1954

# Lack of Effect of Oritavancin on Warfarin Pharmacokinetics in Healthy Adult Subjects

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## Abstract

**Background.** Oritavancin (ORI) is a novel semisynthetic lipoglycopeptide antibiotic administered as a single intravenous (IV) dose for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA). A previous screening study using a cocktail design showed that warfarin clearance may be reduced with a single dose of ORI. Since warfarin is a drug with a narrow therapeutic index and some patients with ABSSSI may receive ORI while on warfarin treatment, this study was conducted to determine warfarin PK at varying intervals following a single ORI dose.

**Methods.** This was an open-label study evaluating the effects of ORI on the pharmacokinetics (PK) of warfarin in 36 healthy subjects enrolled in 3 cohorts at a single center. Subjects were administered with a single 25-mg oral dose of warfarin in the first treatment period of the study. On Day 8, the beginning of the second period of the study, subjects received a single 1200-mg IV infusion of ORI over 3 hours. Warfarin was administered with ORI (Cohort 1), 24 hours after ORI (Cohort 2), or 72 hours after ORI (Cohort 3). Serial blood samples were collected up to 144 hours post-warfarin dose to assess warfarin PK profiles (measured as S-warfarin) alone and when co-administered with ORI. The effect of ORI on warfarin exposure was evaluated within each cohort by comparing the S-warfarin PK parameters of $C_{max}$, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ using 90% confidence intervals for the geometric mean ratios.

**Results.** The 90% CIs lie completely within the range of 80% to 125%; thus, ORI had no effect on the PK of warfarin for up to 72 hours after the start of ORI infusion. Overall, ORI infusion, when administered with warfarin, was generally well tolerated and no AEs of bleeding were reported. There were no clinically meaningful changes in clinical labs, vital signs, 12-lead ECG results, or physical examination findings.

**Conclusions.** ORI did not affect the PK of warfarin when it was administered concurrently with and up to 72 hours after the start of an ORI infusion and no signs of bleeding were observed. Thus, ORI may be considered for use in patients receiving warfarin without any concern for interaction.

## Introduction

Oritavancin is a novel semisynthetic, lipoglycopeptide antibiotic that has been approved by the Food and Drug Administration (FDA) for the treatment of adult subjects with ABSSSIs caused by susceptible isolates of designated Gram-positive microorganisms including methicillin resistant *S. aureus* (1).

In a cocktail type drug-drug interaction (DDI) study (TMC-ORI-12-03), examining the effect of oritavancin on plasma S-warfarin pharmacokinetics when administered as part of the Cooperstown cocktail to screen for PK interactions among different substrates, oritavancin was found to be a weak inhibitor of cytochrome P450 (CYP) 2C9 based on a 31% increase (90% CI [1.294, 1.345]) in the systemic exposure of S-warfarin (2). However, this screening study used a cocktail approach where all the substrate drugs were given simultaneously, and did not examine the effects of oritavancin on a single agent, nor the effect of time after a single dose in a dedicated DDI study design

Since warfarin is a drug with a narrow therapeutic index and some patients with ABSSSI may receive oritavancin while on warfarin treatment, this study was conducted to determine the magnitude and duration of this interaction to determine if an adjustment to warfarin dosing was needed, by assessing the effects of a single 1200 mg IV infusion of oritavancin on warfarin pharmacokinetics.

## Methods

This was a Phase I, open-label study evaluating the effects of oritavancin on the pharmacokinetics of warfarin on 36 healthy subjects (3 cohorts of 12 healthy subjects in each cohort) enrolled at a single study center. Study was designed in accordance with FDA guidance document on drug-drug interactions (3).

Healthy volunteer subjects provided written informed consent before any study-specific procedure was performed at the Screening Visit. Subjects had baseline procedures completed within 24 hours prior to dosing. The subject also had a PK sample collected on Day 1 at time-point 0 (just prior to the warfarin administration). Subjects were administered a single 25-mg oral dose of warfarin in the first treatment period of the study. On Day 8, the beginning of the second period of the study, subjects received a single 1200-mg IV infusion of ORI over 3 hours. Warfarin was administered with ORI (Cohort 1), 24 hours after ORI (Cohort 2), or 72 hours after ORI (Cohort 3). Serial blood samples were collected up to 144 hours post-warfarin dose to assess warfarin PK profiles (measured as S-warfarin) alone and when co-administered with oritavancin due to long (245 hours) terminal half-life of the latter (4).

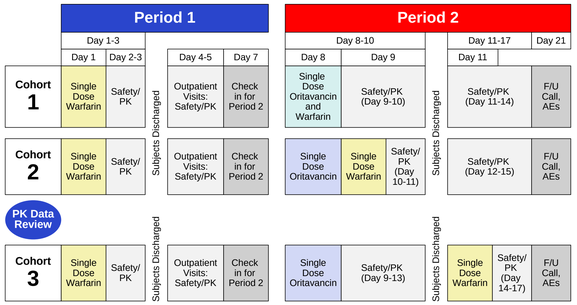
Pharmacokinetic parameters were calculated using noncompartmental methods and actual sampling times were used in all computations. The effect of ORI on warfarin exposure was evaluated within each cohort by comparing the S-warfarin PK parameters of $C_{max}$, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ using 90% confidence intervals for the geometric mean ratios.

