.2 mL of 0.25% cantharidin ointment was applied to forearms
--evening prior to the 3rd dose of 200 mg (Group A)
--evening prior to the 800 mg dose (Group B)

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After 12-14 hours, excess ointment was removed and blisters were sprayed with plastic dressing to maintain integrity

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Oritavancin was administered as an IV infusion
--200 mg over 60 minutes for three days
--800 mg over 90 minutes (single dose)

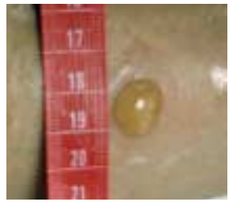
↓

Plasma and blister exudate samples were collected at various timepoints
--0.5, 1, 2, 4, 8, 12, 24, 96, 144, and 216 (plasma only) hours following the last dose

↓

Oritavancin concentrations were quantified utilizing an LC/MS/MS assay
Detection limits:
1.25 µg/mL for blister fluid
0.075 µg/mL for plasma

Figure 2. Cantharidin-induced blister 12 hours after application 0.25% ointment



METHODS (Continued)

Pharmacokinetic Analysis

Noncompartmental Analysis
--performed using WinNonlin® Pro 4.0
---generate PK parameters for each oritavancin dose group

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Parameters estimated include C_{max}, t_{max}, C_{12}, C_{24}, AUC_{0-24}, and AUC_{0-t}

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Statistical Analysis
--90% Confidence Intervals were constructed for C_{max}, AUC_{0-24}, and AUC_{0-t}
--compare oritavancin exposure in plasma and blister fluid for both dose groups

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Ratio of $AUC_{blister\ fluid}/AUC_{plasma}$
--comparison of the 200- and 800-mg dose groups
--evaluated using a *t*-test (α=0.05)

RESULTS

Figure 3. Oritavancin Pharmacokinetics in Plasma and Blister Fluid Following the Third Dose of 200 mg

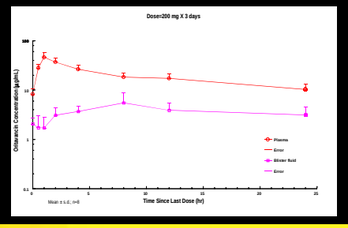

Figure 4. Oritavancin Pharmacokinetics in Plasma and Blister Fluid Following the 800-mg Dose

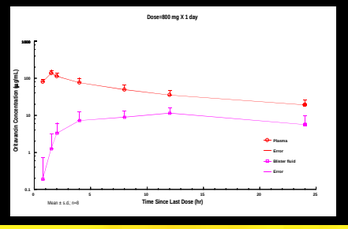

Table 1. Summary Statistics for Noncompartmental PK Parameters for Oritavancin in Plasma and Blister Fluid

PK Parameters Mean (SD)	Plasma		Blister Fluid	
	200 mg QD x 3d	800 mg x 1	200 mg QD x 3d	800 mg x 1
C_{max} (µg/mL)[a]	46.2 (10.7)	137 (28.6)*	5.85 (3.05)	12.2 (4.70)*
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RESULTS (Continued)

- Total oritavancin exposure in blister fluid at 24 h was approximately 19% of that in plasma (both dose groups).
- For the 200 mg and 800 mg doses, mean C_{max} was 8- and 11-fold higher in plasma compared with that in blister fluid, respectively.
- Mean C_{24}, in plasma, was approximately 22% and 14% of the C_{max} for the 200- and 800-mg dose groups, respectively.
- Mean oritavancin concentrations in blister fluid exceed the MIC_{90} of *S. aureus* (2 µg/mL) by 2- to 5.5-fold at 12 h and 1.5- to 3-fold at 24 h.

DISCUSSION

- **Finding I:**
  - Total-drug oritavancin exposure in blister fluid was approximately 19% of that in plasma, regardless of dosing regimen.
  - Modest accumulation was observed in the presence of inflammation.
    - Assuming $C_{blister\ fluid} \sim C_u$ (unbound) and approx. 13% of oritavancin unbound in plasma (Rowe and Brown, ICAAC Poster A-2193, 2001)
      - 200 mg:
        - $AUC_{blister\ fluid}/AUC_{plasma} = 0.19$
        - $AUC_{blister\ fluid}/AUC_{free\text{-}plasma} = 1.5$
- **Finding II:**
  - For either oritavancin regimen (200 mg x 3 days or 800 mg x 1 day), AUC_{0-24}:MIC and C_{max}:MIC ratios associated with *in vivo* efficacy are generally met or exceeded in inflammatory blister fluid.
    - Since oritavancin displays a concentration-dependent pattern of bactericidal activity *in vitro* against a wide variety of pathogens commonly associated with cSSSI, the C_{max}:MIC and AUC:MIC ratios should be the best predictors for *in vivo* efficacy.
      - free drug AUC_{0-24}:MIC =13.6
      - free C_{max}:MIC = 3.36
        - associated with a 99.9% reduction in bacterial density (Boylan et al., AAC 2003; 47:1700.)
      - for the 200-mg regimen, the total mean AUC_{0-24} in blister fluid was 90.7 µg*h/mL and the mean C_{max} was 5.85 µg/mL
  - Assumption I: drug in blister fluid is unbound to proteins
    - Given that the MIC_{90} of *S. aureus* to oritavancin is 2.0 µg/mL,
      - AUC_{0-24}:MIC_{90} = 45.3
      - C_{max}:MIC_{90} = 2.93
  - Assumption II: drug exposure in blister fluid is similar to the free-drug exposure in plasma
    - AUC_{0-24}:MIC_{90} = 29.7
    - C_{max}:MIC_{90} = 3.0

CONCLUSIONS

- Together, these findings support the selection of the 200-mg oritavancin once daily regimen and a potential therapeutic modality for cSSSI.
- Drug exposure in blister fluid also may form the basis for future clinical development of the 800-mg dose.

ACKNOWLEDGMENTS

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