CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206334Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 206-334	Submission Date(s): 12/06/13
Drug	Oritavancin Diphosphate
Trade Name	ORBACTIV (proposed)
OCP Reviewer	Ryan P. Owen, Ph.D.
OCP Team Leader	Kimberly Bergman, Pharm.D.
PM Team Leader	Jeffry Florian, Ph.D.
OCP Division	DCP4
OND division	DAIP
Sponsor	The Medicines Co.
Relevant IND(s)	IND 51,292
Submission Type; Code	Original New Drug Application (New Molecular Entity); Resubmission/After Withdrawal
Formulation; Strength(s)	Single-use, 50 mL clear glass vials containing 400 mg oritavancin sterile lyophilized powder
Indication	For the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible organisms
Dosage and Administration	1200 mg IV on Day 1 infused over 3 hours

Table of Contents

Abbreviations
ABSSSI: acute bacterial skin and skin structure infection
AM: alveolar macrophages
$AUC_{0\text{-}72}$: area under plasma concentration-time for the first 72 hours
AUC: area under plasma concentration-time curve
$AUC_{0\text{-}24}$: area under plasma concentration-time curve over 24 hours
C_{max}: maximum observed plasma concentration
CE: clinically evaluable analysis population
CI: confidence interval
CL: plasma clearance
CL_R: renal clearance
CR: complete response
CrCL: creatinine clearance
cSSSI: complicated skin and skin structure infections
CV: coefficient of variation
CYP450: cytochrome P450
ECE: early clinical evaluation – composite endpoint used in SOLO I and SOLO II, assessed at 48-72 hours
EOT: end of therapy, assessed at Day 7 to 10
ELF: epithelial lining fluid
ESRD: end-stage renal disease
f: free unbound (i.e., microbiologically active) drug
HPLC: high performance liquid chromatography
IRT: Interdisciplinary Review Team for QT Studies
IV: intravenous
LC-MS/MS: liquid chromatography with tandem mass spectrometry
LLOQ: lower limit of quantification
MIC: minimum inhibitory concentration
MIC_{90}: minimum inhibitory concentration for 90% of bacterial population
MRSA: methicillin-resistant *Staphylococcus aureus*
MSSA: methicillin-susceptible *Staphylococcus aureus*
NDA: new drug application
PD: pharmacodynamics
PK: pharmacokinetics
PK/PD: pharmacokinetics/pharmacodynamics
PTE: post-therapy evaluation endpoint, assessed at 7-14 days after the end of therapy
QC: quality control
QTcF: QT interval corrected according to Fridericia's method
ΔQTcF: change in QTcF from baseline
ΔΔQTcF: change in ΔQTcF from placebo
RSE: relative standard error
SAE: serious adverse event
SD: standard deviation
$t_{1/2}$: elimination half-life
TEAEs: treatment-emergent adverse events
T_{max}: time of maximum observed plasma concentration

1 EXECUTIVE SUMMARY

Oritavancin is a lipoglycopeptide antibiotic that is currently being developed to treat acute bacterial skin and skin structure infections (ABSSSI) due to susceptible Gram-positive bacteria. The original oritavancin NDA (22-153) was submitted on 2/8/08 (original clinical pharmacology review dated 12/1/08). The application received a complete response (CR) letter on 12/8/08. The primary reason for the CR letter was that "the application did not contain sufficient evidence to demonstrate the safety and efficacy of oritavancin." The dosing regimen of oritavancin proposed in the original NDA was 200 mg QD, or 300 mg QD for patient's ≥ 110 kg.

Following receipt of the CR letter, the Sponsor re-evaluated their dosing strategy and decided to conduct a Phase 2 trial (TAR-ORI-SD001) which evaluated a 1200 mg single dose of oritavancin to take advantage of oritavancin's long half-life and concentration-dependent antibacterial activity. After performing well in the Phase 2 trial, the 1200 mg once-only dose was selected for further development. Two new identically-designed Phase 3 trials (SOLO I and SOLO II) were conducted in support of the new dosing regimen. The oritavancin resubmission was given a new NDA number (206-334).

The majority of clinical studies were included in the original NDA submission (22-153). The original studies included the following:

- Fourteen Phase 1 studies to assess single and multiple dose pharmacokinetics (4), penetration into skin blister fluid (1) and epithelial lining fluid (ELF) (1), the impact of hepatic impairment (1), the evaluation of drug interactions (2), QT-related effects (4), and vein tolerability/safety (1). The impact of demographics (age, gender, race, and weight) and concomitant medications on the pharmacokinetics of oritavancin were assessed via population pharmacokinetic analysis.
- Three Phase 2 and two Phase 3 clinical studies to evaluate the safety and efficacy of oritavancin for the treatment of bacteremia, and complicated skin and skin structure infections.

In the current NDA submission (206-334), the Sponsor conducted two additional Phase 3 studies (SOLO I and SOLO II) with the new dosing regimen to support the approval of oritavancin based on the current FDA guidelines. Additionally, three other clinical studies were submitted:

- MDCO-ORI-12-02: a thorough QTc study with a supratherapeutic dose of oritavancin (1600 mg)
- MDCO-ORI-12-03: a cocktail drug interaction study
- TAR-ORI-SD001: a Phase 2 dose-ranging study

1.1 Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 4 has reviewed NDA 206-334, and found it is acceptable from a clinical pharmacology perspective.

The reviewer concurs with the proposed oritavancin dosage regimen of 1200 mg single dose infused over 3 hours. No dose adjustments are required on the basis of any intrinsic or extrinsic factor.

The Reviewer concurs with the Sponsor's proposed susceptibility breakpoints for both *S. aureus* and *S. pyogenes*. However, the ultimate determination of *S. aureus* and *S. pyogenes* breakpoints for oritavancin will depend on the totality of information provided by each discipline and continues to be assessed at the time of the completion of this review.

1.2 Phase 4 Commitments

No Phase IV commitments are recommended.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

General PK Characteristics:
Oritavancin pharmacokinetics are linear over the dose range studied. Most of the oritavancin pharmacokinetic data is from the lower doses evaluated in the previous review cycle. The only healthy volunteer PK data for oritavancin at the proposed 1200 mg dose comes from Study MDCO-ORI-12-03. See Figure 1.3.1 for oritavancin's concentration-time profile and Table 1.3.1 for oritavancin's pharmacokinetic parameters in healthy volunteers.

Figure 1.3.1: Mean (±SD) oritavancin plasma concentrations versus time in healthy subjects following IV administration over 3 hours of 1200 mg oritavancin

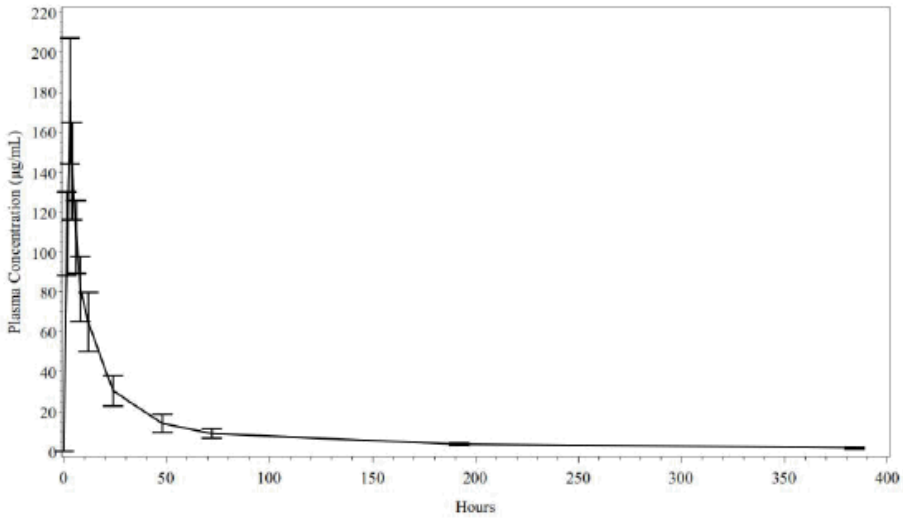


Table 1.3.1: Summary of Plasma Oritavancin Pharmacokinetic Parameters in healthy subjects following IV administration of 1200 mg oritavancin over 3 hours

Parameter (unit)	N	Mean (CV%)	Geometric Mean
AUC_{0-t} (µg·hr/mL)	16	3696.325 (19.55)	3626.674
$AUC_{0-\infty}$ (µg·hr/mL)	16	4006.507 (18.96)	3935.910
C_{max} (µg/mL)	16	175.715 (17.90)	173.056
$t_{1/2}$ (hr)	16	120.476 (16.63)	118.915
CL/F (L/hr)	16	0.311 (21.00)	0.305
Parameter (unit)	**N**	**Median**	**Minimum, Maximum**
T_{max} (hr)	16	3.083	3.083, 3.151

CV%: percent coefficient of variation

It should be noted that there are some differences in oritavancin pharmacokinetics between healthy volunteers and patients. Table 1.3.2 shows a comparison of oritavancin's pharmacokinetics as determined in healthy volunteers and the estimation of oritavancin's patient pharmacokinetics using population PK from SOLO I and SOLO II. Note that the estimated half-life in oritavancin is about twice as long in patients as it is in healthy volunteers. This may in part be due to differences in sample collection. The last oritavancin concentration-time point in MDCO-ORI-12-03 was collected at 384 hours post dose whereas the final oritavancin plasma concentration collection from the sparse sampling in the pharmacokinetic subset of SOLO I and SOLO II was at 576 hours.

Table 1.3.2: Mean (CV%) Oritavancin PK Parameters after Administration of a Single Dose of 1200 mg IV over 3 Hours

Study	C_{max} (µg/mL)	AUC_{0-24} (µg•h/mL)	$AUC_{0-\infty}$ (µg•h/mL)	$t_{1/2}$[a] (h)	CL (L/h)	Vss (L)
MDCO-ORI-12-03	176 (17.9)	NC	4007 (19.0)	120 (16.6)	0.311 (21.0)	NC
SOLO I	144 (23.8)	1200 (37.4)	2950 (31.8)	244 (15.4)	0.443 (32.2)	91.9 (64.8)
SOLO II	134 (22.1)	1060 (29.9)	2710 (25.8)	245 (14.8)	0.472 (26.4)	101 (51.6)

Source: MDCO-ORI-12-03, Table 8; ICPD 00247-1, Table 4-7 and 4-8

[a] Value for MDCO-ORI-12-03 derived using noncompartmental methods; values for SOLO I and SOLO II are the terminal elimination $t_{1/2}$ ($t_{1/2,\gamma}$) derived from the pooled population PK model

NC = Not calculated; CV% = percent coefficient of variation

Note that the C_{max}, AUC, and CL for oritavancin differ in healthy volunteers as compared to patients. Oritavancin exposures are higher and the clearance is lower in healthy volunteers. The same trends (e.g. lower CL and higher AUC in healthy volunteers) were observed at lower doses in the original NDA.

Distribution

No new studies have been conducted to assess the distribution of oritavancin. In brief, studies conducted under NDA 22-153 show that oritavancin is widely distributed into tissues, and that oritavancin penetrates into skin blister fluid (as assessed in Study OSCI-001) and ELF and

alveolar macrophage (AM) (as assessed in Study OPUL-0001). Oritavancin is approximately 85% protein bound across species.

Metabolism
Oritavancin is not metabolized.

Excretion
Less than 5% of oritavancin is excreted unchanged in feces and urine up to 14 days after administration of a single dose.

Intrinsic Factors:
None of the following covariates were identified as clinically relevant during the Sponsor's or Reviewer's population PK analysis: body weight, age, BMI, BSA, Race, or baseline renal function. In addition, summary oritavancin exposures for these covariates, which are shown below in Table 1.3.3, indicate no trend across continuous (body weight, age) or categorical (race, renal function) covariates.

Table 1.3.3: Predicted AUC_{0-72} based on post-hoc parameter estimates from the reviewer's population PK analysis and integration of oritavancin exposures over 72 hours for a subset of covariates following a single 1200 mg dose infused over 3 hours in ABSSSI patients[1]

	Oritavancin AUC72 (ng·h/mL): Mean (median)			
Body weight (kg)	>= 43 & <64	>= 64 & <76	>= 76 & <89	>= 89 & <=178
	1470 (1406)	1534 (1497)	1434 (1419)	1428 (1387)
Age (years)	>= 18 & <36	>= 36 & <47	>= 47 & <55	>= 55 & <=89
	1646 (1677)	1482 (1452)	1369 (1342)	1375 (1306)
BMI (kg/m^2)	>= 15.9 & <22.8	>= 22.8 & <26.2	>= 26.2 & <30.4	>= 30.4 & <=67.4
	1433 (1351)	1464 (1413)	1491 (1459)	1478 (1433)
BSA (m^2)	>= 1.31 & <1.73	>= 1.73 & <1.89	>= 1.89 & <2.04	>= 2.04 & <=2.79
	1514 (1490)	1532 (1511)	1423 (1413)	1404 (1378)
Race	Asian	African American	White	Other
	1578 (1555)	1581 (1511)	1436 (1378)	1468 (1530)
Creatinine Clearance (mL/mL)	>30-50 mL/min	>50-80 mL/min	>80-110 mL/min	>110 mL/min
	1466 (1283)	1387 (1345)	1536 (1504)	1457 (1422)
Gender	Male		Female	
	1403 (1374)		1600 (1605)	

[1]: The categorical divisions for body weight, age, BMI, and BSA represent quartiles

Hepatic impairment

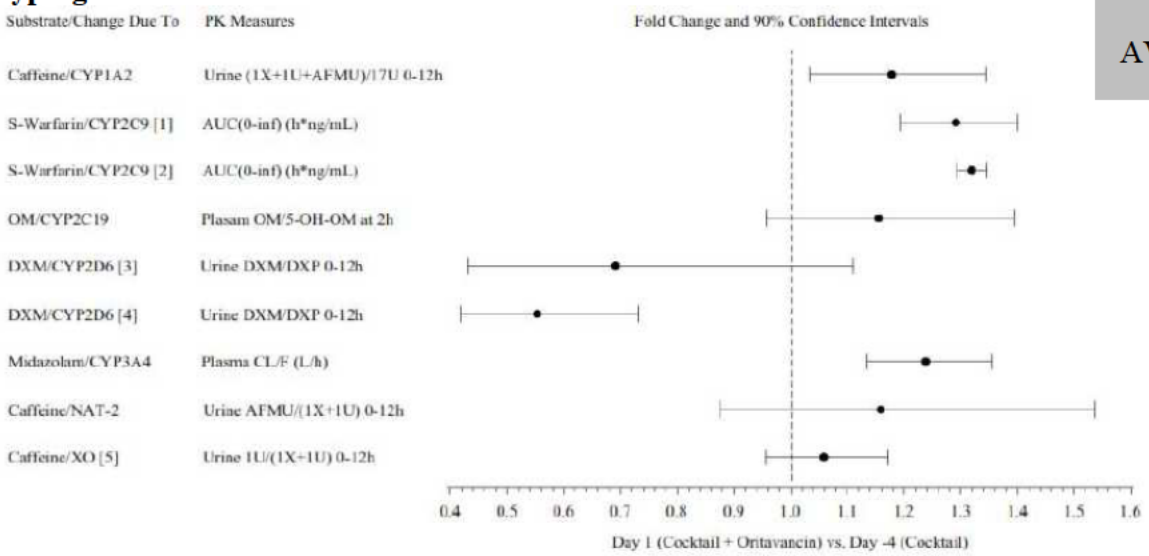
There were very few patients with hepatic impairment enrolled in the oritavancin clinical studies and included in the population PK dataset; thus hepatic impairment was not considered as a potential covariate in the model. However, an independent study of subjects with moderate hepatic impairment (see previous clinical pharmacology review dated 12/01/08) showed that a dosage adjustment for oritavancin on the basis of moderate hepatic impairment was not necessary. There is no information about the pharmacokinetics of oritavancin in subjects with severe hepatic impairment.

Extrinsic Factors:

Drug-Drug Interactions

In vitro evidence suggests that oritavancin may be a weak, non-specific, inhibitor of several different CYP450 isozymes. However, a previous clinical study (OCSI-008) did not result in any observable interaction between oritavancin and desipramine when oritavancin was administered as 800 mg IV daily for 14 days (see Clinical Pharmacology review under NDA 22-153 dated 12/1/08). Given the oritavancin dose proposed in this NDA (1200 mg), the resulting increase in C_{max}, and the in vitro findings, the Sponsor conducted a cocktail drug interaction study (MDCO-ORI-12-03). Study MDCO-ORI-12-03 was a study designed to evaluate the impact of oritavancin on the pharmacokinetics of the probe drugs in the Cooperstown 5+1 cocktail (caffeine, omeprazole, warfarin, vitamin K, dextromethorphan, and midazolam). The enzymatic activities of CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, N-acetyltransferase-2 (NAT-2), and Xanthine oxidase (XO) were also assessed (see Figure 1.3.2).

Figure 1.3.2: Summary of the Effect of Oritavancin on the Probe Substrates of the Cooperstown 5+1 Cocktail Displayed as 90% Confidence Intervals of the Geometric Mean Phenotyping Measure Ratios



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1U: 1-methylurate; 17U: 1, 7-dimethylurate; 1X: 1-methylxanthine; AFMU: 5-acetylamino-6-formylamino-3-methyluracil; AUC_{0-inf}: (also referred to as $AUC_{0-\infty}$) area under the plasma concentration-time curve from time zero to infinity; CL/F: apparent oral clearance; CYP: cytochrome P450; DXM: dextromethorphan; DXP: dextrorphan; h: hour(s); NAT-2: *N*-Acetyltransferase-2; OM: omeprazole; PK: pharmacokinetic; XO: xanthine oxidase

[1] N = 3; predose plasma concentration <5% of the post-dose maximum plasma concentration (C_{max}) on Day 1.
[2] N = 16; all subjects.
[3] N = 13; CYP2D6 activities that were ≤0 or outliers were excluded.
[4] N = 12; CYP2D6 activities that were ≤0 or outliers were excluded. Subject 1001 was also excluded.
[5] N = 14; XO activities that were ≤0 or outliers were excluded.

The lines in Figure 1.3.2 refer to measurements of enzyme activity, and are not consistently representative of the same pharmacokinetic parameter. Co-administration of oritavancin altered the activities of the other enzymes tested (with the exception of XO). However, the highest point estimate is 1.32, and the lowest point estimate is 0.55, which indicates that the observed changes in enzymatic activity are likely not of sufficient magnitude to be clinically significant unless the victim drug in question has a narrow therapeutic range (e.g. warfarin and CYP2C9).

Population PK (PopPK) Analysis:
The Sponsor's population pharmacokinetic model was generally found to be acceptable. However, one of the covariate relationships that they identified was a relationship between height and clearance. In the Reviewer's analyses height was replaced by more biologically plausible covariates such as BMI or BSA since height is likely acting as a surrogate for weight. However, the Reviewer's alterations to the model did not result in differences in the parameter estimates which would be of clinical relevance. Therefore, the population PK model proposed by the Sponsor is acceptable.

The Reviewer's population pharmacokinetic parameter estimates for the final PK model are shown in Table 1.3.4. These parameters are similar to those obtained from the sponsor.

Table 1.3.4: Population PK parameter estimates based on the Reviewer's final model (log-transformed dependent variable)

Parameter	Estimate	RSE(%)	CI95
Fixed-Effects Parameter Estimates			
CL (L/hr)	0.451	1.8	(0.435-0.467)
V1(L)	6.83	3.7	(6.33-7.33)
Q2 (L/h)	0.382	3.5	(0.356-0.408)
V2 (L)	117	8.8	(97-137)
Q3 (L/h)	0.686	10.1	(0.551-0.821)
V3 (L)	8.71	4.4	(7.96-9.46)

Breakpoint Analyses
The Sponsor conducted several analyses to support possible *S. aureus* breakpoints for oritavancin. They presented the probability of PK/PD target attainment for achieving the following: an AUC_{0-72}/MIC of 3,941 corresponding with a bacteriostatic effect in the mouse neutropenic thigh model, an AUC_{0-72}/MIC of 4,581 corresponding with a 1-log kill in the mouse neutropenic thigh model, the probability of achieving an AUC_{0-72}/MIC of 11,982 which corresponds to the AUC/MIC threshold identified for the univariate relationship for achieving a dichotomous efficacy endpoint at post-therapy evaluation (hereafter referred to as PTE). The sponsor also included the probability of achieving model-predicted clinical success by MIC. Note that all AUC/MIC targets are calculated with total AUC rather than free AUC since the protein binding of oritavancin is similar between humans and mice.

The Reviewer conducted comparable analyses to the Sponsor, but also conducted many of the analyses at multiple clinical endpoints (ECE, >20% reduction in lesion size and PTE). The ECE endpoint was included because it was the primary endpoint of the SOLO I and SOLO II trials.

The >20% reduction endpoint was included because it is recommended in the current FDA guidance for ABSSSI treatment as the primary efficacy endpoint in lesion size at 48 to 72 hours compared to baseline. The PTE endpoint was included because it is a point of emphasis for the sponsor's PK/PD analysis. The *S. aureus* breakpoints for oritavancin that would be supported for the different analytical approaches used by the Sponsor and the Reviewer are shown in Table 1.3.5.

Table 1.3.5: Comparison of possible *S. aureus* breakpoints for oritavancin from the Reviewer and the Sponsor using the methods described above

Evidence	Reviewer's Analyses	Sponsor Analyses
Epidemiological Cutoff	0.12 – 0.25 mcg/mL	0.12 – 0.25 mcg/mL
Nonclinical PK/PD Target Attainment	0.25 mcg/mL	0.12 mcg/mL
Clinical PK/PD Target Attainment	0.06 mcg/mL	0.06 mcg/mL
Model-predicted clinical response	0.06 – 0.12 mcg/mL	0.12 mcg/mL
Overall Proposed	0.12 mcg/mL	0.12 mcg/mL

Cardiovascular effects

A thorough QT study was conducted in healthy adults with a single supratherapeutic dose of IV oritavancin (1600 mg). No significant QTc prolongation effects of oritavancin 1600 mg infusion were detected in this study. For a complete assessment of the thorough QT study findings, refer to the Interdisciplinary Review Team review.

2 QUESTION-BASED REVIEW

The majority of clinical studies for oritavancin were reviewed during the original NDA submission review cycle. Details regarding clinical pharmacology information of oritavancin submitted during the original NDA (22-153) submission review cycle can be found in the previous clinical pharmacology review by Dr. Ryan P. Owen dated 12/01/08. The current oritavancin NDA resubmission includes 4 new studies: a cocktail drug interaction study, a thorough QTc study, and 2 new Phase 3 studies. This QBR review focuses on these PK studies and an assessment of the population PK and PK/PD analyses included in the current submission. Only relevant sections of the QBR are addressed.