All PK analyses will be performed using Phoenix® WinNonlin® version 6.3 or later. All statistical analyses will be conducted using SAS® version 9.3 or later using procedures appropriate for the particular analysis.

For Cohorts 1, 2, and 3, at the 3-hour postdose timepoint, the subjects had blood collected for measurement of plasma S-warfarin. The subjects had these samples collected again at 6, 12, 24, 36, 48, 72, 96 and 144 hours after the start of S-warfarin.

## Methods

### Study Design




## Results

### Table 1. Summary of S-Warfarin Plasma Pharmacokinetic Parameters by Cohort (PK Evaluable Population)

| | Cohort 1 (Mean (CV%) | | Cohort 2 Mean (CV%) | | Cohort 3 Mean (CV%) | |
|---|---|---|---|---|---|---|
| **Parameter (units)** | **Period 1 (n = 11)** | **Period 2 (n = 11)** | **Period 1 (n = 11)** | **Period 2 (n = 11)** | **Period 1 (n = 12)** | **Period 2 (n = 12)** |
| **$C_{max}$ (ng/mL)** | 1155.3 (36.4) | 1152.2 (40.6) | 1278.6 (25.1) | 1299.9 (21.5) | 1362.5 (17.1) | 1280.3 (17.5) |
| **$T_{max}$[a] (h)** | 3.000 (3.00, 6.00) | 3.080 (3.01, 6.00) | 3.000 (3.00, 3.04) | 3.000 (3.00, 24.00) | 3.000 (3.00, 6.00) | 3.000 (3.00, 3.00) |
| **$AUC_{0\text{-last}}$ (h*ng/mL)** | 47963.5 (37.9) | 46228.2 (39.3) | 52454.6 (28.1) | 59894.5 (35.4) | 52386.3 (29.6) | 55560.1 (31.2) |
| **$AUC_{0\text{-inf}}$ (h*ng/mL)** | 50870.6 (37.5) | 48802.2 (39.2) | 58157.8 (33.2) | 66079.3 (40.0) | 56586.8 (32.5) | 61160.1 (35.4) |
| **$\lambda_z$ (h)** | 0.02029 (NA) | 0.02070 (NA) | 0.01847 (NA) | 0.01890 (NA) | 0.01948 (NA) | 0.01842 (NA) |
| **$t_{1/2}$ (h)** | 34.501 (NA) | 33.813 (NA) | 39.629 (NA) | 38.561 (NA) | 36.551 (NA) | 39.113 (NA) |

CV%: percent coefficient of variation; NA: not applicable; PK: pharmacokinetic

[a] $T_{max}$ is presented as median (minimum, maximum)

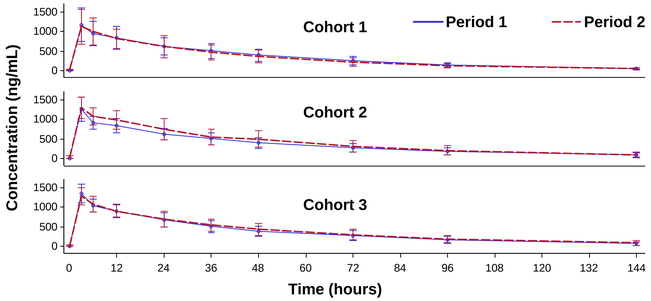
**Cohort 1** Period 1: received warfarin 25 mg and Period 2: concurrently received a single 25-mg warfarin dose at the start of the oritavancin infusion.
**Cohort 2** Period 1: received warfarin 25 mg and Period 2: received a single 25-mg warfarin dose 24 hours after the start of the oritavancin infusion.
**Cohort 3** Period 1: received warfarin 25 mg and Period 2: received a single 25-mg warfarin dose 72 hours after the start of the oritavancin infusion.

### Table 2. Summary of Effect of Oritavancin on the Pharmacokinetics of S-Warfarin: Point Estimates in Period 2 (S-warfarin + Oritavancin) Relative to Period 1 (S-warfarin Alone) and 90% Confidence Intervals

| | Point Estimates (90% Confidence Interval) | | |
|---|---|---|---|
| **Parameter (units)** | **Cohort 1** | **Cohort 2** | **Cohort 3** |
| **$C_{max}$ (ng/mL)** | 98.74 (94.982, 102.638) | 102.03 (97.260, 107.026) | 93.88 (88.891, 99.141) |
| **$AUC_{0\text{-last}}$ (h*ng/mL)** | 95.59 (91.984, 99.331) | 111.75 (106.345, 117.420) | 105.54 (93.742, 118.821) |
| **$AUC_{0\text{-inf}}$ (h*ng/mL)** | 95.18 (91.399, 99.116) | 111.07 (105.925, 116.461) | 107.12 (93.227, 123.073) |