2.1 General Attributes of the Drug

For highlights of the chemistry and physical-chemical properties of the drug substance as it relates to clinical pharmacology, please refer to the previous clinical pharmacology review dated 12/01/08.

2.1.1 What is the formulation of the drug product?

ORBACTIV is supplied as a sterile white to off-white lyophilized powder for IV infusion that contains oritavancin diphosphate, mannitol (an inactive ingredient), and phosphoric acid (to adjust pH 3.1 to 4.3). Each 50 mL capacity glass vial contains 400 mg oritavancin (free base equivalent). Each vial is reconstituted with sterile water for injection and further diluted with 5% dextrose in sterile water for IV infusion. Both reconstituted solution and diluted solution for infusion should be clear, colorless to pale yellow solution.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Oritavancin has three proposed mechanisms of action: i) inhibition of the transglycosylation (polymerization) step of cell wall biosynthesis by binding to the stem peptide of peptidoglycan precursors, ii) inhibition of the transpeptidation (crosslinking) step of cell wall biosynthesis by binding to the peptide bridging segments of the cell wall; and iii) disruption of bacterial membrane integrity, leading to depolarization, premeabilization, and rapid cell death.

The proposed therapeutic indication of oritavancin is acute bacterial skin and skin structure infections (ABSSSI) caused by *Staphylococcus aureus* (including methicillin-susceptible [MSSA] and –resistant [MRSA] isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group, and *Enterococcus faecalis* (vancomycin-susceptible isolates only).

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dosage regimen of oritavancin for adults is 1200 mg on day 1 administered via a 3 hour IV infusion for the treatment of acute bacterial skin and skin structure infections.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The original proposed oritavancin dosing regimen of 200 mg (or 300 mg if >110 kg) infused over 1 hour once daily for 3 to 7 days was considered acceptable from a clinical pharmacology standpoint in the previous review cycle (NDA 22-153). However, after receiving the complete response letter in 2008, the Sponsor changed their dosing strategy to a 1200 mg once-only IV dose of oritavancin infused over 3 hours (NDA 206-334). Table 2.2.1.1 summarizes all of the clinical studies conducted across both oritavancin NDAs. Five new clinical studies have been conducted since NDA 22-153 received a complete response letter: 2 Phase 1 studies (MDCO-ORI-12-03 and MDCO-ORI-12-02), 1 dose-ranging Phase 2 study (TAR-ORI-SD001), and 2 additional Phase 3 studies (SOLO I and SOLO II).

Table 2.2.1.1: Clinical Studies Conducted Under Both Oritavancin NDAs[1]

Study Title	Phase	Study Type	Comments
H4Q-JE-101N	1	SAD (Japanese)	
H4Q-LC-ARRA	1	SAD	
H4Q-LC-ARRB	1	MAD	
H4Q-LC-ARRK	1	SAD	
OCSI-001	1	Blister Fluid	
OPUL-001	1	ELF	
MDCO-ORI-12-02	**1**	**Safety TQT**	**TQT study with 1600 mg dose**
OCSI-004	1	Hepatic Impairment	
OCSI-007	1	CYP2D6 DDI	
OCSI-008	1	CYP2D6 DDI	
MDCO-ORI-12-03	**1**	**DDI Cocktail**	**Only Phase 1 study with 1200 mg single dose pharmacokinetics in healthy volunteers**
H4Q-LC-ARRN	1	QTc	
H4Q-LC-ARRO	1	QTc	
H4Q-MC-ARRC	2	Bacteremia Dose ranging Phase 2	
H4Q-MC-ARRL	2	cSSSI Dose Ranging Phase 2	
H4Q-MC-ARRM	2	Bacteremia Phase 2 dose ranging	
TMC-ORI-10-01 (SOLO I)	**3**	**Pivotal safety and efficacy**	**Contribution to Pop PK model**
TMC-ORI-10-02 (SOLO II)	**3**	**Pivotal safety and efficacy**	**Contribution to Pop PK model**

H4Q-MC-ARRD	3	Legacy Phase 3	
H4Q-MC-ARRI	3	Legacy Phase 3	
TAR-ORI-SD001	**2**	**High dose Phase 2 dose ranging**	**Served as proof-of-concept to take the 1200 mg single dose dosing regimen of oritavancin into Phase 3 trials** **Study arms:** **Oritavancin 1200 mg single dose** **Oritavancin 200 mg for 3-7 days** **Oritavancin 800 mg on Day 1 with an optional 400 mg dose on Day 5**
TAR-ORI-QT002	1	QTc	
TAR-ORI-VT001	1	Vein Tolerability	

[1]: Studies that are new in NDA 206-433 appear in bold. All other studies were originally included in NDA 22-153

Studies conducted under NDA 22-153 are marked as such in Table 2.2.1.1. These studies have been reviewed previously; this review will focus on the 5 newly-conducted studies. The only new study directly contributing to the selection of the new dosing regimen of oritavancin is the Phase 2 trial TAR-ORI-SD001. The Phase 2 trial consisted of three oritavancin dosing arms: 200 mg QD (or 300 mg if over 110 kg) for 3-7 days, 1200 mg once-only dose on Day 1, or 800 mg on Day 1 with an optional 400 mg dose on Day 5. The efficacy results for this trial are presented in Table 2.2.1.2.

Table 2.2.1.2: Primary Efficacy Endpoint: Investigator-Defined Clinical Outcome at First Follow-up in the Clinically Evaluable Population

Response	Oritavancin 200 mg N = 76 n (%)	Oritavancin 1200 mg N = 81 n (%)	Oritavancin 800 mg N = 71 n (%)	Estimated Difference[b] 1200 mg – 200 mg (90% CI)	Estimated Difference[b] 800 mg – 200 mg (90% CI)
Cure[a]	55 (72.4)	66 (81.5)	55 (77.5)	8.6	5.2
Failure	21 (27.6)	15 (18.5)	16 (22.5)	(-2.5, 18.2)	(-6.8, 15.4)

Abbreviations: CI = confidence interval.

[a] Includes cure and improvement outcomes.

[b] Difference in response rate between patients by using Mantel-Haenszel method stratified by disease

Source: Table 14.2.1.1.2.2.

Based on this data, the 1200 mg single dose of oritavancin performed as well or better than the other dosing regimens, and was therefore selected for further evaluation in Phase 3.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

In the current development program, 2 identically-designed Phase 3 trials were conducted with the oritavancin 1200 mg single dose regimen, SOLO I and SOLO II. SOLO I and SOLO II were designed using current guidance from FDA and EMA.

The primary analyses of efficacy were performed using a modified intent-to-treat (mITT) population, defined as all randomized patients who received any study drug. The primary efficacy endpoint in SOLO I and SOLO II was early clinical response, a composite endpoint defined as the cessation of spread or reduction in size of the baseline lesion, absence of fever, and no rescue antibiotic medication at the Early Clinical Evaluation (ECE, 48-72 hours after initiation of study drug). This endpoint was pre-specified for non-inferiority testing with a margin of 10% using the mITT and CE populations. See Table 2.2.2.1 for the response rates in SOLO I, SOLO II, and for the overall population

Table 2.2.2.1: Early Clinical Response in SOLO I, SOLO II, and the SOLO Pool (mITT Population)

	SOLO I		SOLO II		All Patients	
	Oritavancin (N=475) n (%)	Vancomycin (N=479) n (%)	Oritavancin (N=503) n (%)	Vancomycin (N=502) n (%)	Oritavancin (N=978) n (%)	Vancomycin (N=981) n (%)
Early Clinical Response Rate, n (%)	391 (82.3)	378 (78.9)	403 (80.1)	416 (82.9)	794 (81.2)	794 (80.9)
Diff and 95% CI	3.4 (-1.6, 8.4)		-2.7 (-7.5, 2.0)		0.2 (-3.3, 3.7)	

CI: Confidence Interval; mITT: modified Intent-to-Treat

% Success rate is calculated as no. of patients with success/no. of patients with success or failure * 100 (%). Patients with missing outcomes are defined as failure per protocol.

Source: Table 4.1.2

There were no response endpoints evaluated in the clinical pharmacology studies.

2.2.3 Exposure-Response

2.2.3.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to onset and offset of the desirable pharmacological response or clinical endpoint.

The following review questions were identified and addressed based on the sponsor's population PK and exposure-response analyses included in the current submission.

2.2.3.1.1 Does the population pharmacokinetic analysis support the Sponsor's proposed labeling claims regarding effects of sex, age, race, body weight, and renal status on oritavancin dosing?

The population PK model supports that no dose adjustments are necessary based on sex, age, race, body weight, or renal function status.

None of the listed covariates were identified as clinically relevant from the Sponsor's or Reviewer's population PK analysis. In addition, summary oritavancin exposures for these covariates, which are shown below in Table 2.2.3.1.1.1, indicate no trend across continuous (body weight, age) or categorical (race, renal function) covariates.

Table 2.2.3.1.1.1: Predicted AUC_{0-72} based on post-hoc parameter estimates from the reviewer's population PK analysis and integration of oritavancin exposures over 72 hours for a subset of covariates following a single 1200 mg dose infused over 3 hours in ABSSSI patients[1]

	Oritavancin AUC72 (ng·h/mL): Mean (median)			
Body weight (kg)	>= 43 & <64	>= 64 & <76	>= 76 & <89	>= 89 & <=178
	1470 (1406)	1534 (1497)	1434 (1419)	1428 (1387)
Age (years)	>= 18 & <36	>= 36 & <47	>= 47 & <55	>= 55 & <=89
	1646 (1677)	1482 (1452)	1369 (1342)	1375 (1306)
BMI (kg/m^2)	>= 15.9 & <22.8	>= 22.8 & <26.2	>= 26.2 & <30.4	>= 30.4 & <=67.4
	1433 (1351)	1464 (1413)	1491 (1459)	1478 (1433)
BSA (m^2)	>= 1.31 & <1.73	>= 1.73 & <1.89	>= 1.89 & <2.04	>= 2.04 & <=2.79
	1514 (1490)	1532 (1511)	1423 (1413)	1404 (1378)
Race	Asian	African American	White	Other
	1578 (1555)	1581 (1511)	1436 (1378)	1468 (1530)
Creatinine Clearance (mL/mL)	>30-50 mL/min	>50-80 mL/min	>80-110 mL/min	>110 mL/min
	1466 (1283)	1387 (1345)	1536 (1504)	1457 (1422)
Gender	Male		Female	
	1403 (1374)		1600 (1605)	

[1]: The categorical divisions for body weight, age, BMI, and BSA represent quartiles

2.2.3.1.2 Are the proposed S. aureus and S. pyogenes in vitro susceptibility test interpretive criteria for oritavancin supported based on the available clinical data and nonclinical data?

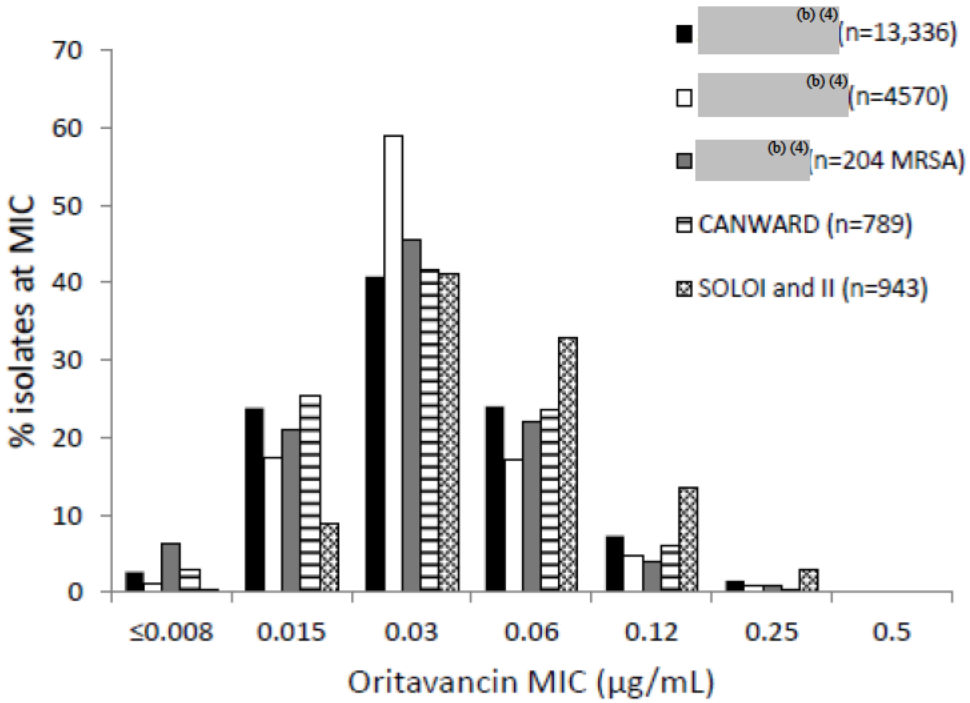
For oritavancin, the Sponsor proposed a susceptibility breakpoint of ≤0.12 mcg/mL for *S. aureus* and a susceptibility breakpoint of ≤0.25 mcg/mL for *S. pyogenes*. The analyses that inform these decisions are discussed below under individual subheadings (with a focus on *S. aureus* since the *S. pyogenes* data are more limited). The Reviewer concurs that the Sponsor's proposed breakpoints are acceptable for *S. aureus* and *S. pyogenes*.

Oritavancin MIC distributions in clinical trials and surveillance programs

A MIC frequency distribution was compiled using oritavancin MIC values from the oritavancin Phase 3 studies and several surveillance studies (see Figure 2.2.3.1.2.1).

The MIC distribution shows that a larger percentage of higher MIC isolates were found in the clinical trials as compared to the surveillance studies. However, the majority of oritavancin MICs fall between 0.015 and 0.12 mg/L, with few isolates at 0.25 and 0.5 mg/L. These data suggest that the epidemiological cutoff would be either 0.12 or 0.25 mg/L.

Figure 2.2.3.1.2.1: Comparative Oritavancin MIC Distributions for *S. aureus* Clinical Trial (SOLO I and II) and Surveillance Isolates



Probability of Target Attainment Using Animal Data

AUC/MIC was previously determined to be the PK/PD parameter of relevance for oritavancin in animal models of infection. The nonclinical AUC_{0-72}/MIC targets for oritavancin against *S. aureus* and *S. pyogenes* are described in Table 2.2.3.1.2.1.

Table 2.2.3.1.2.1: Summary of nonclinical AUC_{0-72}/MIC targets for oritavancin efficacy against *S. aureus* and *S. pyogenes*

Pathogen [reference]	Median (min – max) AUC_{0-72}:MIC ratio associated with the bacterial reduction endpoint	
	Net bacterial stasis	1-log_{10} CFU reduction from baseline
S. aureus [11]	3,941 (265 - 30,255)	4,581 (305 - 35,348)
S. pyogenes [12]	120 (10.2 - 963)	198 (16.2 – 1,376)

CFU = Colony forming units.

The Sponsor used the AUC_{0-72} values for simulated patients receiving a single 1200 mg IV dose of oritavancin (which were informed by the population PK model discussed in Section 2.3 and Appendix 4.2) and calculated the percent probability of attaining the nonclinical AUC_{0-72}/MIC targets for *S. aureus* and *S. pyogenes* for the simulated patients. The Reviewer conducted similar analyses. See Figure 2.2.3.1.2.2 for a graphical representation of the probability of target attainment for the *S. aureus* nonclinical static and cidal targets and Table 2.2.3.1.2.2 for a comparison of the Sponsor's results and the Reviewer's results.

Figure 2.2.3.1.2.2: Probability of target attainment simulations for the nonclinical static and 1-log kill AUC_{0-72}/MIC targets for *S. aureus*

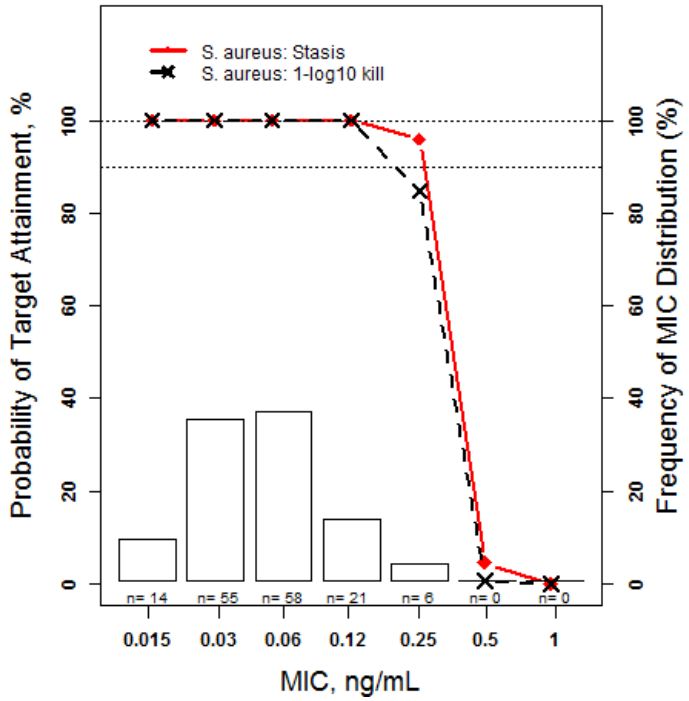


Table 2.2.3.1.2.2: Probability of target attainment based on nonclinical AUC_{0-72}/MIC targets (Reviewer and Sponsor Analyses shown)

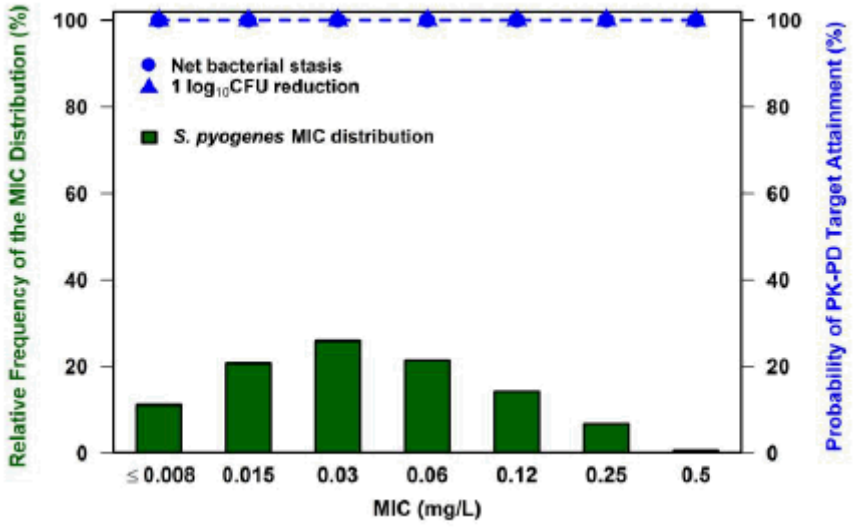
	Reviewer Analyses		Sponsor Analyses	
MIC	Stasis	1-log kill	Stasis	1-log kill
0.016	100	100	Not reported	Not reported
0.031	100	100	Not reported	Not reported
0.062	100	100	100	100
0.125	100	100	99.8	99.4
0.25	95.6	83.7	85.1	74.8
0.5	5.2	0.8	20.0	10.0
1	0	0	Not reported	Not reported

The numerical AUC_{0-72}/MIC target utilized in the Reviewer and Sponsor analyses were identical. However, the population PK model used by the Reviewer had some modifications from that used by the Sponsor as discussed above which accounts for the difference in the analyses. Using the Reviewer's analysis, a breakpoint of up to 0.25 mcg/mL for *S. aureus* could be supported as the probability of attaining the nonclinical bacteriostatic target at an MIC of 0.25 mcg/mL is above 90%. Using the same benchmark for the Sponsor's analyses, a breakpoint of up to 0.125 mcg/mL would be supported for *S. aureus*.

The Sponsor's probability of target attainment analyses for the nonclinical AUC_{0-72}/MIC targets for *S. pyogenes* are shown in Figure 2.2.3.1.2.3. The Reviewer did not conduct an independent analysis because the nonclinical AUC_{0-72}/MIC target for *S. pyogenes* was significantly lower than for *S. aureus*, and no decline in probability of target attainment was observed across the

MIC range in the SOLO I and SOLO II trials. These analyses support a *S. pyogenes* breakpoint of up to 0.5 mcg/mL for oritavancin.

Figure 2.2.3.1.2.3: Probability of target attainment for nonclinical AUC_{0-72}/MIC targets for *S. pyogenes*



Probability of Target Attainment Using Clinical Data

The Sponsor conducted a univariate analysis based on AUC_{0-72}/MIC as both a categorical (two-group with a single cut off) and continuous variable. The categorical analysis identified an AUC_{0-72}/MIC target of 11,982 at PTE, which in turn was used in a probability of target attainment analysis by MIC as the clinical PK/PD target (refer to Appendix 4.2 for further information). The Reviewer repeated this analysis with the revised population PK model and the Reviewer-generated clinical PK/PD targets. The Reviewer's analysis also is shown graphically in Figure 2.2.3.1.2.4 and shows the probability of target attainment for the clinical PK/PD targets for various clinical endpoints. A comparison of the Reviewer's and Sponsor's results is shown in Table 2.2.3.1.2.3.

Figure 2.2.3.1.2.4: Probability of target attainment for the clinical PK/PD univariate AUC_{0-72}/MIC targets for *S. aureus* for different clinical endpoints

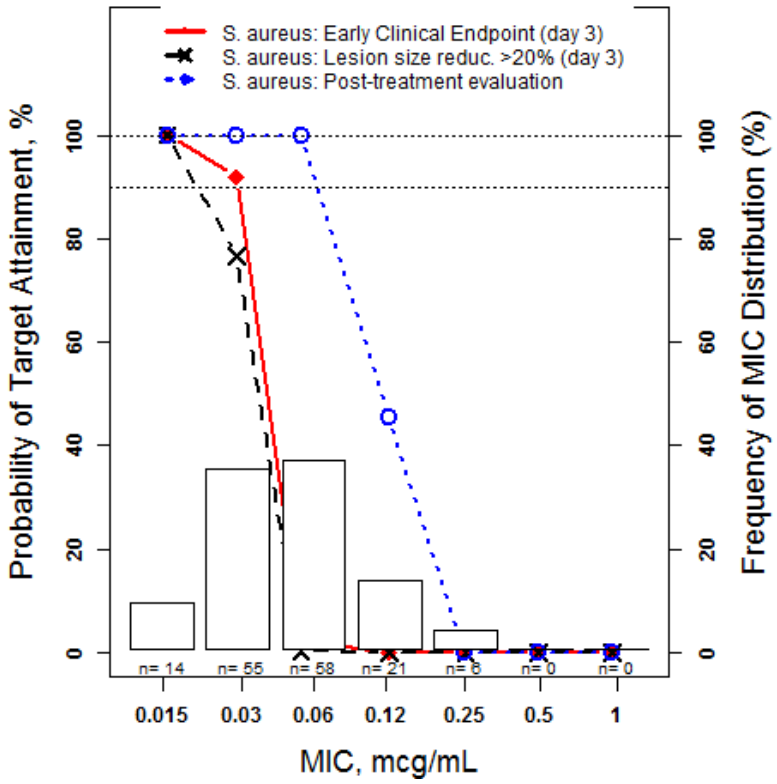


Table 2.2.3.1.2.3: Probability of target attainment based on clinical AUC_{0-72}/MIC targets for *S. aureus* (Reviewer and Sponsor Analyses shown)

	Reviewer Analyses			Sponsor Analysis
MIC	ECE	>20% reduction	PTE	PTE
0.016	100	100	100	Not reported
0.031	91.8	76.6	100	Not reported
0.062	2.1	0.4	99.9	96.9
0.125	0	0	45.4	51.9
0.25	0	0	0	1.9
0.5	0	0	0	0
1	0	0	0	Not reported

Interestingly, different conclusions as to which breakpoint would be appropriate would be reached depending on which clinical endpoint was chosen. Using the Reviewer's analyses, the chosen breakpoints for PTE, ECE, and >20% reduction in lesion size would be 0.006, 0.03, and 0.016 mcg/mL, respectively. The Sponsor's analysis was confined to PTE and would support a breakpoint of 0.06 mcg/mL. The Reviewer's analysis differed from the Sponsor's in the following ways: a revised population PK model was used, different clinical PK/PD targets were identified, and multiple clinical endpoints were examined (refer to Appendix 4.2 for more information). Given the overall cure rates observed in the trial (see Table 2.2.3.1.2.4), all of

these potential breakpoints are likely overly conservative with the possible exception of 0.06 mcg/mL.

Table 2.3.2.1.2.4: Primary Efficacy Outcome at ECE and Clinical Response at PTE by Oritavancin MIC for Oritavancin-Treated patients with *S. aureus* (MSSA and MRSA) at Baseline (MicroITT population; SOLO I and SOLO II pooled)

Oritavancin MIC (µg/mL)	Primary Efficacy Outcome at ECE[a]	Clinical Response at PTE
0.004	-	-
0.008	0/1 (0.0)	1/1 (100.0)
0.015	39/46 (84.8)	36/38 (94.7)
0.03	175/203 (86.2)	170/181 (93.9)
0.06	116/146 (79.5)	123/134 (91.8)
0.12	45/58 (77.6)	46/51 (90.2)
0.25	13/17 (76.5)	14/17 (82.4)
0.5	-	-
Total	**388/471 (82.4)**	**390/422 (92.4)**

[a] Primary efficacy outcome is from Table 5.9.5 in Appendix K.
[b] Clinical response at PTE is from Table 5.7.5 in Appendix K.
Source: Table 5.9.5 in Appendix K.; Table 5.7.5 in Appendix K.

PK-PD Relationships for informing model-predicted probability of clinical response

The Sponsor used the above-mentioned clinical PK/PD target (AUC_{0-72}/MIC of 11,982 for S. aureus at PTE) identified through their univariate analysis to calculate the probability of model-predicted clinical response by MIC (refer to Appendix 4.2 for further information). The comparable Reviewer's analysis also included the probability of clinical response at ECE and >20% reduction in lesion size in addition to the PTE. The Reviewer's analysis is shown graphically in Figure 2.2.3.1.2.5 and shows the model-predicted probability of clinical response at various clinical endpoints. A comparison of the Reviewer's and Sponsor's results is shown in Table 2.2.3.1.2.5.

Figure 2.2.3.1.2.5: Model-predicted probability of clinical response for *S. aureus* infections at different clinical endpoints by MIC

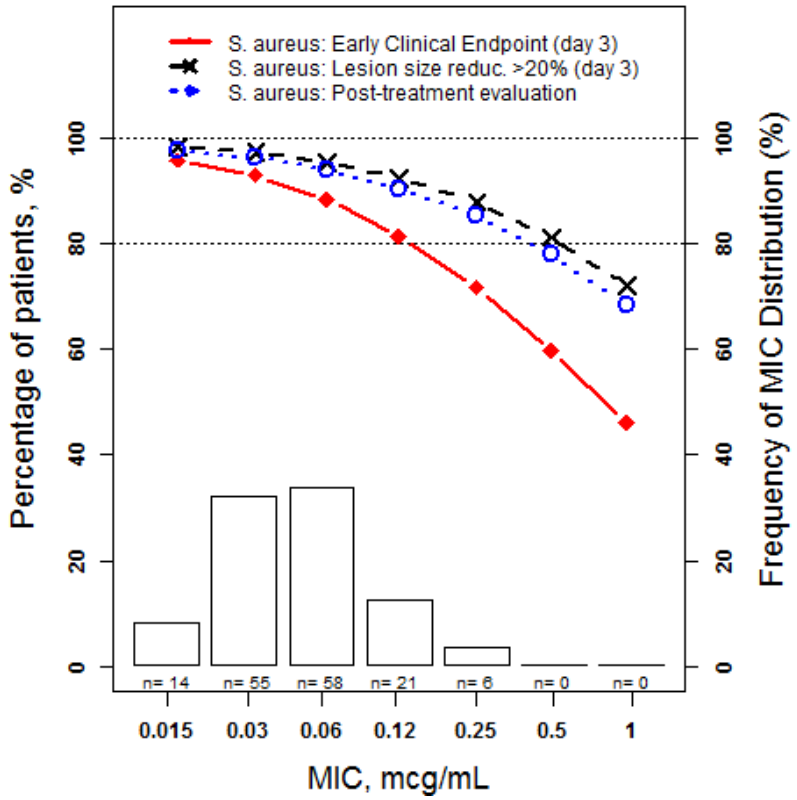


Table 2.2.3.1.2.5: Model-predicted probability of clinical response for *S. aureus* at different clinical endpoints (Reviewer and Sponsor Analyses shown)

	Reviewer Analyses			Sponsor Analysis
MIC	ECE	>20% reduction	PTE	PTE
0.016	95.7	98.2	97.6	Not reported
0.031	92.8	97.1	96.1	Not reported
0.062	88.2	95.2	93.8	95.8
0.125	81.3	92.3	90.3	89.7
0.25	71.7	87.8	85.1	82.9
0.5	59.7	81.1	77.8	82.6
1	46.3	72	68.3	Not reported

The probability of clinical response analysis by endpoints is an exploratory analysis with no pre-established cutoffs for acceptability. However, it is interesting to note that the different clinical endpoints examined resulted in different model-predicted probabilities of response. Given that the majority of the patients enrolled in the trials had MIC values of 0.06 mcg/mL or lower, and that oritavancin appears to be non-inferior to vancomycin, we can assume that the probability of response values that correspond with an MIC of 0.06 mcg/mL represent an acceptable threshold. However, there also appears to be sufficient data at an MIC of 0.125 mcg/mL to suggest that oritavancin is also efficacious at this MIC level. The Reviewer's analysis of the PTE endpoint

results in predictions similar to that of the Sponsor's analysis at MICs of 0.062 and 0.125 mcg/mL.

Overall Summary of S. aureus Breakpoint Determination for oritavancin
Different approaches were employed by the Sponsor and the Reviewer for determination of a *S. aureus* susceptibility breakpoint for oritavancin. Key differences between the Sponsor and Reviewer approach are that the Reviewer conducted independent analyses on the population PK model which was used to inform simulations and predictions, and the Reviewer examined data at different clinical endpoints. A summary of the *S. aureus* breakpoints supported by the Reviewer and the Sponsor for the different endpoints is shown in Table 2.2.3.1.2.6.

Table 2.2.3.1.2.6: Comparison of possible *S. aureus* breakpoints for oritavancin from the Reviewer and the Sponsor using the methods described above

Evidence	Reviewer's Analyses	Sponsor Analyses
Epidemiological Cutoff	0.12 – 0.25 mcg/mL	0.12 – 0.25 mcg/mL
Nonclinical PK/PD Target Attainment	0.25 mcg/mL	0.12 mcg/mL
Clinical PK/PD Target Attainment	0.06 mcg/mL	0.06 mcg/mL
Model-predicted clinical response	0.06 – 0.12 mcg/mL	0.12 mcg/mL
Overall Proposed	0.12 mcg/mL	0.12 mcg/mL

It should be also noted that the determination of breakpoints involves input from multiple disciplines including clinical and microbiological perspectives in addition to the above analyses of the clinical pharmacology reviewer. The ultimate determination of the *S. aureus* breakpoint for oritavancin will depend on the totality of information provided by each discipline and continues to be assessed at the time of the completion of this review.

2.2.3.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to onset and offset of the desirable pharmacological response or clinical endpoint.

The safety of the original oritavancin dosing regimen is discussed in the previous clinical pharmacology review dated 12/01/2008. An overview of the adverse events in both oritavancin development programs is shown in Table 2.2.3.2.1.

Table 2.2.3.2.1: Overview of Adverse Events (Safety Population)

	SOLO Pool		ARRD/I Pool		All Treated Pool	
Category	Oritavancin (N=976) n (%)	Vancomycin (N=983) n (%)	Oritavancin (N=1173) n (%)	Vancomycin (N=590) n (%)	Oritavancin (N=3017) n (%)	Comparator (N=1954) n (%)
No. of Patients with any AE	540 (55.3)	559 (56.9)	627 (53.5)	368 (62.4)	1712 (56.7)	1076 (55.1)
No. of Patients with any AE Leading to Study Drug Discontinuation	36 (3.7)	41 (4.2)	46 (3.9)	40 (6.8)	131 (4.3)	90 (4.6)
No. of Patients with SAE	57 (5.8)	58 (5.9)	107 (9.1)	68 (11.5)	256 (8.5)	144 (7.4)
No. of Patients with any AE Leading to Death	2 (0.2)	3 (0.3)	19 (1.6)	12 (2.0)	53 (1.8)	24 (1.2)

Source: Table 01.6.1.P4; Table 02.6.1.P4; and Table 03.6.1.P4.
AE = adverse event; SAE = serious adverse event.
AEs are adverse events which occurred or whose severities worsened on or after the initiation of study drug.

The ARRD/I Pool refers to the previous development program and dosing regimen of oritavancin, and is therefore not as relevant as the SOLO Pool. The serious adverse events occurring in 2 or more patients across the oritavancin development programs are shown in Table 2.2.3.2.2.

Table 2.2.3.2.2: Serious Adverse Events in ≥2 Patients in the Oritavancin Group in Any Pool (Safety Population)

	SOLO Pool		ARRD/I Pool		All Treated Pool	
System Organ Class Preferred Term	Oritavancin (N=976) n (%)	Vancomycin (N=983) n (%)	Oritavancin (N=1173) n (%)	Vancomycin (N=590) n (%)	Oritavancin (N=3017) n (%)	Comparator (N=1954) n (%)
Number of Patients with Any SAE	57 (5.8)	58 (5.9)	107 (9.1)	68 (11.5)	256 (8.5)	144 (7.4)
Cellulitis	11 (1.1)	12 (1.2)	10 (0.9)	4 (0.7)	26 (0.9)	16 (0.8)
Osteomyelitis	4 (0.4)	1 (0.1)	5 (0.4)	0	11 (0.4)	2 (0.1)
Abscess Limb	3 (0.3)	0	6 (0.5)	1 (0.2)	12 (0.4)	1 (0.1)
Pneumonia	3 (0.3)	0	2 (0.2)	2 (0.3)	10 (0.3)	2 (0.1)
Skin Infection	3 (0.3)	3 (0.3)	0	0	3 (0.1)	3 (0.2)
Subcutaneous Abscess	3 (0.3)	1 (0.1)	0	3 (0.5)	4 (0.1)	4 (0.2)
Diabetic Ketoacidosis	2 (0.2)	1 (0.1)	0	0	2 (0.1)	1 (0.1)
Hypoxia	2 (0.2)	1 (0.1)	0	0	2 (0.1)	1 (0.1)
Tenosynovitis	2 (0.2)	0	0	0	2 (0.1)	0
Abdominal Pain	1 (0.1)	0	1 (0.1)	0	5 (0.2)	1 (0.1)
Abscess	1 (0.1)	1 (0.1)	7 (0.6)	2 (0.3)	9 (0.3)	3 (0.2)
Arthritis Bacterial	1 (0.1)	2 (0.2)	0	0	2 (0.1)	2 (0.1)
Asthenia	1 (0.1)	0	1 (0.1)	0	2 (0.1)	0
Bacteraemia	1 (0.1)	0	1 (0.1)	1 (0.2)	4 (0.1)	1 (0.1)
Bipolar Disorder	1 (0.1)	0	0	0	2 (0.1)	0
Bronchitis	1 (0.1)	0	1 (0.1)	0	2 (0.1)	1 (0.1)
Cardiac Failure Congestive	1 (0.1)	1 (0.1)	2 (0.2)	0	4 (0.1)	2 (0.1)
Chest Pain	1 (0.1)	0	3 (0.3)	1 (0.2)	6 (0.2)	1 (0.1)
Deep Vein Thrombosis	1 (0.1)	2 (0.2)	0	1 (0.2)	2 (0.1)	3 (0.2)
Dyspnoea	1 (0.1)	2 (0.2)	0	2 (0.3)	5 (0.2)	4 (0.2)
Gangrene	1 (0.1)	0	1 (0.1)	0	3 (0.1)	0
Necrotising Fasciitis	1 (0.1)	1 (0.1)	1 (0.1)	0	2 (0.1)	1 (0.1)
Peripheral Vascular Disorder	1 (0.1)	0	1 (0.1)	0	2 (0.1)	0
Sepsis	1 (0.1)	1 (0.1)	7 (0.6)	4 (0.7)	11 (0.4)	6 (0.3)
Suicidal Ideation	1 (0.1)	1 (0.1)	0	0	2 (0.1)	1 (0.1)
Urosepsis	1 (0.1)	0	0	0	2 (0.1)	0
Acute Pulmonary Oedema	0	0	2 (0.2)	0	2 (0.1)	0
Acute Respiratory Distress Syndrome	0	0	0	1 (0.2)	2 (0.1)	1 (0.1)
Arteriovenous Graft Site Infection	0	0	2 (0.2)	0	3 (0.1)	0
Ascites	0	0	2 (0.2)	1 (0.2)	3 (0.1)	1 (0.1)
Atrial Fibrillation	0	0	1 (0.1)	0	2 (0.1)	0
Atrial Flutter	0	0	1 (0.1)	0	2 (0.1)	0

Source: Table 04.6.8.P4
Patients with multiple adverse events are counted once within each MedDRA level.

System Organ Class Preferred Term	SOLO Pool Oritavancin (N=976) n (%)	SOLO Pool Vancomycin (N=983) n (%)	ARRD/I Pool Oritavancin (N=1173) n (%)	ARRD/I Pool Vancomycin (N=590) n (%)	All Treated Pool Oritavancin (N=3017) n (%)	All Treated Pool Comparator (N=1954) n (%)
Cardiac Arrest	0	0	3 (0.3)	4 (0.7)	9 (0.3)	4 (0.2)
Cardiac Failure	0	0	1 (0.1)	1 (0.2)	2 (0.1)	1 (0.1)
Cardio-Respiratory Arrest	0	1 (0.1)	3 (0.3)	0	5 (0.2)	1 (0.1)
Chronic Obstructive Pulmonary Disease	0	0	1 (0.1)	1 (0.2)	2 (0.1)	1 (0.1)
Dehydration	0	1 (0.1)	1 (0.1)	1 (0.2)	3 (0.1)	2 (0.1)
Depressed Level Of Consciousness	0	0	0	0	2 (0.1)	0
Diabetes Mellitus	0	0	2 (0.2)	0	2 (0.1)	0
Empyema	0	0	2 (0.2)	0	2 (0.1)	0
Febrile Neutropenia	0	0	0	0	3 (0.1)	0
Femoral Artery Occlusion	0	0	2 (0.2)	0	2 (0.1)	0
Gastric Fistula	0	0	2 (0.2)	0	2 (0.1)	0
Gastrointestinal Haemorrhage	0	0	2 (0.2)	0	5 (0.2)	0
Hydronephrosis	0	0	1 (0.1)	0	2 (0.1)	0
Hypotension	0	0	0	1 (0.2)	7 (0.2)	3 (0.2)
Hypovolaemic Shock	0	0	2 (0.2)	0	2 (0.1)	0
Localised Infection	0	0	2 (0.2)	0	2 (0.1)	0
Mental Status Changes	0	0	2 (0.2)	0	2 (0.1)	0
Multi-Organ Failure	0	0	0	0	3 (0.1)	2 (0.1)
Myocardial Infarction	0	0	3 (0.3)	1 (0.2)	7 (0.2)	2 (0.1)
Neoplasm Progression	0	0	0	0	2 (0.1)	0
Pain In Extremity	0	0	1 (0.1)	1 (0.2)	2 (0.1)	1 (0.1)
Peritonitis	0	0	2 (0.2)	1 (0.2)	3 (0.1)	1 (0.1)
Pulmonary Embolism	0	1 (0.1)	1 (0.1)	4 (0.7)	4 (0.1)	5 (0.3)
Pyrexia	0	2 (0.2)	2 (0.2)	2 (0.3)	3 (0.1)	4 (0.2)
Respiratory Arrest	0	0	2 (0.2)	0	2 (0.1)	0
Respiratory Distress	0	0	0	2 (0.3)	2 (0.1)	2 (0.1)
Respiratory Failure	0	2 (0.2)	1 (0.1)	1 (0.2)	3 (0.1)	3 (0.2)
Schizoaffective Disorder	0	0	2 (0.2)	0	2 (0.1)	0
Septic Shock	0	1 (0.1)	4 (0.3)	0	9 (0.3)	2 (0.1)
Staphylococcal Bacteraemia	0	0	0	0	2 (0.1)	0
Tachycardia	0	0	2 (0.2)	0	2 (0.1)	0
Urinary Tract Infection	0	0	1 (0.1)	0	2 (0.1)	0

Source: Table 04.6.8.P4
Patients with multiple adverse events are counted once within each MedDRA level.

The serious adverse events for oritavancin and vancomycin in the SOLO pool were comparable in frequency. Although the Sponsor did not conduct a formal analysis on the dose-response for safety relationship for oritavancin, there are safety data available from a Phase 2 trial (TAR-ORI-SD-001) that evaluated the following oritavancin dosing regimens: 200 mg (or 300 mg of oritavancin if >100 kg), 1200 mg single dose, and 800 mg oritavancin on Day 1 followed by an optional 400 mg dose on Day 5. The treatment-emergent AEs observed in this trial are shown in Table 2.2.3.2.3.

Table 2.2.3.2.3: Treatment-Emergent Adverse Events in Descending Order of Frequency in ≥3% of the Total ITT Population

Preferred Term	200 mg Ori Daily Dose N = 100 n (%)	1200 mg Ori Single Dose N = 99 n (%)	800 mg Ori Infrequent Dose N = 103 n (%)	Total N = 302 n (%)
Nausea	6 (6.0)	9 (9.1)	7 (6.8)	22 (7.3)
Phlebits	5 (5.0)	5 (5.1)	10 (9.7)	20 (6.6)
Diarrhoea	6 (6.0)	6 (6.1)	4 (3.9)	16 (5.3)
Headache	2 (2.0)	8 (8.1)	4 (3.9)	14 (4.6)
Infusion Site Extravasation	4 (4.0)	5 (5.1)	4 (3.9)	13 (4.3)
Vomiting	5 (5.0)	1 (1.0)	7 (6.8)	13 (4.3)
Constipation	5 (5.0)	5 (5.1)	2 (1.9)	12 (4.0)
Blood Creatine Phosphokinase Increased	2 (2.0)	6 (6.1)	2 (1.9)	10 (3.3)
Insomnia	3 (3.0)	4 (4.0)	2 (1.9)	9 (3.0)

Abbreviations: ITT = intent-to-treat; Ori = oritavancin.

Source: Table 14.3.1.3.

The Sponsor did not analyze the exposure-safety relationship for any of the serious adverse events. The Sponsor did conduct analyses of the exposure-safety relationship for liver-related laboratory abnormalities because a higher proportion of patients in both treatment groups of the SOLO pool had potentially clinically significant liver function test elevations compared to what was observed during the Phase 3 trials that supported the initial NDA submission. However, they did not see any relationship between oritavancin exposure and liver function test elevation (refer to Appendix 4.2 for more details).

2.2.3.3 Does this drug prolong the QT or QTc interval?

Preclinical studies indicated that oritavancin inhibited hERG with an IC_{50} of 22 μM, suggesting that it had some potential to inhibit cardiac ion channels. However, the in vitro effects of oritavancin on cardiac ion channels have not translated into an in vivo effect. A thorough QT study (MDCO-ORI-12-02) was conducted in healthy subjects receiving a single 1600 mg supratherapeutic dose of IV oritavancin, IV placebo, or 400 mg moxifloxacin tablet. No significant QTc prolongation effects of oritavancin 1600 mg infusion were detected in this study. The largest upper bound of the 2-sided 90% CI for the mean difference between oritavancin and placebo for ΔΔQTcF was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the ΔQTcF moxifloxacin profile over time is adequately demonstrated in Figure 2.2.3.3.1, indicating that assay sensitivity was established. An overall summary of findings is presented in Table 2.2.3.3.1.