## Results

### Figure 1. Mean ±SD S-Warfarin Concentration (ng/mL) Time Profile by Cohort, Linear Scale (PK Evaluable Population)




**Cohort 1** Period 1: received warfarin 25 mg and Period 2: concurrently received a single 25-mg warfarin dose at the start of the oritavancin infusion
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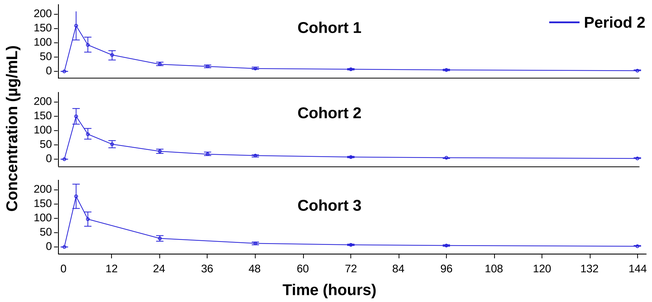
**Cohort 3** Period 1: received warfarin 25 mg and Period 2: received a single 25-mg warfarin dose 72 hours after the start of the oritavancin infusion

### Figure 2. Mean ± SD Oritavancin Concentration (µg/mL) Time Profile, Linear Scale (PK Evaluable Population)



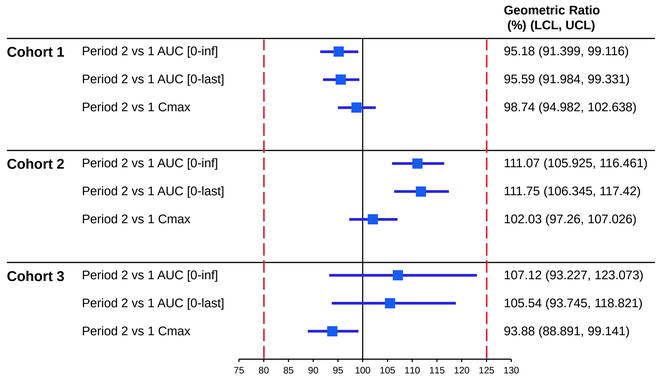

**Cohort 1** Period 1 received warfarin 25 mg and Period 2: concurrently received a single 25-mg warfarin dose at the start of the oritavancin infusion.
**Cohort 2** Period 1: received warfarin 25 mg and Period 2: received a single 25-mg warfarin dose 24 hours after the start of the oritavancin infusion.
**Cohort 3** Period 1: received warfarin 25 mg and Period 2: received a single 25-mg warfarin dose 72 hours after the start of the oritavancin infusion.

### Statistical Analysis of Drug-Drug Interactions

The effect of oritavancin on the pharmacokinetics of warfarin was evaluated within each cohort by comparing the S-warfarin PK parameters $C_{max}$, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$. The point estimate of the ratio of the PK parameter following Period 2 (S-warfarin in combination with oritavancin) relative to Period 1 (S-warfarin alone) and the 90% CIs are presented in Table 2.

The same information is presented graphically using Forrest plot in Figure 3 as recommended in the FDA guidance "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations, February 2012". The 90% CIs lie completely within the range of 80.00% to 125.00%; thus, oritavancin had no effect on the pharmacokinetics of S-warfarin. The lack of an effect was demonstrated when warfarin was administered concurrently with oritavancin, or up to 72 hours after the start of the oritavancin infusion.

### Figure 3: The Effect of Oritavancin on S-Warfarin Pharmacokinetics Using Geometric Mean Ratios and 90% Confidence Interval of Geometric Mean Ratios (PK Evaluable Population)




**Cohort 1** Period 1: received warfarin 25 mg and Period 2: concurrently received a single 25-mg warfarin dose at the start of the oritavancin infusion.
**Cohort 2** Period 1: received warfarin 25 mg and Period 2: received a single 25-mg warfarin dose 24 hours after the start of the oritavancin infusion.
**Cohort 3** Period 1: received warfarin 25 mg and Period 2: received a single 25-mg warfarin dose 72 hours after the start of the oritavancin infusion.

## Summary and Conclusions

- Oritavancin did not affect the PK of S-warfarin when it was administered concurrently with and up to 72 hours after the start of a single oritavancin infusion.
- Oritavancin and warfarin were well tolerated and no signs of bleeding were observed in this single dose design with both drugs in normal subjects
- These data indicate that oritavancin does not affect the pharmacokinetics of warfarin; thus individualized warfarin dosage should be determined based on usual considerations, including monitoring for bleeding and monitoring of PT/INR in samples collected at least 12 hrs following a single oritavancin dose.

## Disclosures

This study was sponsored by The Medicines Company. S. E. Bellibas, B. Lohse, K. Fusaro, J. Loutit and M.N. Dudley are employees of The Medicines Company. C. Sanabria is an employee of Spaulding Clinical.

## References

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