Figure 2.2.3.3.1: Mean and 90% CI ΔΔQTcF Time Course for Oritavancin 1600 mg Infusion, and Moxifloxacin 400 mg

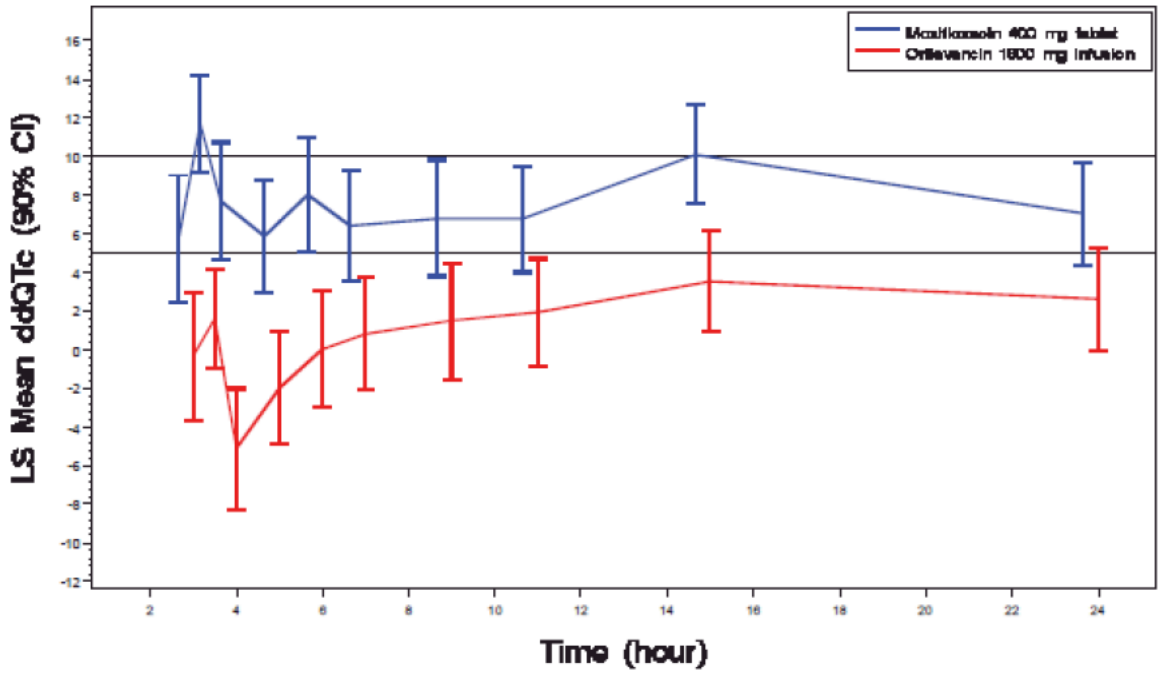


Table 2.2.3.1: Point Estimates and 90% CIs for ΔΔQTcF Corresponding to the Largest Upper Bound for Oritavancin 1600 mg and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Oritavancin 1600 mg Infusion	15	3.5	(0.9, 6.1)
Moxifloxacin 400 mg*	3.5	11.7	(9.2, 14.2)

*Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 8.3 ms

For a complete assessment of the thorough QT study findings, refer to the Interdisciplinary Review Team review (see review by Dr. Moh Jee Ng, dated 12/17/13 under IND 51,292).

2.2.3.4 Is the dose and dosing regimen selected by the Sponsor consistent with the known relationship between dose-concentration response, and are there any unresolved dosing or administration issues?

The oritavancin dose and single dose dosing regimen selected by the Sponsor is consistent with the known relationship between dose-concentration response. The Sponsor's original animal infection models found that AUC/MIC was the PK/PD parameter that best correlated with oritavancin efficacy. Additionally, dose-fractionation studies in both *S. aureus* (mouse neutropenic thigh) and *S. pneumoniae* (mouse lung) infection models indicated that decreasing the dosing interval of oritavancin resulted in less bacterial killing than the single dose, which suggested that concentration-dependent killing was important, and that large, infrequent doses

would be beneficial. The proposed single 1200 mg oritavancin dose regimen is further supported by oritavancin's long half-life and concentration-dependent killing properties. It is likely the 1200 mg dose is in the plateau of the dose-response curve.

2.2.4 What are the PK characteristics of the drug and its major metabolite?

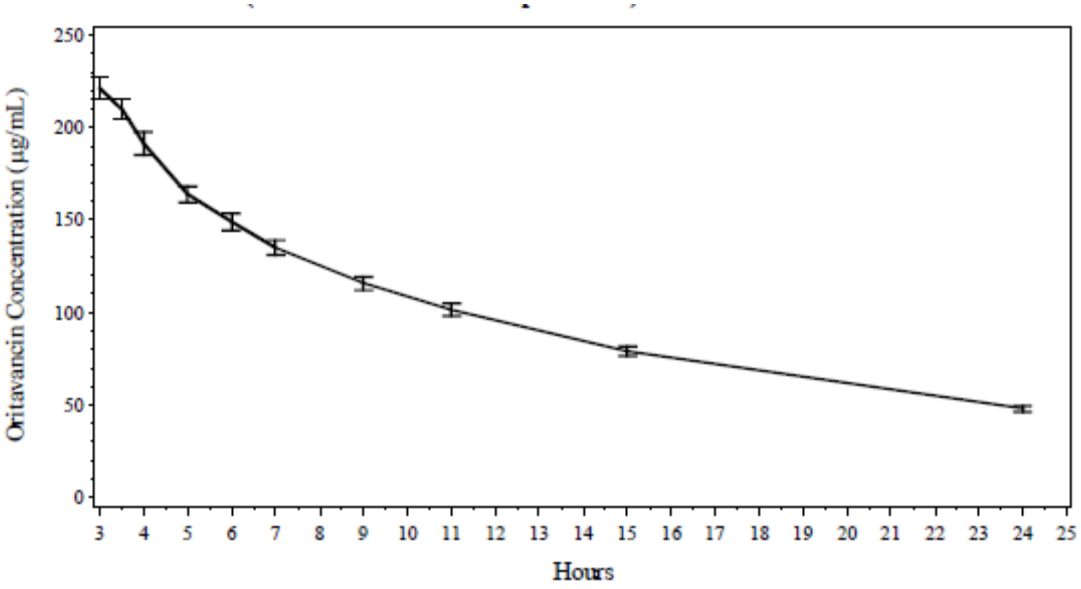
The majority of clinical pharmacology studies for oritavancin were reviewed during the original NDA submission review cycle (refer to the previous clinical pharmacology review dated 12/01/2008). The current oritavancin NDA resubmission includes one new pharmacokinetic (MDCO-ORI-12-03) study which was reviewed in the current cycle. Only relevant questions in section 2.2.4 are addressed. Oritavancin is not metabolized.

2.2.4.1 What are the single dose and multiple dose PK parameters?

The pharmacokinetics of oritavancin were assessed in healthy subjects following the administration of single intravenous oritavancin doses ranging from 100 mg to 600 mg (and up to 3.0 mg/kg as weight based regimens were also explored) and multiple doses from 100 mg to 200 mg/day for 10 days in the original NDA submission (refer to the previous clinical pharmacology review dated 12/01/2008). The current NDA resubmission included 4 studies that contained oritavancin pharmacokinetics; 2 in healthy volunteers (MDCO-ORI-12-02 and MDCO-ORI-12-03) and 2 Phase 3 trials (SOLO I and SOLO II). The single dose concentration-time profiles and pharmacokinetic parameters for 1200 mg (MDCO-ORI-12-03) and 1600 mg (MDCO-ORI-12-02) are shown below. The patient pharmacokinetics observed in SOLO I and SOLO II are addressed in section 2.2.4.2. There are no new multiple dose oritavancin pharmacokinetic parameters available in the resubmission as oritavancin is intended for single dose administration only.

<u>MDCO-ORI-12-02 (1600 mg single dose of oritavancin, TQT trial)</u>
The concentration-time profile of oritavancin is shown in Figure 2.2.4.1.1 and the resulting pharmacokinetic parameters are shown in Table 2.2.4.1.1. Note that the last pharmacokinetic sampling time for this trial was at 24 hours, so only the AUC_{0-24} is reported.

Figure 2.2.4.1.1: Mean (±SD) Plasma Oritavancin Concentration-Time Profile (Linear Scale) following the IV administration of 1600 mg of oritavancin over 3 hours to healthy volunteers



Note: Values below the limit of quantitation were set to zero.
Source: Figure 14.2.3

Table 2.2.4.1.1: Summary of Plasma Oritavancin Pharmacokinetic Parameters following the IV administration of 1600 mg of oritavancin over 3 hours to healthy volunteers

Parameter (unit)	**N**	**Mean (CV%)**	**Geometric Mean**
$AUC_{0\text{-}24}$ (µg·hr /mL)	47	2420.65 (16.93)	2388.31
C_{max} (µg/mL)	47	231.67 (15.57)	228.83
Parameter (unit)	**N**	**Median**	**Minimum, Maximum**
T_{max} (hr)	47	3.06	3.0, 5.1

CV%: percent coefficient of variation
Source: Table 14.2.2

MDCO-ORI-12-03 (1200 mg single dose of oritavancin, cocktail DDI study)
The concentration-time profile of oritavancin is shown in Figure 2.2.4.1.2 and the resulting pharmacokinetic parameters are shown in Table 2.2.4.1.2.

Figure 2.2.4.1.2: Mean (±SD) Plasma Oritavancin Concentration-Time Profile (Linear Scale) following the IV administration of 1200 mg of oritavancin over 3 hours to healthy volunteers

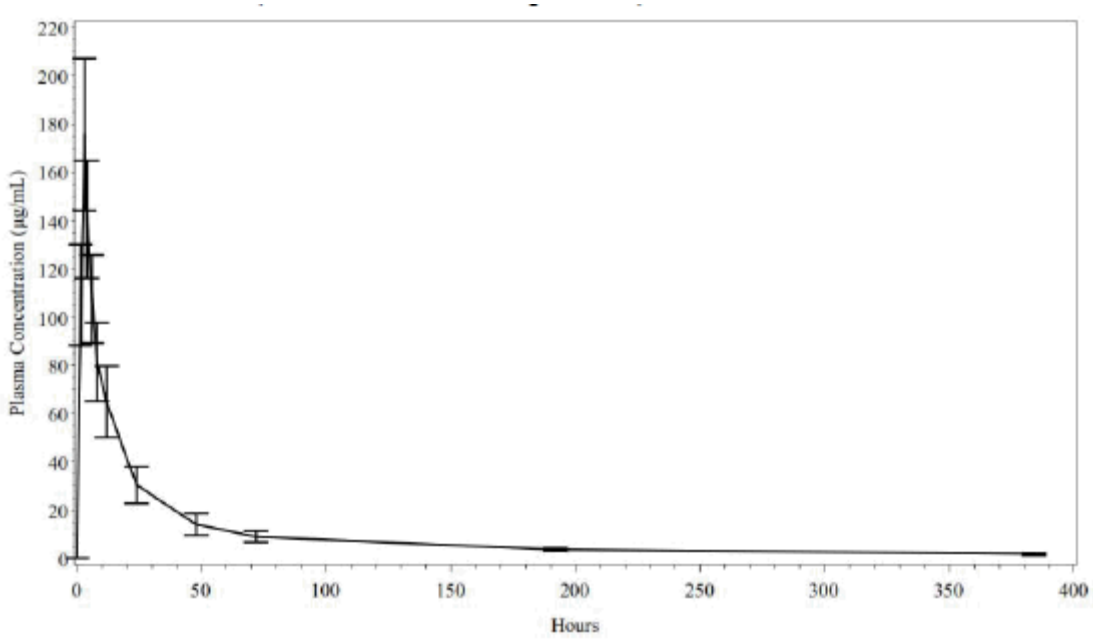


Table 2.2.4.1.2: Summary of Plasma Oritavancin Pharmacokinetic Parameters on Day 1 following the IV administration of 1200 mg of oritavancin over 3 hours to healthy volunteers

Parameter (unit)	N	Mean (CV%)	Geometric Mean
AUC_{0-t} (µg·hr/mL)	16	3696.325 (19.55)	3626.674
$AUC_{0-\infty}$ (µg·hr/mL)	16	4006.507 (18.96)	3935.910
C_{max} (µg/mL)	16	175.715 (17.90)	173.056
$t_{1/2}$ (hr)	16	120.476 (16.63)	118.915
CL/F (L/hr)	16	0.311 (21.00)	0.305
Parameter (unit)	**N**	**Median**	**Minimum, Maximum**
T_{max} (hr)	16	3.083	3.083, 3.151

CV%: percent coefficient of variation

The C_{max} from the 1200 mg and 1600 mg appears to be dose proportional. The AUCs were calculated over different intervals in the two studies, but the AUC does appear to be dose proportional as well from a visual examination.

2.2.4.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The majority of the Phase 1 studies conducted with oritavancin involved dosing regimens other than a 1200 mg single dose. The healthy volunteer oritavancin pharmacokinetic data following the administration of the 1200 mg single dose is limited to study MDCO-ORI-12-03. Patient pharmacokinetics of oritavancin following the 1200 mg single dose are limited to population

pharmacokinetics as assessed in the Phase 3 trials SOLO I and SOLO II. Table 2.2.4.2.1 shows the summary of oritavancin's pharmacokinetics following the 1200 mg single dose.

Table 2.2.4.2.1: Mean (CV%) Oritavancin PK Parameters after Administration of a Single Dose of 1200 mg IV over 3 Hours

Study	C_{max} (µg/mL)	AUC_{0-24} (µg•h/mL)	$AUC_{0-\infty}$ (µg•h/mL)	$t_{1/2}$[a] (h)	CL (L/h)	Vss (L)
MDCO-ORI-12-03	176 (17.9)	NC	4007 (19.0)	120 (16.6)	0.311 (21.0)	NC
SOLO I	144 (23.8)	1200 (37.4)	2950 (31.8)	244 (15.4)	0.443 (32.2)	91.9 (64.8)
SOLO II	134 (22.1)	1060 (29.9)	2710 (25.8)	245 (14.8)	0.472 (26.4)	101 (51.6)

Source: MDCO-ORI-12-03, Table 8; ICPD 00247-1, Table 4-7 and 4-8

[a] Value for MDCO-ORI-12-03 derived using noncompartmental methods; values for SOLO I and SOLO II are the terminal elimination $t_{1/2}$ ($t_{1/2,\gamma}$) derived from the pooled population PK model

NC = Not calculated; CV% = percent coefficient of variation

The pharmacokinetics of oritavancin in the 2 Phase 3 trials appear to be similar. However, there are some differences between patients and healthy volunteers. Namely, the C_{max} and AUC are about 25-40% higher in healthy volunteers as compared to patients. Although different methods were used to analyze the PK data from the original NDA, the same trends (e.g. lower CL and higher AUC in healthy volunteers) was observed. The reasons for this difference are unclear, and the Sponsor does not speculate as to what may be causing it other than to point out that the clinical relevance of this difference is not meaningful since healthy subjects will not be receiving oritavancin. Also note that the estimated half-life in oritavancin is about twice as long in patients as it is in healthy volunteers. This may in part be due to differences in sample collection. The last oritavancin concentration-time point in MDCO-ORI-12-03 was collected at 384 hours post dose whereas the final oritavancin plasma concentration collection from the sparse sampling in the pharmacokinetic subset of SOLO I and SOLO II was at 576 hours.

2.2.4.3 What are the characteristics of drug absorption?

Oritavancin is intended for intravenous administration only.

2.2.4.4 What are the characteristics of drug distribution?

No new studies have been conducted to assess the distribution of oritavancin. In brief, studies conducted under NDA 22-153 show that oritavancin is widely distributed into tissues, and that oritavancin penetrates into skin blister fluid (as assessed in Study OSCI-001) and ELF and AM (as assessed in Study OPUL-0001). Oritavancin is approximately 85% protein bound across species.

2.2.4.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

No formal radiolabelled mass-balance studies have assessed the disposition of oritavancin in humans. The results of 3 Phase 1 studies showed that less than 5% of oritavancin is excreted unchanged in feces and urine up to 14 days after administration of a single dose.

2.2.4.6 What are the characteristics of drug metabolism?

Oritavancin is not metabolized.

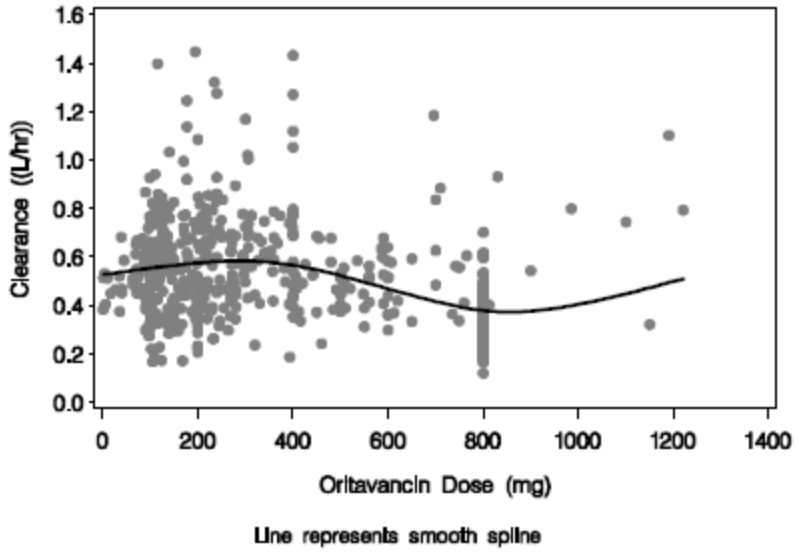
2.2.4.7What are the characteristics of drug excretion?

Oritavancin is excreted unchanged in urine and feces. However, due to tissue accumulation and slow elimination of oritavancin, very little oritavancin was excreted in urine or in feces up to 2 weeks after administration of a single dose (see Section **2.2.4.5**).

2.2.4.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Oritavancin pharmacokinetics are linear over the dose range studied (see previous clinical pharmacology review dated 12/1/08 and Section **2.2.4.1**). The relationship between oritavancin clearance and dose administered (from the original NDA) is shown in Figure 2.2.4.8.1.

Figure 2.2.4.8.1: Scatterplot of Individual Post-Hoc Oritavancin Clearance vs. Dose from the Original Population PK Analysis



Source: ICPD 00142-01, Figure 4-26

2.2.4.9 How do the PK parameters change with time following chronic dosing?

Oritavancin is intended for single use only. Therefore, there is no information about the change in PK parameters following chronic dosing.

2.2.4.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The Sponsor developed a population PK model based on the sparse sampling that was conducted during the SOLO I and SOLO II trials. The model contained the same structure as the previously

developed oritavancin population PK model (3-compartment open model with first-order elimination). The Reviewer conducted an independent analysis of the population PK model (see Appendix 4.2). The inter- and intra-subject variability of the pharmacokinetic parameters in the population PK model are shown in Table 2.2.5.10.1.

The variability observed in the parameters pertaining to the third compartment may in part be due to the sparse sampling strategy employed to generate the population PK model. While there is strong evidence that a third compartment exists, a rich sampling strategy would be necessary to reduce variability in parameter estimates.

Table 2.2.5.10.1: Inter- and intra-subject variability in oritavancin population PK parameters estimates based on the Reviewer's final model

Inter-Individual Variability Parameters (CV%)	**Estimate**	**RSE(%)**	**Shrinkage**
Omega (CL)	25.7	8.9	16
Omega (V1)	46.2	24.9	26
Omega (Q2)	50.5	8.7	16
Omega (V2)	34.5	28.1	61
Omega (Q3)	0	-	-
Omega (V3)	12.9	260	76
Residual Variability Parameters	**Estimate**	**RSE (%)**	**CI95**
Proportional Error	0.27	13.13	(0.20-0.34)

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

For a review of the impact of intrinsic factors on the pharmacokinetics of oritavancin from the previous NDA, please refer to the clinical pharmacology review dated 12/01/2008. There were no dedicated PK studies to evaluate the effect of gender, age, race, or renal impairment on the pharmacokinetics of oritavancin. The previously developed population PK model (three-compartment model with zero order IV input and linear elimination) fit the pooled oritavancin concentration-time data from SOLO I and SOLO II with no structural changes required. The effects of these intrinsic factors on the exposure or response to oritavancin were evaluated based on analyses of the population PK data. The effect of moderate hepatic impairment on the pharmacokinetics of oritavancin was evaluated in a dedicated PK study.

The Sponsor identified two significant covariate relationships: age on the central volume of distribution (Vc) where Vc decreased with increasing age, and a relationship between height and clearance where CL increased with increasing height. Collectively, these relationships explained a clinically insignificant amount of the inter-individual variability for oritavancin. No dose adjustments were deemed necessary on the basis of age, height, gender, body weight, race, renal function, or diabetic status.

The Reviewer conducted an independent population PK analysis (see Appendix 4.2), and found that the Sponsor's model was generally acceptable. However, one of the covariate relationships identified by the Sponsor was a relationship between height and clearance. In the Reviewer's analysis, height was replaced by more biologically plausible covariates such as BMI or BSA since height is likely acting as a surrogate for weight. The Reviewer's alterations to the model did not result in differences in the parameter estimates that would be of clinical relevance.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

There are no dosage adjustment recommendations for oritavancin on the basis of any intrinsic factor.

2.3.2.1 Elderly patients

In the Sponsor's covariate analysis, age was found to have a modest impact on Vc, and no impact on CL. Although the relationship between age and Vc was found to be statistically significant, the resulting C_{max} and AUC changes are not anticipated to be clinically significant (see Table 2.3.2.1.1). Figure 2.3.2.1.1 shows that the oritavancin C_{max} does not significantly increase with increasing age. There were no observed trends for changes in other pharmacokinetic parameters with age.

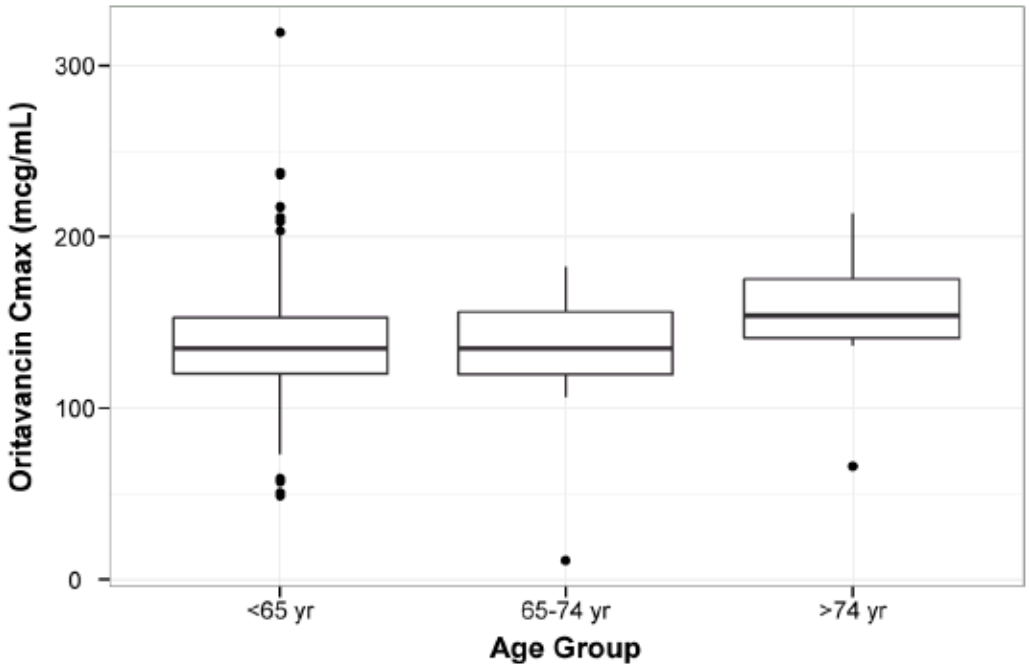
Table 2.3.2.1.1: Summary statistics of oritavancin plasma exposures for all patients included in the pooled SOLO I and SOLO II PK population, stratified by age (n=297)

Age Category	< 65 yr (n=272)		65-74 yr (n=17)		>74 yr (n=8)	
Variable	Mean (SD)	Median (Min- Max)	Mean (SD)	Median (Min- Max)	Mean (SD)	Median (Min- Max)
C_{max} (µg/mL)	137 (30.8)	135 (49.2 - 319)	132 (38.1)	135 (11.1 - 183)	154 (44.8)	154 (66.1 - 214)
AUC_{0-24} (µg·h/mL)	1130 (378)	1070 (258 - 4060)	868 (278)	909 (109 - 1370)	1040 (397)	1030 (320 - 1540)
AUC_{0-48} (µg·h/mL)	1420 (510)	1330 (298 - 5370)	1040 (322)	1090 (172 - 1630)	1230 (468)	1210 (395 - 1860)
AUC_{0-72} (µg·h/mL)	1560 (569)	1470 (325 - 5900)	1130 (340)	1170 (223 - 1770)	1330 (500)	1310 (443 - 2030)
AUC_{0-576} (µg·h/mL)	2560 (790)	2390 (607 - 7750)	1880 (432)	1900 (818 - 2730)	2150 (697)	2150 (915 - 3200)
$AUC_{0-\infty}$ (µg·h/mL)	2840 (804)	2680 (832 - 8070)	2160 (424)	2180 (1180 - 3020)	2480 (729)	2520 (1170 - 3500)

Abbreviations:

C_{max} = Maximum plasma concentration; peak plasma concentration, AUC_{0-24} = Area under the plasma concentration-time curve from time zero to 24 hours, AUC_{0-48} = Area under the plasma concentration-time curve from time zero to 48 hours, AUC_{0-72} = Area under the plasma concentration-time curve from time zero to 72 hours, AUC_{0-576} = Area under the plasma concentration-time curve from time zero to 576 hours, $AUC_{0-\infty}$ = Area under the plasma concentration-time curve from time zero to infinity, SD = Standard deviation, Min = Minimum, Max = Maximum.

Figure 2.3.2.1.1: Box-and-whisker plots of oritavancin C_{max} versus patient age category for all patients included in the pooled SOLO I and SOLO II pharmacokinetic population (n=297)



The Reviewer's analysis is shown in Table 2.3.2.1.2, which shows the mean (median) AUC_{0-72} values of oritavancin by subsets of different possible covariates. The AUC_{0-72} or oritavancin did not demonstrate significant variation across quartiles of body weight, age, BMI, or BSA. There also did not appear to be a relationship between oritavancin exposure and patient race, baseline renal function, or baseline MIC value.

Table 2.3.2.1.2: Predicted AUC_{0-72} based on post-hoc parameter estimates from the reviewer's population PK analysis and integration of oritavancin exposures over 72 hours for a subset of covariates following a single 1200 mg dose infused over 3 hours in ABSSSI patients[1]

	Oritavancin AUC72 (ng·h/mL): Mean (median)			
Body weight (kg)	>= 43 & <64	>= 64 & <76	>= 76 & <89	>= 89 & <=178
	1470 (1406)	1534 (1497)	1434 (1419)	1428 (1387)
Age (years)	>= 18 & <36	>= 36 & <47	>= 47 & <55	>= 55 & <=89
	1646 (1677)	1482 (1452)	1369 (1342)	1375 (1306)
BMI (kg/m^2)	>= 15.9 & <22.8	>= 22.8 & <26.2	>= 26.2 & <30.4	>= 30.4 & <=67.4
	1433 (1351)	1464 (1413)	1491 (1459)	1478 (1433)
BSA (m^2)	>= 1.31 & <1.73	>= 1.73 & <1.89	>= 1.89 & <2.04	>= 2.04 & <=2.79
	1514 (1490)	1532 (1511)	1423 (1413)	1404 (1378)
Race	Asian	African American	White	Other

	1578 (1555)	1581 (1511)	1436 (1378)	1468 (1530)
Creatinine Clearance (mL/mL)	>30-50 mL/min	>50-80 mL/min	>80-110 mL/min	>110 mL/min
	1466 (1283)	1387 (1345)	1536 (1504)	1457 (1422)
Gender	Male		Female	
	1403 (1374)		1600 (1605)	

[1]: The categorical divisions for body weight, age, BMI, and BSA represent quartiles

2.3.2.2 Pediatric patients. What is the status of pediatric studies and/or any pediatric plan for study?

Pediatric patients were not enrolled during the oritavancin development program. The Sponsor has requested a deferral of the pediatric studies. The Sponsor has initiated discussions with the Division on a pediatric plan, and has submitted the initial Phase 1 dose finding PK, safety, and tolerability protocol.

2.3.2.3 Gender
Gender was not found to affect oritavancin's pharmacokinetics.

2.3.2.4 Race, in particular differences in exposure and/or response in Caucasians, African-Americans, and/or Asians
Refer to Table 2.3.2.1.2.

2.3.2.5 Renal impairment
Refer to Table 2.3.2.1.2.

2.3.2.6 Hepatic impairment

There were very few patients with hepatic impairment in the population PK dataset; thus hepatic impairment was not considered as a potential covariate in the model. However, an independent study of subjects with moderate hepatic impairment (see previous clinical pharmacology review dated 12/01/08) showed that a dosage adjustment for oritavancin on the basis of moderate hepatic impairment was not necessary. There is no information about the pharmacokinetics of oritavancin in subjects with severe hepatic impairment.

2.3.2.7 What pregnancy and lactation use information is there in the application?

No adequate and well-controlled studies with oritavancin have been conducted in pregnant women. Across all clinical studies of oritavancin, a total of 5 pregnancies were reported on oritavancin. Three of the pregnancies in the oritavancin group were reported in ABSSSI patients in the Phase 3 SOLO studies that utilized the single 1200 mg dose and two of the pregnancies were reported in the Phase 1 studies in healthy volunteers. A brief summary of pregnancy outcomes is described below.

Single 1200 mg Dose of Oritavancin (ABSSSI Patients)

- Patient 101005032 in SOLO I: pregnancy was detected 15 days after receiving a single infusion of oritavancin, with subsequent spontaneous abortion. Relevant medical history included hypertension, gastrointestinal diabetes, and two previous spontaneous abortions in (b) (6)
- Patient 201001122 in SOLO II: pregnancy was detected 59 days after a single oritavancin exposure. The patient retained the pregnancy and completed Day 60 follow-up. Final outcome of the pregnancy is unknown, pending an anticipated (b) (6) delivery date. Relevant medical history included IV drug use, obesity, and placenta previa; pregnancy history was unknown.
- Patient 201001122 in SOLO II: pregnancy was detected 44 days following a single infusion of oritavancin. On Day 57, the patient fell down. On the following day, the patient had a miscarriage. Relevant medical history included IV drug use, hypertension, depression, anxiety, and alcohol ingestion.

Healthy Volunteers

- Subject OSCI-007-001-0003 had a positive urine pregnancy test on Study Day 15 (7 Nov 2002), 3 days after receiving her fifth and final oritavancin infusion. This subject had a negative serum pregnancy test at screening and a negative pregnancy test at baseline. The subject had received 13 days of desipramine plus five oritavancin infusions. The pregnancy was terminated on 13 December 2002.
- Subject OPUL-00101-016 became pregnant approximately 7 weeks after completing her last dose of oritavancin. She gave birth to a healthy male on (b) (6)

It is unknown whether oritavancin is excreted into human milk, but it is known that oritavancin is excreted in the milk of lactating rats.

2.3.2.8 Obesity
Refer to Table 2.3.2.1.2.

2.4 Extrinsic Factors

Following receipt of the CR letter dated 12/08/2008, the Sponsor revisited the proposed dosing regimen of oritavancin for future development. Under NDA 22-153, the dosing regimen of oritavancin was 200 mg (or 300 mg for patients weighing more than 110 kg) by intravenous infusion over approximately 60 minutes every 24 hours for 3-7 days. In the current NDA, the proposed dose of oritavancin is a one-time-only 1200 mg IV dose on Day 1 administered via a 3 hour infusion. The conclusion of the clinical pharmacology review for NDA 22-153 was that oritavancin was unlikely to experience or contribute to drug interactions. However, the new dosing strategy led to an increased C_{max} of oritavancin; therefore, concerns about potential drug interactions needed to be addressed. In order to address potential drug interaction concerns, the Sponsor conducted a cocktail drug interaction study (MDCO-ORI-12-03, see Appendix 4.1 for study report review). The QBR questions contained below refer to the newly-conducted drug interaction trial. For a comprehensive review of the impact of extrinsic factors on the pharmacokinetics of oritavancin as assessed during the previous development program, please refer to the previous clinical pharmacology review dated 12/01/2008.

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The impact of extrinsic factors on the pharmacokinetics of oritavancin other than drug interactions has not been assessed.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

The ability of oritavancin to inhibit the metabolism of probe drugs by select CYP enzymes (CYP3A, CYP2D6, CYP2C9, CYP1A2) was examined in vitro (Study ADME-23 under NDA 22-153). Human hepatocytes were incubated with probe drugs with and without oritavancin. The metabolism of the probe drug under each set of conditions was determined. Oritavancin showed the strongest inhibition of the CYP2D6-catalyzed conversion of bufuralol to 1'-OH bufuralol (K_i = 12.6 μM or 25.1μg/mL, noncompetitive inhibition). The potential order of CYP inhibition was determined to be CYP2D6>CYP3A>CYP1A2>CYP2C9.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

No. Oritavancin is not metabolized.

2.4.2.3 Is the drug an inhibitor and/or inducer of CYP enzymes?

In vitro evidence suggests that oritavancin may be a weak, non-specific, inhibitor of several different CYP450 isozymes. However, a previous clinical study (OCSI-008) did not result in any observable interaction between oritavancin and desipramine when oritavancin was administered as 800 mg IV daily for 14 days (see Clinical Pharmacology review under NDA 22-153 dated 12/1/08). Given the oritavancin dose proposed in this NDA (1200 mg), the resulting increase in C_{max}, and the in vitro findings, the Sponsor conducted a cocktail drug interaction study (MDCO-ORI-12-03). Study MDCO-ORI-12-03 was designed to evaluate the impact of oritavancin on the pharmacokinetics of the probe drugs in the Cooperstown 5+1 cocktail (caffeine, omeprazole, warfarin, vitamin K, dextromethorphan, and midazolam). The enzymatic activities of CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, N-acetyltransferase-2 (NAT-2), and Xanthine oxidase (XO) were also assessed (see Appendix 4.1).

Sixteen subjects were enrolled in the trial, and all 16 subjects completed the study. On the morning of Day -4, subjects were administered the Cooperstown 5+1 cocktail alone, and on Day 1, oritavancin was administered concomitantly with the probe drugs in the Cooperstown 5+1 cocktail. The pharmacokinetics of the probe drugs were assessed with and without oritavancin. The specific enzymatic phenotyping measures that were used to define drug metabolizing enzyme activities were calculated according to Table 2.4.2.3.1. Table 2.4.2.3.2 shows the summary of the effect of oritavancin on the probe substrates of the Cooperstown 5+1 cocktail, and Figure 2.4.2.3.1 is a forest plot that graphically displays the data in Table 2.4.3.2.2.

Table 2.4.2.3.1: Phenotyping measures used to determine drug metabolizing enzyme activities in MDCO-ORI-12-03

Enzyme	*Phenotyping measure*
CYP1A2	Urinary molar ratio of (1X + 1U + AFMU)/17U
CYP2C9	Plasma *S*-warfarin $AUC_{0-\infty}$
CYP2C19	Plasma concentration ratio of omeprazole to 5-hydroxyomeprazole
CYP2D6	Urinary molar ratio of dextromethorphan to dextrorphan
CYP3A4	Plasma midazolam CL/F
NAT-2	Urinary molar ratio of AFMU/(1X + 1U)
XO	Urinary molar ratio of 1U/(1X + 1U)

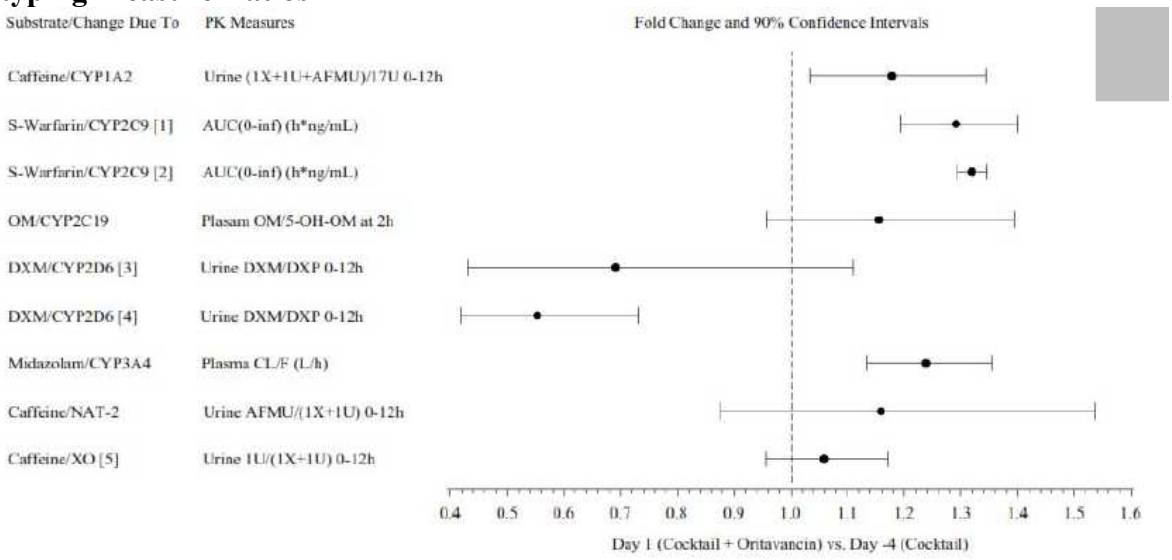
1U: 1-methylurate; 17U: 1, 7-dimethylurate; 1X: 1-methylxanthine; AFMU: 5-acetylamino-6-formylamino-3-methyluracil; $AUC_{0-\infty}$: area under the plasma concentration-time curve from time zero to infinity; CL/F: apparent oral clearance; CYP: cytochrome P450; NAT-2: *N*-Acetyltransferase-2; XO: xanthine oxidase.

Table 2.4.2.3.2: Summary of the Effect of Oritavancin on the Probe Substrates of the Cooperstown 5+1 Cocktail

Substrate	Isozyme	Biological Matrix	PK Parameter	Units	N	Geometric Mean		Ratio	90% Confidence Interval	
						Day -4	Day 1	Day 1/Day-4	Low	High
Midazolam	CYP 3A4	Plasma	CL/F	L/hr	16	79.745	98.814	1.239	1.135	1.353
		Plasma	AUC(0-inf)	hr*ng/mL	16	70.220	57.091	0.813	0.744	0.888
S-Warfarin	CYP 2C9	Plasma	AUC(0-inf)	hr*ng/mL	16	15623	20610	1.319	1.294	1.345
S-Warfarin	CYP 2C9	Plasma	AUC(0-inf)	hr*ng/mL	3	11340	14650	1.292	1.192	1.400
Omeprazole	CYP 2C19	Plasma	OM/5-OM at 2 Hr	Ratio	16	1.501	1.734	1.155	0.957	1.395
Dextromethorphan	CYP 2D6	Urine	Ratio of DXM/DXP in -12Hr Urine	Ratio	13	0.206	0.142	0.692	0.431	1.110
				Ratio	12	0.230	0.127	0.553	0.419	0.731
Caffeine	CYP 1A2	Urine	Ratio of [(1X+1U+AFMU/17U] in -12Hr Urine	Ratio	16	4.125	4.863	1.179	1.033	1.345
Caffeine	NAT-2	Urine	Ratio of [AFMU/(1X+1U)] in -12Hr Urine	Ratio	16	0.180	0.208	1.159	0.875	1.535
Caffeine	XO	Urine	Ratio of [1U/(1X+1U)] in -12Hr Urine	Ratio	14	0.524	0.555	1.058	0.956	1.172

1U: 1-methylurate; 17U: 1, 7-dimethylurate; 1X: 1-methylxanthine; AFMU: 5-acetylamino-6-formylamino-3-methyluracil; AUC_{0-inf}: (also referred to as $AUC_{0-\infty}$) area under the plasma concentration-time curve from time zero to infinity; CL/F: apparent oral clearance; CYP: cytochrome P450; DXM: dextromethorphan; DXP: dextrorphan; Hr: hour(s); NAT-2: *N*-Acetyltransferase-2; OM: omeprazole; PK: pharmacokinetic; XO: xanthine oxidase Source: Table 14.2.1.3.1, Table 14.2.2.1.1, Table 14.2.2.1.2, Table 14.2.2.1.3

Figure 2.4.2.3.1: Summary of the Effect of Oritavancin on the Probe Substrates of the Cooperstown 5+1 Cocktail Displayed as 90% Confidence Intervals of the Geometric Mean Phenotyping Measure Ratios



1U: 1-methylurate; 17U: 1, 7-dimethylurate; 1X: 1-methylxanthine; AFMU: 5-acetylamino-6-formylamino-3-methyluracil; $AUC_{0\text{-}inf}$: (also referred to as $AUC_{0\text{-}\infty}$) area under the plasma concentration-time curve from time zero to infinity; CL/F: apparent oral clearance; CYP: cytochrome P450; DXM: dextromethorphan; DXP: dextrorphan; h: hour(s); NAT-2: *N*-Acetyltransferase-2; OM: omeprazole; PK: pharmacokinetic; XO: xanthine oxidase
[1] N = 3; predose plasma concentration <5% of the post-dose maximum plasma concentration (C_{max}) on Day 1.
[2] N = 16; all subjects.
[3] N = 13; CYP2D6 activities that were ≤0 or outliers were excluded.
[4] N = 12; CYP2D6 activities that were ≤0 or outliers were excluded. Subject 1001 was also excluded.
[5] N = 14; XO activities that were ≤0 or outliers were excluded.

Examination of Figure 2.4.2.3.1 reveals that only the activity of XO has the point estimate and lower and upper bounds of the 90% confidence interval fall within the traditional boundary of 80-125%. Thus, co-administration with oritavancin alters the activities of the other enzymes tested. However, the highest point estimate is 1.32, and the lowest point estimate is 0.55, which indicates that the observed changes in enzymatic activity may not be of sufficient magnitude to be clinically significant. It is important to note that although oritavancin has a long terminal elimination half-life (245 hours), its reduction from the plasma is much more rapid. The concentration of oritavancin in the plasma would be predicted to drop below the in vitro IC_{50s} at 48 hours post dose. Taken together, these data suggest that mild drug interactions due to the disruption (inhibition or induction) of several CYP isoforms or NAT-2 may occur, but the magnitude of the resulting drug interactions is not likely to be clinically significant and that any drug interaction that does occur will likely be brief in duration.

Oritavancin was shown to be a weak inhibitor of CYP2C19 and CYP2C9 and a weak inducer of CYP2D6 and CYP3A4. The clinical implications of these interactions are likely to be minimal because the observed interactions are not large in magnitude, and the duration of any interaction is likely to be brief as the concentration of oritavancin in plasma would be expected to fall below the observed IC_{50s} within 48 hours after administration. However, warfarin (the CYP2C9 probe substrate) is known to have a narrow therapeutic range. In this instance, an increase of approximately 30% could be clinically significant. The Sponsor has proposed (and the Reviewer agrees with) including language in the oritavancin label regarding this potential interaction and recommends that patients should be monitored for signs of bleeding if taking both medications concomitantly.

2.4.2.4 Is the drug a substrate and/or inhibitor of P-glycoprotein transport processes?

Oritavancin is neither a P-gp substrate nor a P-gp inhibitor.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

Other metabolic/transporter pathways are unlikely important. Oritavancin is intended for intravenous administration, so absorptive transporters will not be affected. Additionally, oritavancin is eliminated very slowly, so the renal and hepatic transport systems are not likely to play a major role in the distribution or elimination of oritavancin.

2.4.2.6 Does the label specify co-administration of another drug, and if so, has the interaction potential between these drugs been evaluated?

The proposed label does not specify co-administration of another drug with oritavancin.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

Gram-negative antibiotics are likely to be co-administered with oritavancin, which is indicated for Gram-positive pathogens. Oritavancin may also be given with a number of other drugs that target the disease state and co-morbidities that may occur in a population of ABSSSI patients.

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

See section **2.4.2.3**.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

There is no known basis for pharmacodynamic drug-drug interactions with oritavancin.

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

There are no unresolved issues related to metabolism, active metabolites, or metabolic drug interactions. The protein binding of oritavancin is estimated at 85% in human plasma.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

The impact of oritavancin on transporter-mediated drug interactions has not been assessed. A transporter-mediated drug interaction affecting oritavancin's pharmacokinetics is unlikely for the reasons discussed in section **2.4.2.5**. Oritavancin acting as a perpetrator in a transporter-mediated drug interaction with a concomitant substrate cannot be ruled out, but this scenario is

unlikely to result in a clinically significant drug interaction given the proposed single dose regimen of oritavancin therapy.

2.5 General Biopharmaceutics

Not applicable, as oritavancin is intended for intravenous infusion.

2.6 Analytical Section

For a comprehensive review of the bioanalytical methods employed during the previous review cycle (NDA 22-153), please refer to the previous clinical pharmacology review dated 12/01/2008. For the current NDA, concentrations of oritavancin were obtained as part of the drug-drug interaction trial (MDCO-ORI-12-03) and the two Phase 3 trials (SOLO I and SOLO II). Concentrations for probe drugs midazolam, warfarin, omeprazole, dextromethorphan, and caffeine (as well as resulting metabolites) were reported for MDCO-ORI-12-03. The following section will refer to bioanalytical methods pertaining to the assessment of oritavancin concentrations. For the bioanalytical information referencing the probe drugs used in the Cooperstown 5+1 cocktail, please refer to Appendix 4.1. The bioanalytical methods included in this NDA resubmission were acceptable.

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Oritavancin was the active moiety measured in human plasma via LC-MS/MS methods in clinical pharmacology and clinical studies.

2.6.2 Which metabolites have been selected for analysis and why?

Oritavancin is not metabolized. Therefore, no metabolites were selected for analysis.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The total concentration of oritavancin was measured. Although no specific justification was provided for this decision, the protein binding of oritavancin is not concentration-dependent, so the assessment of total concentrations is appropriate.

2.6.4 What bioanalytical methods are used to assess concentrations?

LC-MS/MS was used to assess the concentrations of oritavancin.

2.6.4.1What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

Two LC-MS/MS methods were used. Method BTM-1379-R0 had a calibration range of 12.5 to 1000 ng/mL, and method BTM-1379H-R0 had a calibration range of 0.5 to 300 mcg/mL. These methods were adequate to assess the concentrations of oritavancin

encountered in clinical studies. Linear regression was used with a weighting factor of $1/x^2$ for both methods.

2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

BTM-1379-RO
LLOQ: 12.5 ng/mL
ULOQ: 1000 ng/mL

BTM-1379H-R0
LLOQ: 0.5 mcg/mL
ULOQ: 300 mcg/mL

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?
BTM-1379-RO
Accuracy: 89.8 – 104.2%
Precision: 2.0 – 7.9% (%CV)
Selectivity: No interfering peaks were detected at the retention times of oritavancin and the internal standard in blank human plasma.

BTM-1379H-R0
Accuracy: 92 – 104.2%
Precision: 0.4 – 6.8% (%CV)
Selectivity: No interfering peaks were detected at the retention times of oritavancin and the internal standard in blank human plasma.

2.6.4.4 What is the sample stability under the conditions used in the study (long term freeze-thaw, sample-handling, sample transport, autosampler)?

BTM-1379-RO
QC sample bench-top stability: At least 72 hours at room temperature.

Stock solution stability: At least 382 days at 4 ºC for oritavancin and internal standard. At least 6 hours at room temperature for oritavancin and internal standard.

Processed sample stability: At least 168 hours at room temperature.

QC freeze/thaw stability: 3 freeze (-20 ºC)/thaw cycles

QC sample long-term storage stability: At least 376 days at -20 ºC, and at least 671 days at -70 ºC

BTM-1379H-RO
QC sample bench-top stability: At least 72 hours at room temperature.

Stock solution stability: At least 94 and 92 days at 4 ºC for oritavancin and internal standard. At least 6 hours at room temperature for oritavancin and internal standard.

Processed sample stability: At least 168 hours at room temperature.

QC freeze/thaw stability: 3 freeze (-20 ºC)/thaw cycles

QC sample long-term storage stability: At least 367 days at -20 ºC, and at least 681 days at -70 ºC

2.6.4.5 What is the QC sampling plan?

Eight non-zero calibration standards and three levels of QC samples (low, mid, and high QC) for oritavancin were prepared for use during sample analysis.

3 DETAILED LABELING RECOMMENDATIONS

Detailed labeling recommendations will be provided in a separate addendum.

4 APPENDICES

4.1 Individual Clinical Pharmacology Study Reviews

An Open-Label Study Evaluating the Effects of a Single Oritavancin Infusion on Cytochrome P450 (CYP) 1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A, N-Acetyltransferase-2, and Xanthine Oxidase Activities in Healthy Adults using the Cooperstown 5 + 1 Cocktail

Dates: Jan 23 – March 4, 2013
Investigator: (b) (4)
Analysis: (b) (4)

OBJECTIVES:
The primary objective was to examine the effects of a single IV infusion of oritavancin on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A, N-Acetyltransferase-2 (NAT-2), and xanthine oxidase (XO) activities using the Cooperstown 5 + 1 cocktail (consisting of the probe drugs caffeine, warfarin, vitamin K, omeprazole, dextromethorphan, and midazolam) in healthy adults.

BACKGROUND:
In vitro preclinical studies with human cytochrome P450 (CYP) 3A4, CYP2D6, CYP2C9, CYP2C19, CYP2B6, and CYP1A2 indicated that oritavancin may inhibit metabolism of a co-administered drug that is dependent on the same CYP pathways. Oritavancin was an inhibitor of all CYP isoforms tested, with 50% inhibitory concentration (IC_{50}) values ranging from 16 μM (for CYP3A) to 40.5 μM (for CYP1A2). In a previous clinical study, there did not appear to be any observable interaction between oritavancin and desipramine when oritavancin was administered as 800 mg IV daily for 14 days. At present, oritavancin is proposed to be dosed as a 1200 mg single dose. The current study is a cocktail drug interaction study to evaluate the impact of oritavancin on the pharmacokinetics of several probe substrates.

Reviewer comment: The C_{max} of oritavancin in the Phase 3 trials following the 1200 mg once only dose was 138 mcg/mL, which is equivalent to 69.4 μM. The mean C_{max} of oritavancin in patients during the initial review cycle (during which a dose of 200 or 300 mg [if over 110 kg] once daily for 3-7 days was used) was 27.3 mcg/mL or 13.7 μM. The increased maximum concentration could conceivably make drug-drug interactions more likely.

STUDY DESIGN:
Subjects were admitted to the study center on Day -5 for completion of pre-dose procedures. In the morning of Day -4, subjects received the Cooperstown 5 + 1 cocktail (consisting of the probe drugs caffeine, warfarin, vitamin K, omeprazole, dextromethorphan, and midazolam). Midazolam was administered at approximately 7 am and the remainder of the cocktail was administered at approximately 10 am. In the morning of Day 1 at approximately 7 am, 1200 mg oritavancin was administered as a single IV infusion over 3 hours and the midazolam portion of the Cooperstown 5 + 1 cocktail was administered at the start of the oritavancin infusion. At approximately 10:00 am, the remainder of the cocktail was administered. Subjects were asked to

return to the study center on Days 8 and 16 for collection of additional blood samples and on Day 28 for the final post-treatment follow-up visit.

The specific phenotyping measures used to determine drug metabolizing enzyme activities were as follows:

Enzyme	*Phenotyping measure*
CYP1A2	Urinary molar ratio of (1X + 1U + AFMU)/17U
CYP2C9	Plasma *S*-warfarin $AUC_{0-\infty}$
CYP2C19	Plasma concentration ratio of omeprazole to 5-hydroxyomeprazole
CYP2D6	Urinary molar ratio of dextromethorphan to dextrorphan
CYP3A4	Plasma midazolam CL/F
NAT-2	Urinary molar ratio of AFMU/(1X + 1U)
XO	Urinary molar ratio of 1U/(1X + 1U)

1U: 1-methylurate; 17U: 1, 7-dimethylurate; 1X: 1-methylxanthine; AFMU: 5-acetylamino-6-formylamino-3-methyluracil; $AUC_{0-\infty}$: area under the plasma concentration-time curve from time zero to infinity; CL/F: apparent oral clearance; CYP: cytochrome P450; NAT-2: *N*-Acetyltransferase-2; XO: xanthine oxidase.

On Day -4 and Day 1, subjects fasted overnight and continued fasting for at least 4 hours after midazolam administration. Safety was evaluated by the assessment of adverse events (AEs), serious adverse events (SAEs), clinical safety laboratory results, vital sign measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings. Sixteen subjects were enrolled and assigned to treatment, and all subjects completed the study. All 16 subjects were included in the safety and pharmacokinetic analysis populations.

PHARMACOKINETIC SAMPLING AND ANALYSES

Blood samples for the analysis of oritavancin in plasma were collected on Day 1 before dosing (0 hour) and at 1.5, 3, 4, 6, 8, 12, 24, 48, 72, 192 (±24), and 384 (±24) hours after the start of oritavancin infusion. Samples for pharmacokinetic analysis of the probe drugs were collected at the following time points:

Probe drug	*Specimen*	*Sampling time point(s)*[a]
Caffeine	Urine	Before dosing (0 hour) and over a 12-hour interval after dosing
Warfarin	Blood	0, 3, 6, 12, 24, 36, 48, 72, and 96 hours
Vitamin K	Not applicable	Not applicable
Omeprazole	Blood	0 and 2 hours
Dextromethorphan	Urine	Before dosing (0 hour) and over a 12-hour interval after dosing
Midazolam	Blood	0, 5 minutes and 0.5, 1, 2, 4, 5, 6, and 8 hours

a Sampling time point was relative to the dosing time of each probe drug.

Plasma concentrations of oritavancin were used to calculate the following PK parameters: AUC from time zero to the time of the last measurable concentration ($AUC_{0\text{-last}}$); AUC from time zero to infinity ($AUC_{0\text{-inf}}$); maximum measured plasma concentration (C_{max}); time to reach C_{max} (T_{max}); elimination half-life ($t_{1/2}$); and total body clearance (CL). Plasma concentrations of S-warfarin were used to obtain $AUC_{0\text{-inf}}$ and plasma concentrations of midazolam were used to obtain apparent oral clearance (CL/F); these parameters were used to obtain the estimates of the phenotyping measure for the specific enzyme. The $AUC_{0\text{-inf}}$ of S-warfarin was calculated as the sum of the $AUC_{0\text{-last}}$ plus the ratio of the last measurable concentration divided by the elimination rate constant. The CL/F value of midazolam was calculated as dose/$AUC_{0\text{-inf}}$.

Pharmacokinetics statistical methods: Based on two 1-sided tests, a sample size of 16 subjects provided ≥80% power to detect equivalence, such that the 90% confidence interval (CI) of the ratio of 2 geometric means was within the no-effect boundary of 80% to 125%, assuming that the true ratio was 1 and the percent coefficient of variation (CV%) was approximately 20%. Non-compartmental methods were applied to calculate all PK parameters using WinNonlin version 5.3. Oritavancin PK parameters were presented using descriptive statistics. For each enzyme (CYP1A2, CYP2C19, CYP2D6, CYP3A, NAT-2, and XO), the log (phenotyping measure) values were analyzed using a 1-way repeated measures analysis of variance (ANOVA) model with a categorical term for day (where Day -4 = cocktail alone versus Day 1 = cocktail + oritavancin) and a subject random effect.

The least squares geometric mean ratios (LS-GMRs) and 90% CIs were calculated, and the CIs were relative to the LS-GMR of the phase with cocktail alone. No statistically significant drug interaction was concluded if the 90% CIs for the ratios of geometric means for the phenotyping measures were entirely contained within the interval of 80% to 125%.

Pharmacokinetic Analyses

Plasma concentrations versus time data were analyzed by non-compartmental analysis using the program WinNonlin Professional. Actual sampling times were used for the evaluation.

Plasma concentration and PK data for oritavancin were presented in data listings and summarized using descriptive statistics. Mean (±SD) concentration-time plots were provided using linear and semi-logarithmic scales.

Values below the lower limit of quantitation (LLOQ) of the assay were set to zero for the descriptive statistics of the concentrations. For AUC calculations, values below the LLOQ were set to zero if no quantifiable concentrations were found before the value, as LLOQ/2 if quantifiable concentrations were found before and after the value and as missing if quantifiable concentrations were found before but not after the value.

All phenotyping measures were presented in data listings. For each enzyme (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A, NAT-2, and XO), the log (phenotyping measure) values were analyzed using a 1-way repeated measures analysis of variance (ANOVA) model with a categorical term for day (where Day -4=cocktail alone versus Day 1 = cocktail + oritavancin) and a subject random effect. The LS-GMRs and 90% CIs were calculated, and the CIs were relative to the LS-GMR of the phase with cocktail alone. No statistically significant drug interaction was concluded if the 90% CIs for the ratios of the geometric means for the phenotyping measures were entirely contained within the interval of 80% to 125%.

A Forrest plot was provided displaying the 90% CIs of each enzyme. In addition, line plots for each phenotype measure of interest were provided, with each subject plotted reflecting values with and without oritavancin (connected with a line) and the geometric mean of the phenotypic measure with and without oritavancin.

ASSAY METHODOLOGY:

Plasma samples were analyzed for oritavancin, midazolam, S-warfarin, omeprazole, and 5-hydroxyomeprazole concentrations. Urine samples were analyzed for determination of 1-methylxanthine, 1-methylurate, and dextrorphan. Assay method specifics are as follows and assay performance summarized in the table below:

Method BTM-1379-R0 is an LC-MS/MS method for the determination of oritavancin in K_2EDTA human plasma using TT99000808 as the internal standard (IS). Method BTM-1379-R0 was fully validated with a calibration range of 12.5-1000 ng/mL and reported in the validation report, TMC-R1536. A second method, BTM-1379H-R0 was developed based on BTM-1379-R0 with a higher calibration range of 0.5-300 µg/mL and was partially validated and reported in the validation addendum report, TMC-R1536A1. The results of the long-term storage stability study for method BTM-1379H-R0 that demonstrated that oritavancin in human plasma (K_2EDTA) samples were stable at a storage temperature of -20° C and -70° C for at least 681 days were presented in validation addendum No. 5, TMC-R1536A5. This established stability sufficiently covers the amount of storage time for the study samples from date of collection until the last date of sample analysis. Oritavancin and TT99000808 (IS) stock solutions, prepared in diluent (0.5% formic acid in 50:50 methanol:water), were stable for 382 days at 4° C. The stock solution stability results were presented in the addendum to the validation report, TMC-R1536A4.

Method BTM-1372-R0 is an LC-MS/MS method for the determination of R-(+)-warfarin and S-(-)-warfarin in K_2EDTA human plasma using warfarin-d_5 as the internal standard (IS). Method BTM-1372-R0 was fully validated and reported in the validation report, (b) (4)-R1502. The results of the long-term stability study for method BTM-1372-R0 that demonstrated that R-(+)-warfarin and S-(-)-warfarin in human plasma (K_2EDTA) samples were stable at a nominal storage temperature of -20° C for at least 127 days, were presented in the addendum to the

validation report, (b) (4)-R1502A1. This established stability sufficiently covers the amount of storage time for the study samples from date of collection until the last date of sample analysis. The results of the stock solution (prepared in methanol) stability at -20° C for 196 days and the spike solution (prepared in 50:50 methanol:water) stability at -20° C for 191 days were presented in the addendum report, (b) (4)-R1502A2.

Method BTM-1015-R0 is an LC-MS/MS method for the determination of MID and 1'-hydroxymidazolam (HMID) in K_2EDTA human plasma using midazolam-d_4 and α-hydroxymidazolam-d_4 as the respective internal standards (IS). Method BTM-1015-R0 validation was successfully completed and reported. To update the method to current industry standards and (b) (4) SOP BIO-201, additional parameters were evaluated. These results updated method BTM-1015-R0, and were reported in the partial validation report, (b) (4)-R2267. The results of the long-term stability study for method BTM-1015-R0 that demonstrated that MID and HMID in human plasma (K_2EDTA) samples were stable at a nominal storage temperature of -20° C for at least 85 days, were presented in the addendum to the validation report, (b) (4)-R2267A1. This established stability sufficiently covers the amount of storage time for the study samples from date of collection until the last date of sample analysis. Stock and spike solutions in diluent (0.01N HCl in 50:50 methanol:water) were stable for 65 days at 4° C, results that were also presented in addendum report, (b) (4)-R2267A1.

Method BTM-1574-R0 is an LC-MS/MS method for the determination of OME and HOME in K_2EDTA human plasma using omeprazole-d_3 and 5-hydroxy omeprazole-d_3 as the respective internal standards (IS). Method BTM-1574-R0 validation was successfully completed and reported in the validation report, (b) (4)-R2231. The results of the long-term storage stability study for method BTM-1574-R0 that demonstrated that OME and HOME in human plasma (K_2EDTA) samples were stable at a storage temperature of -20° C and -70° C for at least 82 days, were presented in the addendum to the validation report, (b) (4)-R2231A1. This established stability sufficiently covers the amount of storage time for the study samples from date of collection until the last date of sample analysis. Spike solution samples prepared in diluent (50:50 methanol/water) were stable at -20° C for 82 days, and cycle 3 (-20° C) freeze/thaw data was confirmed, results that were also presented in addendum report (b) (4)-R2231A1.

Method BTM-1605-R0 is an LC-MS/MS method for the determination of DEX and DOR in acidified human urine using dextromethorphan-d_3 and dextrorphan-d_3 as the respective internal standards (IS). Method BTM-1605-R0 was fully validated, and the results were reported in the validation report, TMC-R2457. Long-term storage stability results are pending and will be reported separately in an addendum to the validation report.

Method BTM-1589-R0 is an LC-MS/MS method for the determination of 1U and 17U in acidified human urine using 1-methyluric acid-d_3 and 1,7-dimethyluric

(b) (4)

Reviewer comment: The long-term stability results that were referred to as pending in the above paragraphs were later submitted as an addendum to the study reports and were found to be acceptable.

Analyte	**Concentration Range**	**LLOQ**	**Linearity**	**Accuracy**	**Precision**
Oritavancin	0.5 – 300 mcg/mL	0.5 mcg/mL	0.998-0.999	92.0-104.5	0.4-9.5% (%CV)
Midazolam	0.1-100 ng/mL	0.1 ng/mL	0.995-0.999	94.5-111.3	1.6-6.5% (%CV)
S-warfarin	5-1500 ng/mL	5 ng/mL	0.994-0.999	88.5-104.8	0.8-6.0% (%CV)
Omeprazole	1-1000 ng/mL	1 ng/mL	0.991-0.996	93.0-116.1* *LLOQ	1.4-10.5% (%CV)
5-hydroxyomeprazole	1-1000 ng/mL	1 ng/mL	0.991-0.999	91.3-109.3	2.0-12.4% (%CV)
1-methylxanthine[1]	0.5-50 mcg/mL	0.5 mcg/mL	0.989-0.993	84.6* - 111.6 *LLOQ	4.5-16.7%* (%CV) *LLOQ
1-methylurate[2]	0.5-100 mcg/mL	0.5 mcg/mL	0.995-0.998	88.6-114.9	0.6-4.7% (%CV)
Dextrorphan[3]	5-2000 ng/mL	5 ng/mL	0.996-0.998	92.7-106.6	1.7-4.7% (%CV)

[1]: includes both 1-methylxanthine and AFMU
[2]: includes 1U and 17U
[3]: includes dextromethorphan and dextrorphan

RESULTS:

Demographics

Subject demographics and baseline characteristics are summarized in the table below.

Parameter Statistic	Overall (N = 16)
Age (years)	
Mean (SD)	32.4 (7.15)
Minimum, Maximum	23, 45
Gender, n (%)	
Female	8 (50.0)
Male	8 (50.0)
Weight (kg)	
Mean (SD)	76.02 (11.753)
Minimum, Maximum	58.4, 100.7
Height (cm)	
Mean (SD)	171.7 (9.61)
Minimum, Maximum	157, 195
Body mass index (kg/m^2)	
Mean (SD)	25.45 (3.063)
Minimum, Maximum	21.6, 31.9
Race, n (%)	
White	12 (75.0)
African American	4 (25.0)
Ethnicity, n (%)	
Hispanic or Latino	1 (6.3)
Not Hispanic or Latino	15 (93.8)

SD: standard deviation
Note: The denominator was based on the number of subjects in the safety population.

Protocol Deviations

Protocol deviations occurred when pulse oximetry and vital signs were collected late for all subjects on Day -3 and for 2 subjects on Day 1, dosing finished late for 3 subjects on Day 1, and the Day 28 final follow-up visit was conducted outside the 3-day window for 1 subject. None of these deviations were deemed to have impacted the safety results or informed consent in the study.

Reviewer comment: Agree with the Sponsor's assessment. The protocol deviations appear to be minor and unlikely to influence the study's conclusions.

Oritavancin Pharmacokinetics

The mean (±SD) plasma oritavancin concentration-time profile is presented (on a linear scale) in Figure 1 and the pharmacokinetic parameters of oritavancin are presented in Table 1.

Figure 1: Mean (±SD) Plasma Oritavancin Concentration-Time Profile: Linear Scale

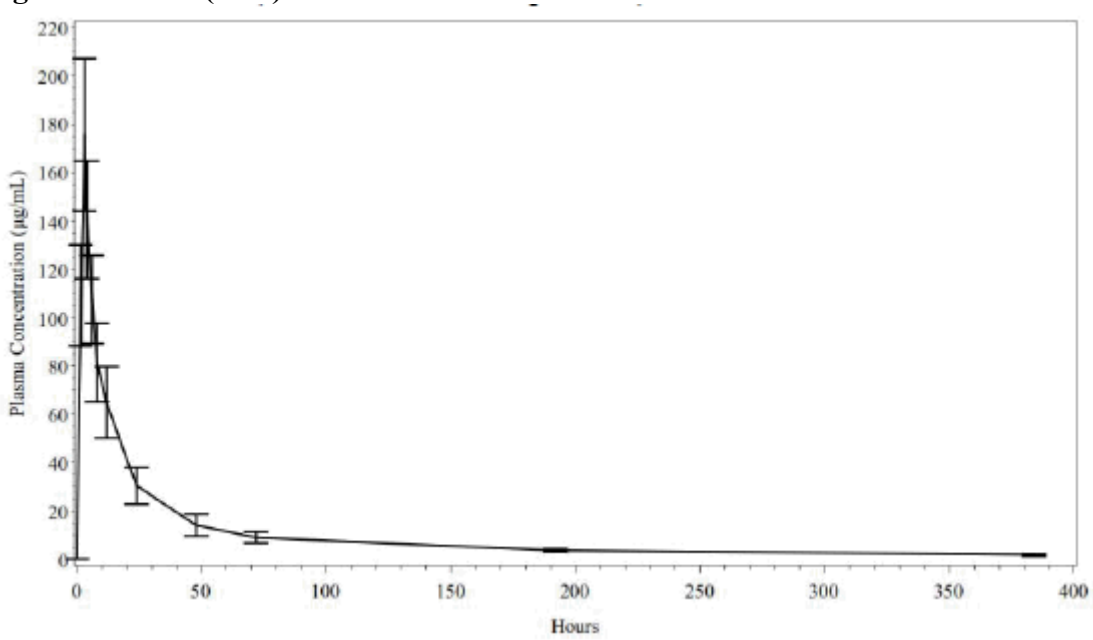


Table 1: Summary of Plasma Oritavancin Pharmacokinetic Parameters on Day 1

Parameter (unit)	N	Mean (CV%)	Geometric Mean
AUC_{0-t} (µg·hr/mL)	16	3696.325 (19.55)	3626.674
$AUC_{0-\infty}$ (µg·hr/mL)	16	4006.507 (18.96)	3935.910
C_{max} (µg/mL)	16	175.715 (17.90)	173.056
$t_{1/2}$ (hr)	16	120.476 (16.63)	118.915
CL/F (L/hr)	16	0.311 (21.00)	0.305
Parameter (unit)	**N**	**Median**	**Minimum, Maximum**
T_{max} (hr)	16	3.083	3.083, 3.151

CV%: percent coefficient of variation

Reviewer comment: Note that the oritavancin half-life that is estimated from the population PK analysis derived from sparse sampling in the Phase 3 ABSSSI trials is 245 hours. This may in part be due to differences in the collection of pharmacokinetic samples as this trial finished collections

Effect of Oritavancin on Enzyme Activity Using the Cooperstown 5 + 1 Cocktail

The effect of oritavancin on enzyme activity by day is summarized in Table 2. An overall summary of the effect of oritavancin on the probe substrates of the Cooperstown 5 + 1 cocktail is presented in Table 3. A forest plot illustrating the effect of oritavancin on the systemic exposures of the probe substrates of the Cooperstown 5 + 1 cocktail is presented in Figure 2.

Table 2: Summary of Enzyme Activity by Day[1]

Phenotyping Measure Day	N	Mean (CV%)	Geometric Mean
CYP1A2			
Day –4 (Cocktail)	16	4.4321 (34.88)	4.1253
Day 1 (Cocktail + Oritavancin)	16	5.1169 (31.95)	4.8626
CYP2C9			
Day –4 (Cocktail)	3	11354.740 (6.316)	11339.974
Day 1 (Cocktail + Oritavancin)	3	14650.937 (1.455)	14649.907
CYP2C19			
Day –4 (Cocktail)	16	1.9204 (80.14)	1.5009
Day 1 (Cocktail + Oritavancin)	16	1.9973 (51.11)	1.7340
CYP2D6			
Day –4 (Cocktail)	12	0.2887 (64.48)	0.2301
Day 1 (Cocktail + Oritavancin)	12	0.1647 (89.16)	0.1273
CYP3A			
Day –4 (Cocktail)	16	82.915 (28.94)	79.745
Day 1 (Cocktail + Oritavancin)	16	103.671 (32.32)	98.814
NAT-2			
Day –4 (Cocktail)	16	0.2930 (108.42)	0.1796
Day 1 (Cocktail + Oritavancin)	16	0.3743 (119.18)	0.2082
XO			
Day –4 (Cocktail)	14	0.5380 (20.46)	0.5241
Day 1 (Cocktail + Oritavancin)	14	0.5576 (10.26)	0.5547

CV%: percent coefficient of variation; CYP: cytochrome P450; NAT-2: *N*-Acetyltransferase-2; XO: xanthine oxidase
Note: Table excludes enzyme activities that were ≥0 or outliers, CYP2C9 activities on Day –4 and Day 1 for any subject whose S-warfarin concentration was ≥5% of the post-dose maximum plasma concentration (C_{max}) on Day 1, and CYP2D6 activities for Subject 1001.

[1]: The numbers in the mean column correspond to the various enzyme phenotyping measures that were used in the study. Refer to the "Study Design" portion of the review. The values in the mean column do not consistently refer to one measure, as both ratios and AUCs are presented depending on the specific phenotyping measure used for an enzyme.

Table 3: Summary of the Effect of Oritavancin on the Probe Substrates of the Cooperstown 5 + 1 Cocktail

Substrate	Isozyme	Biological Matrix	PK Parameter	Units	N	Geometric Mean		Ratio	90% Confidence Interval	
						Day -4	Day 1	Day 1/Day-4	Low	High
Midazolam	CYP 3A4	Plasma	CL/F	L/hr	16	79.745	98.814	1.239	1.135	1.353
		Plasma	AUC(0-inf)	hr*ng/mL	16	70.220	57.091	0.813	0.744	0.888
S-Warfarin	CYP 2C9	Plasma	AUC(0-inf)	hr*ng/mL	16	15623	20610	1.319	1.294	1.345
S-Warfarin	CYP 2C9	Plasma	AUC(0-inf)	hr*ng/mL	3	11340	14650	1.292	1.192	1.400
Omeprazole	CYP 2C19	Plasma	OM/5-OM at 2 Hr	Ratio	16	1.501	1.734	1.155	0.957	1.395
Dextromethorphan	CYP 2D6	Urine	Ratio of DXM/DXP in -12Hr Urine	Ratio	13	0.206	0.142	0.692	0.431	1.110
				Ratio	12	0.230	0.127	0.553	0.419	0.731
Caffeine	CYP 1A2	Urine	Ratio of [(1X+1U+AFMU/17U] in -12Hr Urine	Ratio	16	4.125	4.863	1.179	1.033	1.345
Caffeine	NAT-2	Urine	Ratio of [AFMU/(1X+1U)] in -12Hr Urine	Ratio	16	0.180	0.208	1.159	0.875	1.535
Caffeine	XO	Urine	Ratio of [1U/(1X+1U)] in -12Hr Urine	Ratio	14	0.524	0.555	1.058	0.956	1.172

1U: 1-methylurate; 17U: 1, 7-dimethylurate; 1X: 1-methylxanthine; AFMU: 5-acetylamino-6-formylamino-3-methyluracil; $AUC_{0\text{-}inf}$: (also referred to as $AUC_{0\text{-}\infty}$) area under the plasma concentration-time curve from time zero to infinity; CL/F: apparent oral clearance; CYP: cytochrome P450; DXM: dextromethorphan; DXP: dextrorphan; Hr: hour(s); NAT-2: *N*-Acetyltransferase-2; OM: omeprazole; PK: pharmacokinetic; XO: xanthine oxidase Source: Table 14.2.1.3.1, Table 14.2.2.1.1, Table 14.2.2.1.2, Table 14.2.2.1.3

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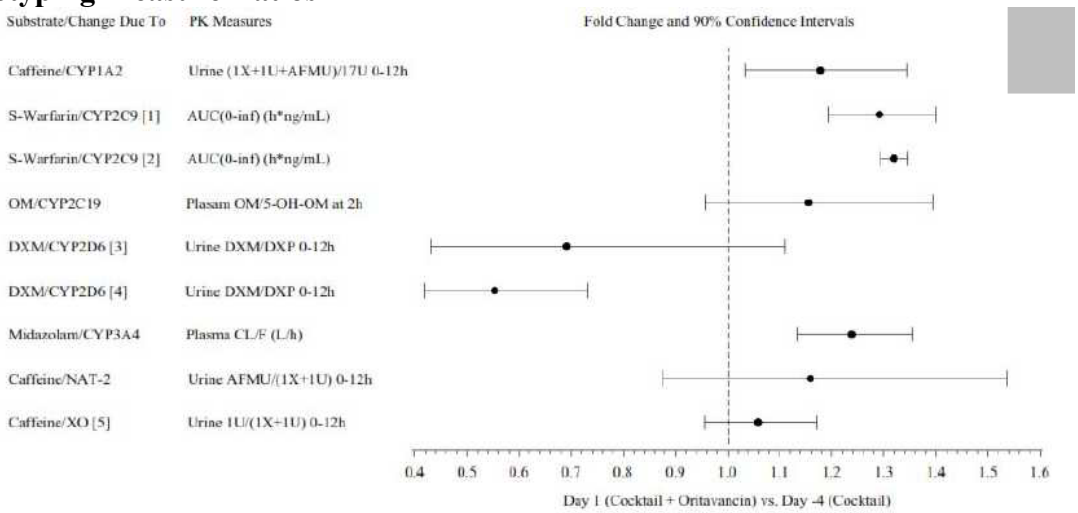
Figure 2: Summary of the Effect of Oritavancin on the Probe Substrates of the Cooperstown 5 + 1 Cocktail Displayed as 90% Confidence Intervals of the Geometric Mean Phenotyping Measure Ratios



1U: 1-methylurate; 17U: 1, 7-dimethylurate; 1X: 1-methylxanthine; AFMU: 5-acetylamino-6-formylamino-3-methyluracil; $AUC_{0\text{-}inf}$: (also referred to as $AUC_{0\text{-}\infty}$) area under the plasma concentration-time curve from time zero to infinity; CL/F: apparent oral clearance; CYP: cytochrome P450; DXM: dextromethorphan; DXP: dextrorphan; h: hour(s); NAT-2: *N*-Acetyltransferase-2; OM: omeprazole; PK: pharmacokinetic; XO: xanthine oxidase
[1] N = 3; predose plasma concentration <5% of the post-dose maximum plasma concentration (C_{max}) on Day 1.
[2] N = 16; all subjects.
[3] N = 13; CYP2D6 activities that were ≤0 or outliers were excluded.
[4] N = 12; CYP2D6 activities that were ≤0 or outliers were excluded. Subject 1001 was also excluded.
[5] N = 14; XO activities that were ≤0 or outliers were excluded.

Reviewer comment: The point estimates and confidence intervals used to assess the activities of CYP3A4, CYP2C19, CYP1A2, and NAT-2 used data from all 16 subjects from the trial. The

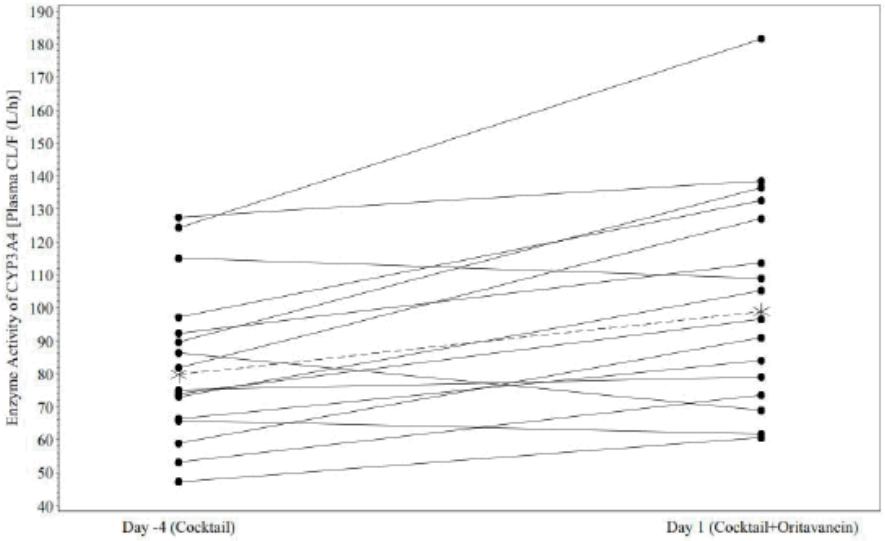
activities of CYP2C9, CYP2D6, and XO were assessed with less than 16 subjects. The reasons for this will be discussed in the section for each individual probe drug.

Examination of the forest plot above reveals that only the activity of XO has the point estimate and lower and upper bounds of the 90% confidence interval fall within the traditional boundary of 80-125%. Thus, co-administration with oritavancin alters the activities of the other enzymes tested. However, the highest point estimate is ~1.3, and the lowest point estimate is ~0.55, which indicates that the observed changes in enzymatic activity may not be clinically significant. It is important to note that although oritavancin has a long terminal elimination half-life (245 hours), its disappearance from the plasma is much more rapid (refer to Figure 1 for the concentration-time profile of oritavancin). For example, the mean C_{max} of oritavancin from the population pharmacokinetic analysis of the Phase 3 patient data was reported as 138 mcg/mL, but 48 hours later, the mean plasma concentration of oritavancin is below 20 mcg/mL which, in turn, is below the in vitro IC_{50} for any of the tested CYP isoforms. Taken together, these data suggest that mild drug interactions due to the disruption (inhibition or induction) of several CYP isoforms or NAT-2 may occur, but the magnitude of the resulting drug interactions is not likely to be clinically significant and that any drug interaction that does occur will likely be brief in duration.

Midazolam

A line plot showing CYP3A enzyme activity (plasma midazolam CL/F [L/hr]) with and without oritavancin is presented in Figure 3. In the presence of oritavancin (Day 1) the $AUC_{0\text{-inf}}$ of midazolam was decreased by 18% and the CL/F was increased by 24%. The Day 1/Day -4 geometric mean ratio (point estimate) and 90% CI for CL/F was 1.239 (1.135, 1.353). The 24% increase in the midazolam CL/F and decrease (18%) in the midazolam $AUC_{0\text{-inf}}$ indicates that oritavancin is a weak inducer of CYP3A4.

Figure 3: Line plot for CYP3A4 Activity: Individual Values and Geometric Mean with and without Oritavancin (N=16)

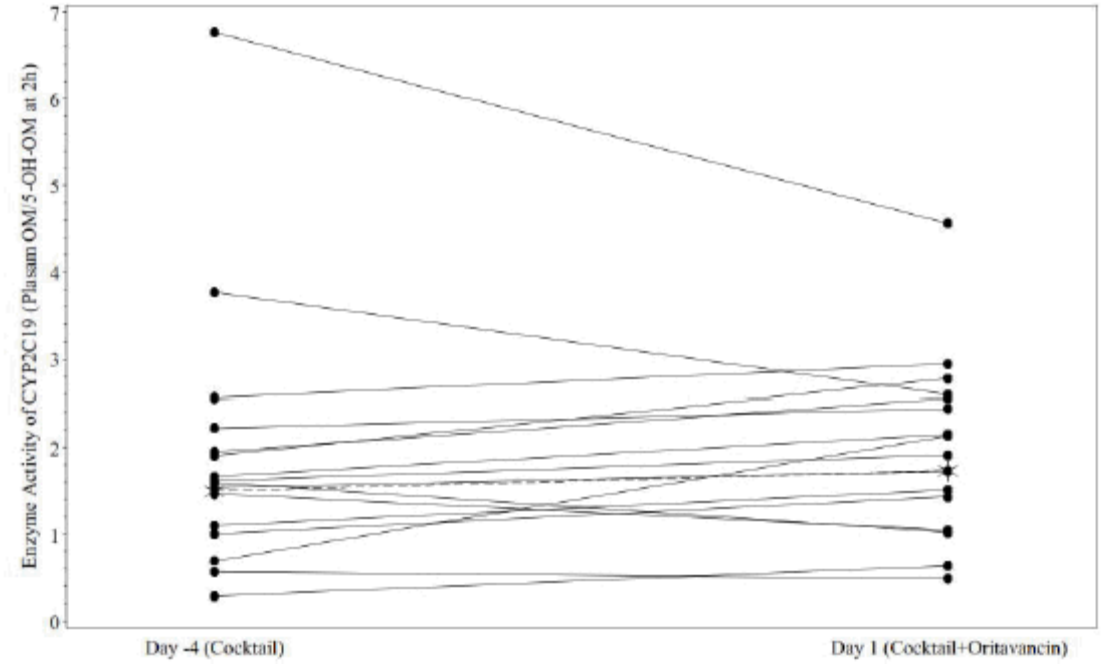


CYP: cytochrome P450
Note: Solid lines = individual values; dashed line = geometric mean.

Omeprazole

A line plot showing CYP2C19 enzyme activity (plasma omeprazole/5-OH omeprazole molar ratio in plasma at 2 hours) with and without oritavancin is presented in Figure 4. The effect of oritavancin on omeprazole, a CYP2C19 substrate, was determined from the omeprazole/5-OH omeprazole ratio in the plasma at 2 hours. There was an increase of 15% in this metabolic ratio. The Day 1/Day-4 geometric mean ratio (point estimate) and 90% CI was 1.155 (0.957, 1.395), suggesting that oritavancin may be a weak inhibitor of CYP2C19.

Figure 4: Line Plot for CYP2C19 Activity: Individual Values and Geometric Mean with and without Oritavancin (N=16)

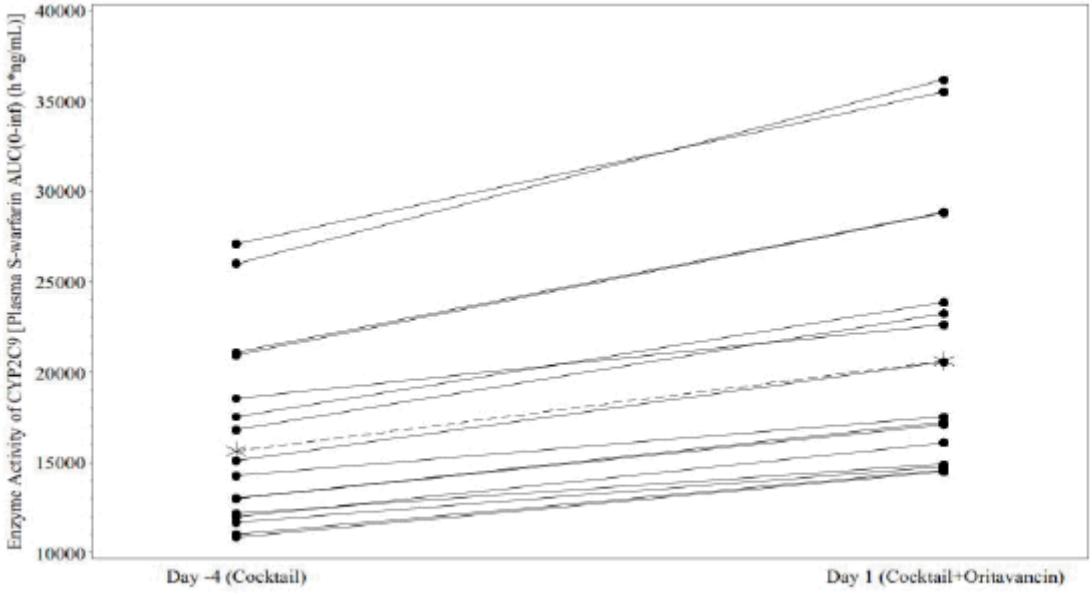


CYP: cytochrome P450; OM: omeprazole
Note: Solid lines = individual values; dashed line = geometric mean.

S-Warfarin

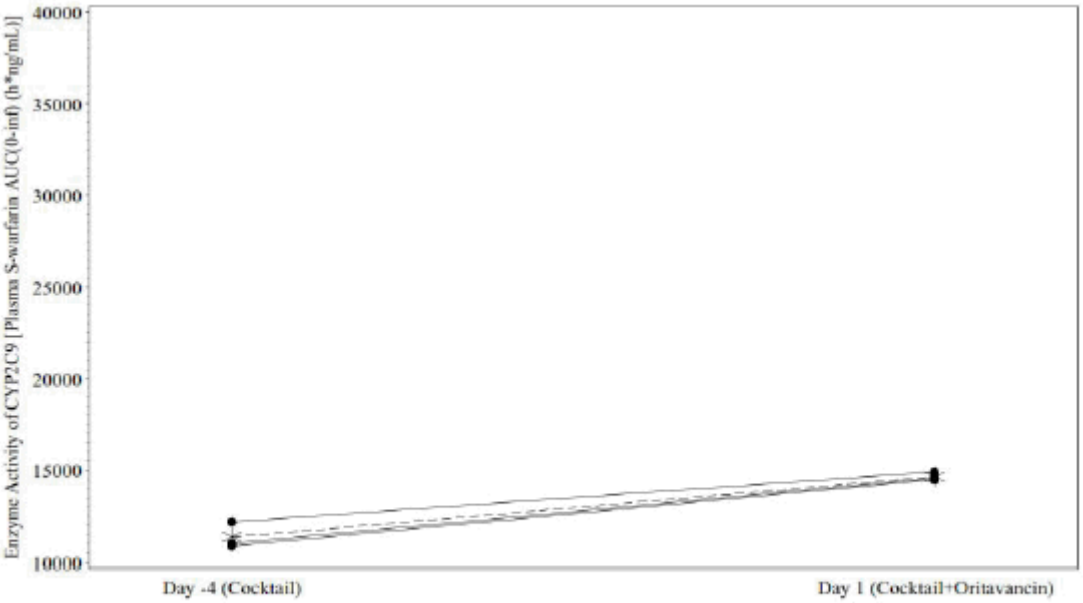
A line plot showing CYP2C9 enzyme activity (plasma S-warfarin $AUC_{0\text{-}inf}$ [mcg*hr/mL]) with and without oritavancin for all 16 subjects is presented in Figure 5, and a line plot for the 3 subjects who had pre-dose plasma concentrations of S-warfarin that were less than 5% of the post-dose C_{max} on Day 1 is presented in Figure 6. In the overall population (N=16), plasma S-warfarin $AUC_{0\text{-}inf}$ values increased by 31%. The Day 1/Day-4 geometric mean ratio (point estimate) and 90% CI was 1.319 (1.294, 1.345). In the 3 subjects who had pre-dose plasma concentrations that were less than 5% of the post-dose C_{max} on Day 1, the corresponding geometric mean ratio (point estimate) and 90% CI was 1.292 (1.192, 1.400). This indicated that co-administration of warfarin with oritavancin resulted in an approximate 29% increase in the systemic exposure ($AUC_{0\text{-}inf}$) of S-warfarin, and that oritavancin is a weak inhibitor of CYP2C9. Since warfarin is a drug with a narrow therapeutic window, caution should be exercised when warfarin is co-administered with oritavancin.

Figure 5: Line Plot for CYP2C9 Activity: Individual Values and Geometric Mean with and without Oritavancin (N=16)



CYP: cytochrome P450
Note: Solid lines = individual values; dashed line = geometric mean.

Figure 6: Line Plot for CYP2C9 Activity: Individual Values and Geometric Mean with and without Oritavancin (N=3)



CYP: cytochrome P450
Note: Solid lines = individual values; dashed line = geometric mean. Figure shows values for the 3 subjects who had predose plasma concentrations of S-warfarin that were <5% of the post-dose maximum plasma concentration (C_{max}) on Day 1.

Reviewer comment: The Sponsor states the following in their discussion section: "13 of 16 subjects had pre-dose plasma concentrations that exceeded 5% of the post-dose C_{max} on Day 1 of the second treatment period due to a carryover effect. This finding was probably due to

insufficient washout period of 4 days for warfarin. Three subjects had pre-dose plasma concentrations that were less than 5% of the post-dose C_{max} on Day 1; statistical analysis of S-warfarin in these subjects showed a 29% increase in the $AUC_{0\text{-}inf}$ of S-warfarin. However, in the overall subject population (N=16), plasma S-warfarin values increased by 31%."

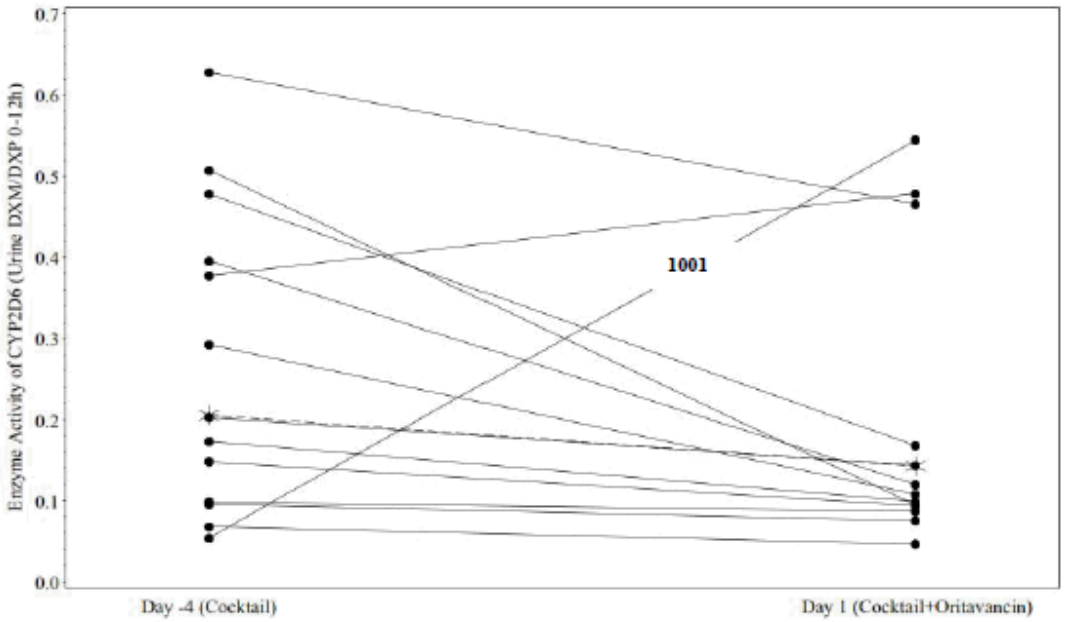
It is unclear why less than 5% of the post-dose C_{max} was used as a criterion to remove the subjects for a separate analysis as it is fairly clear from Figure 5 that these subjects are not obvious outliers. Furthermore, their inclusion or exclusion does not impact the conclusion – oritavancin appears to be a weak inhibitor of CYP2C9.

Dextromethorphan

A line plot showing CYP2D6 enzyme activity (dextromethorphan over dextrorphan molar ratios in urine samples collected over a 12-hour interval after dosing) with and without oritavancin is presented in Figure 7. Of the 16 overall subjects, 13 subjects were used in the line plot for CYP2D6. This decision was based on the fact that 2 subjects had metabolic ratio values of zero (Subject 1004 on Day -4 and Subject 1012 on Day 1) and 1 subject (Subject 1015) had outlier metabolic ratio values on Day -4 (69.471; range for the remaining subjects 0.054 to 0.628) and Day 1 (1111.271; range for remaining subjects 0.047 to 0.545). The effect of oritavancin on dextromethorphan, a CYP2D6 substrate, was determined from the dextromethorphan over dextrorphan molar ratio in urine samples collected over a 12-hour interval after dosing. The Day 1/Day -4 geometric mean ratio (point estimate) and 90% CI (N=13 subjects) was 0.692 (0.431, 1.110). These findings indicate a 31% decrease in the urinary dextromethorphan/dextrorphan ratio, and that oritavancin is a weak inducer of CYP2D6.

The line plot illustrates that the metabolic ratio for Subject 1001 was atypical, which is reflective of the variability in the study. When the analysis was also completed without this subject's data, the geometric mean ratio (point estimate) and 90% CI (N=12 subjects) was 0.553 (0.419, 0.731). These findings indicate a 45% decrease in the urinary dextromethorphan/dextrorphan ratio, and also support that oritavancin is a weak inducer of CYP2D6.

Figure 7: Line Plot for CYP2D6 Activity: Individual Values and Geometric Mean with and without Oritavancin (N=13)



CYP: cytochrome P450; DXM: dextromethorphan; DXP: dextrorphan
Note: Solid lines = individual values; dashed line = geometric mean. CYP2D6 activities that were ≤0 or outliers were excluded. Figure shows atypical response for Subject 1001.

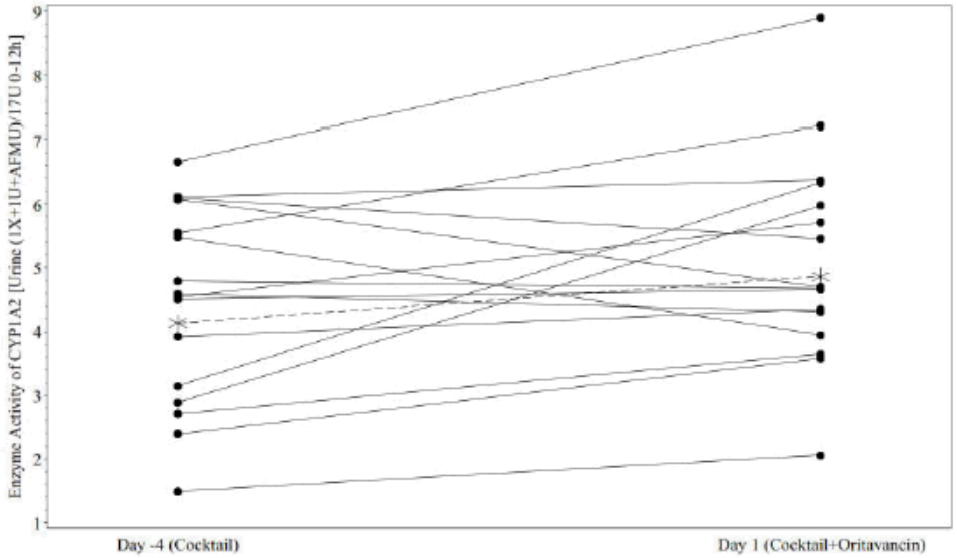
Reviewer comment: Subjects 1004 and 1012 were excluded from the analysis because of an inability to calculate a metabolic ratio due to a BLQ concentration on Day -4 at the 12 hour post dose collection for Subject 1004 and a BLQ concentration on Day 1 at the 12 hour collection time point for Subject 1012. Subject 1015 was also removed from the analysis; this subject had dextromethorphan concentrations at least 10x higher than all the other subjects at every time point, and was the only subject to have a detectable dextromethorphan concentration prior to administration of the probe drug cocktail. Additionally, this patient's conversion to dextrorphan was quite low. The initial presence of dextromethorphan, the increased concentrations compared to the other subjects, and the low conversion rate to dextrorphan suggest that Subject 1015 may be a CYP2D6 poor metabolizer. This is not addressed or speculated on in the study report, but the protocol did exclude poor metabolizers of CYP2D6 if that metabolizer status was known. In the Reviewer's opinion, it was appropriate to exclude all of these subjects from the analysis as Subject 1015 had high concentrations of dextromethorphan and low conversion to dextrorphan on Day – 4 and Day 1, indicating that oritavancin did not significantly contribute to the low enzymatic activity. Subject 1001, who was included in the analysis, may be a CYP2D6 ultrarapid metabolizer, which could explain the high concentrations of dextrorphan observed in this subject.

Caffeine

The effect of oritavancin on the activities of CYP1A2, NAT-2, and XO was evaluated in the urinary excretion of caffeine metabolites over a 12-hour interval after dosing. A line plot showing CYP1A2 enzyme activity (molar ratio of [AFMU+1X+1U]/17U) with and without oritavancin is presented in Figure 8. The geometric mean ratio (point estimate) and 90% CI of

the (AFMU+1X+1U)/17U ratio in 16 subjects was 1.179 (1.033, 1.345), indicating an increase of 18% in CYP1A2 activity by oritavancin.

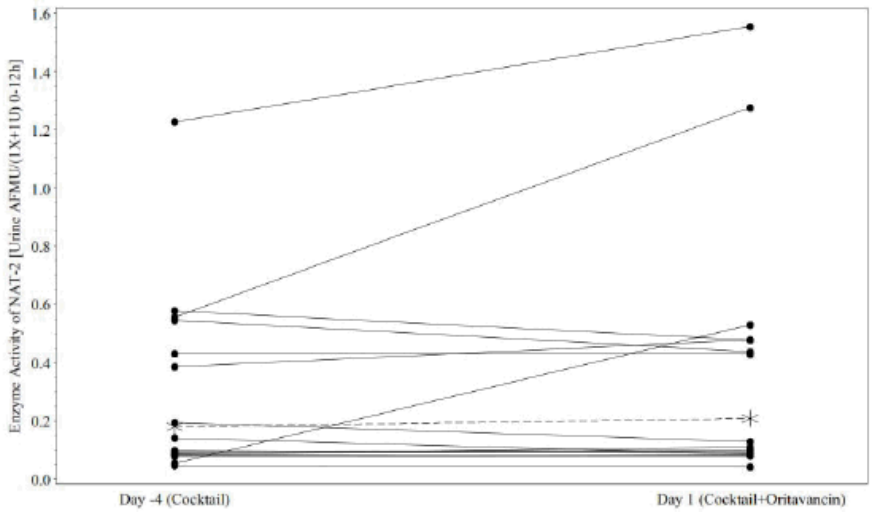
Figure 8: Line Plot for CYP1A2: Individual Values and Geometric Mean with and without Oritavancin (N=16)



1U: 1-methylureate; 17U: 1, 7-dimethylurate; 1X: 1-methylxanthine; AFMU: 5-acetylamino-6-formylamino-3-methyluracil; CYP: cytochrome P450
Note: Solid lines = individual values; dashed line = geometric mean.

A line plot showing NAT-2 enzyme activity (ratio of AFMU/[1X+1U]) with and without oritavancin is presented in Figure 9. The geometric mean ratio (point estimate) and 90% CI of the AFMU/(1X+1U) ratio in 16 subjects was 1.159 (0.875, 1.535), indicating an increase of 16% in NAT-2 activity by oritavancin.

Figure 9: Line Plot for NAT-2: Individual Values and Geometric Mean with and without Oritavancin (N=16)

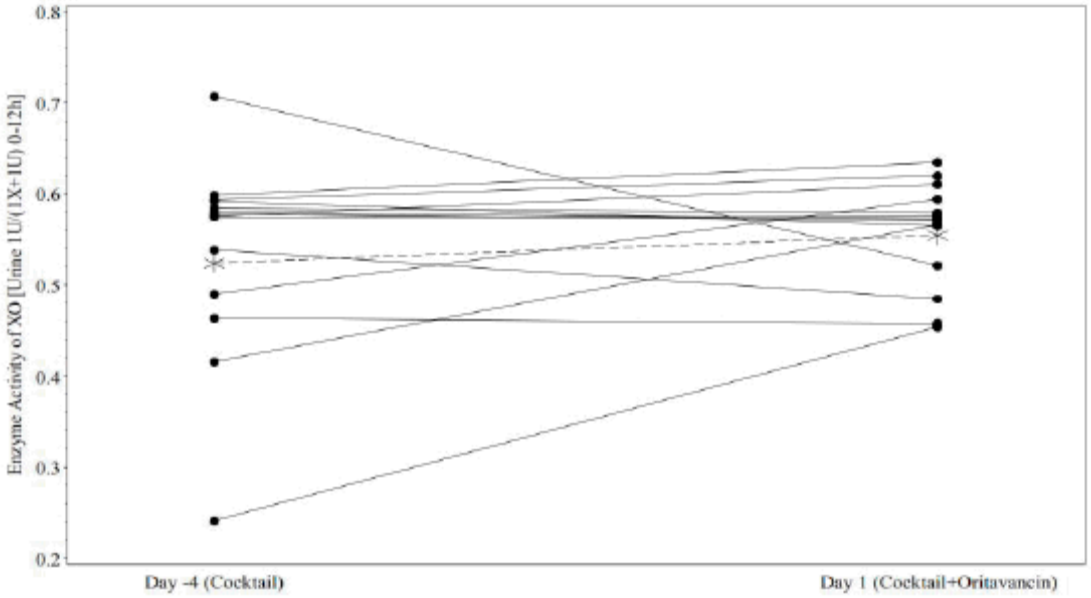


1U: 1-methylureate; 1X: 1-methylxanthine; AFMU: 5-acetylamino-6-formylamino-3-methyluracil; NAT-2: *N*-Acetyltransferase-2
Note: Solid lines = individual values; dashed line = geometric mean.

APPEARS THIS WAY ON ORIGINAL

A line plot showing XO enzyme activity (ratio 1U/[1X+1U]) with and without oritavancin is presented in Figure 10. The geometric mean ratio (point estimate) and 90% CI of the 1U/(1X+1U) ratio in 14 subjects was 1.058 (0.956, 1.172), indicating an increase of 6% in XO activity by oritavancin. Co-administration of oritavancin did not change the mean systemic exposure of caffeine metabolite (XO probe substrate).

Figure 10: Line Plot for XO: Individual Values and Geometric Mean with and without Oritavancin (N=14)



1U: 1-methylureate; 1X: 1-methylxanthine; XO: xanthine oxidase
Note: Solid lines = individual values; dashed line = geometric mean. XO activities that were ≤0 or outliers were excluded.

Reviewer comment: The analysis for the enzymatic activity includes 14 subjects rather than the 16 subjects used for most of the analyses. The study report does not specifically comment on why 2 subjects were excluded from the analysis. Review of the study appendices show that two subjects, 1002 and 1012, had a negative result for the calculation of XO activity. These are presumably the subjects that were excluded, and the calculation of a negative enzymatic activity is likely why they were excluded.

Safety Results

Overall, 2 subjects (12.5%) reported at least 1 TEAE after administration of the Cooperstown 5+1 cocktail and 7 subjects (43.8%) reported at least 1 TEAE after administration of the cocktail + oritavancin. No deaths, SAEs, or TEAEs leading to study drug discontinuation were reported. A summary of TEAEs by system organ class and MedDRA preferred term is presented in Table 4.

Table 4: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term, n (%)	Cocktail (N = 16)	Cocktail + Oritavancin (N = 16)	Overall (N = 16)
Number of Subjects with at least one TEAE	2 (12.5)	7 (43.8)	8 (50.0)
Gastrointestinal disorders	1 (6.3)	2 (12.5)	3 (18.8)
Abdominal disorders	1 (6.3)	0	1 (6.3)
Constipation	1 (6.3)	0	1 (6.3)
Nausea	0	2 (12.5)	2 (12.5)
General disorders and administration site conditions	1 (6.3)	0	1 (6.3)
Vessel puncture site reaction	1 (6.3)	0	1 (6.3)
Infections and infestations	0	1 (6.3)	1 (6.3)
Rhinitis	0	1 (6.3)	1 (6.3)
Musculoskeletal and connective tissue disorders	0	1 (6.3)	1 (6.3)
Musculoskeletal chest pain	0	1 (6.3)	1 (6.3)
Nervous system disorders	0	4 (25.0)	4 (25.0)
Dysgeusia	0	1 (6.3)	1 (6.3)
Headache	0	3 (18.8)	3 (18.8)
Somnolence	0	1 (6.3)	1 (6.3)
Psychiatric disorders	0	1 (6.3)	1 (6.3)
Anxiety	0	1 (6.3)	1 (6.3)
Vascular disorders	0	1 (6.3)	1 (6.3)
Phlebitis	0	1 (6.3)	1 (6.3)

TEAE: treatment-emergent adverse event
The denominator for percentages overall was based on the number of subjects in the safety population. The denominator for percentages by treatment period was based on the number of subjects exposed to that period in the safety population. Adverse events were classified according to MedDRA version 13.1.

TEAEs reported for more than 1 subject were headache reported for 3 subjects (18.8%) and nausea reported for 2 subjects (12.5%), all after administration of the cocktail + oritavancin.

All reported TEAEs were mild in severity except moderately severe headache reported for 1 subject (6.3%) and moderately severe phlebitis reported for 1 subject (6.3%), both after administration of the cocktail + oritavancin.

Treatment-related AEs considered possibly or probably related to administration of the cocktail + oritavancin were reported for 4 subjects (25%). These TEAEs were nausea reported for 2 subjects (12.5%), dysgeusia reported for 1 subject (6.3%), and phlebitis reported for 1 subject (6.3%). No reported TEAEs were considered possibly or probably related to administration of the cocktail alone.

All TEAEs reported were resolved. Concomitant medication was taken for an AE by 2 subjects (12.5%): 1 subject (6.3%) for headache and the other for phlebitis.

Reviewer comment: Per the oritavancin summary of clinical safety: "The most common AEs (≥4%) in the oritavancin group were nausea, headache, and vomiting; the incidence of each of

these AEs was ≤ 10% and similar in the vancomycin group." While the frequency of some adverse events (e.g. headache and nausea) was more frequent in this study than the Phase 3 study, the types of adverse events that occurred were consistent with what was observed during oritavancin' s Phase 3 program. The low number of subjects enrolled in this trial (n=16) is likely responsible for some of the higher overall percentages of adverse events.

APPLICANT'S CONCLUSION:

Overall Conclusions

This was a well-conducted Phase 1, open-label study that evaluated the effects of a single 1200 mg IV oritavancin infusion on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, NAT-2, and XO activities using a multiple-probe cocktail. Results showed that oritavancin is a weak inducer of CYP3A4 and CYP2D6 and a weak inhibitor of CYP2C19 and CYP2C9. Determination of caffeine urinary metabolic ratios indicated that CYP1A2 activity and NAT-2 enzyme activity were increased by 18% and 16%, respectively. There was no change in XO activity by oritavancin.

In summary, oritavancin 1200 mg IV infusion over 3 hours with the Cooperstown 5 + 1 cocktail was well-tolerated by the healthy adult subjects in this study. Considering the single-dose administration of oritavancin and relatively small changes in the pharmacokinetics of the CYP substrates observed in this study, a clinically significant DDI is not likely when oritavancin co-administered with CYP substrates. However, caution should be used when administering oritavancin concomitantly with drugs with a narrow therapeutic window that are predominantly metabolized by CYP2C9 (i.e. warfarin), as co-administration may increase the concentrations of CYP2C9 substrate.

REVIEWER ASSESSMENT:

Under oritavancin's original NDA submission (22-153), an in vitro screen showed that oritavancin had the potential to inhibit several CYP450 enzymes, with the most potent interaction with CYP3A (IC_{50} of 16 µM). The proposed dosing regimen of oritavancin for NDA 22-153 was 200 or 300 (if >110 kg) mg once daily for 3-7 days. This dosing regimen resulted in a C_{max} of 27.3 mcg/mL, or 13.7 µM. Additionally, a drug-drug interaction study between oritavancin and desipramine (a CYP2D6 probe substrate) conducted under NDA 22-153 did not suggest an interaction.

Following receipt of a complete response letter for NDA 22-153, the Sponsor revisited the dosing strategy of oritavancin, and opted to pursue a 1200 mg once only dose (the regimen for the current NDA - 206-334). The higher dose of oritavancin resulted in a higher C_{max} of oritavancin (138 mcg/mL or 69.4 µM), which renewed concerns about possible drug-drug interactions.

To address these concerns, the Sponsor conducted a cocktail drug interaction study with oritavancin and the Cooperstown 5 + 1 cocktail (midazolam, S-warfarin, vitamin K, omeprazole, dextromethorphan, and caffeine) to assess the impact of oritavancin on the enzymatic activities of CYP3A4, CYP2C9, CYP2C19, CYP2D6, CYP1A2, NAT-2, and XO).

The results of the study indicate that oritavancin exhibits non-specific inhibition or induction of all enzymatic activities tested with the exception of XO (the point estimate and lower and upper bounds of the 90% confidence interval fell within the 0.8 to 1.25 no-effect boundary). Oritavancin appears to be a weak inducer of CYP3A4, CYP2D6, CYP1A2, and NAT-2, and a weak inhibitor of CYP2C9 and CYP2C19. However, the magnitude of the observed interactions is not overly concerning with the highest and lowest point estimates across all of the studied interactions being 1.32 and 0.55, respectively.

It is important to note that although oritavancin has a long terminal elimination half-life in patients (245 hours), its disappearance from the plasma is much more rapid - the mean plasma concentration of oritavancin is below 20 mcg/mL (10 μM) at approximately 48 hours after administration – a concentration lower than all of the IC_{50}s from the in vitro screen. Taken together, these data suggest that mild drug interactions due to the disruption (inhibition or induction) of several CYP isoforms or NAT-2 may occur, but the magnitude of the resulting drug interactions is not likely to be clinically significant and that any drug interaction that does occur will likely be brief in duration.

The Sponsor has included a Warning in their proposed labeling about the possible increase in warfarin concentrations due to possible CYP2C9 inhibition by oritavancin. Since warfarin is a narrow therapeutic range drug, the Reviewer considers this Warning appropriate. However, the Reviewer also agrees with the Sponsors conclusions that no dose adjustments to concomitant medications are required on the basis of a drug interaction with oritavancin.

4.2 Pharmacometric Review

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

NDA:	206-334
Drug	Oritavancin Diphosphate
Trade Name	ORBACTIV
PM Reviewer	Ryan Owen, Ph.D.
PM Team Leader	Jeffry A. Florian, Ph.D.
Clinical Pharmacology Review	Ryan Owen, Ph.D.
Clinical Pharmacology Team Leader	Kimberly Bergman, Pharm.D.
Sponsor	The Medicines Co, Parsippany, NJ
Submission Type; Code	Original New Drug Application (New Molecular Entity), Priority
Indication	For the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of Gram-positive microorganisms.
Dosage and Administration	1200 mg once-only dose infused over 3 hours

1 Summary of Findings

1.1 Key Review Questions

The purpose of this review is to address the following key questions:

1. Does the population pharmacokinetic analysis support the sponsor's proposed labeling claims regarding effects of sex, age, race, body weight, and renal status on oritavancin dosing?
2. Are the proposed *S. aureus* and *S. pyogenes* in vitro susceptibility test interpretive criteria for oritavancin supported based on the available clinical and nonclinical data?

1.1.1 Does the population pharmacokinetic analysis support the sponsor's proposed labeling claims regarding effects of sex, age, race, body weight, and renal function status on oritavancin dosing?

Yes, the developed population PK model supports that no dose adjustments are necessary based on sex, age, race, body weight, or renal function status. None of the listed covariates were identified as clinically relevant during the sponsor's or reviewer's population PK analysis. A summary of oritavancin exposures for these covariates is shown below in Table 1.1.

An increase of 20% and 14% in exposure was observed between the youngest and oldest age quartiles and between females and males, respectively, from the Phase III population. However, the difference in exposure observed with respect to these covariates was not determined to be clinically significant, and no dose adjustments are recommended based on these covariates.

No trends in oritavancin exposures were observed across other continuous (body weight, BSA, BMI) or categorical (race, renal function) covariates, and no dose adjustments are recommended based on these covariates. It should be noted that no patients with severe renal impairment (CrCL <30 mL/min based on Cockcroft-Gault) were included in the Phase III trials; however, there were 4 patients with baseline CrCL <32 mL/min. No trends were observed in oritavancin exposure with respect to renal function. These observations, as well as the observation that oritavancin is slowly eliminated over the course of multiple weeks unchanged in the urine and feces supports that no dose adjustments are anticipated for oritavancin in patients with severe renal impairment.

Table 1.1: Predicted AUC_{0-72} based on post-hoc parameter estimates from the reviewer's population PK analysis and integration of oritavancin exposures over 72 hours for a subset of covariates following a single 1200 mg dose infused over 3 hours in ABSSSI patients[1]

	Oritavancin AUC72 (ng·h/mL): Mean (median)			
Body weight (kg)	>= 43 & <64	>= 64 & <76	>= 76 & <89	>= 89 & <=178
	1470 (1406)	1534 (1497)	1434 (1419)	1428 (1387)
Age (years)	>= 18 & <36	>= 36 & <47	>= 47 & <55	>= 55 & <=89
	1646 (1677)	1482 (1452)	1369 (1342)	1375 (1306)
BMI (kg/m^2)	>= 15.9 & <22.8	>= 22.8 & <26.2	>= 26.2 & <30.4	>= 30.4 & <=67.4
	1433 (1351)	1464 (1413)	1491 (1459)	1478 (1433)
BSA (m^2)	>= 1.31 & <1.73	>= 1.73 & <1.89	>= 1.89 & <2.04	>= 2.04 & <=2.79
	1514 (1490)	1532 (1511)	1423 (1413)	1404 (1378)
Race	Asian	African American	White	Other
	1578 (1555)	1581 (1511)	1436 (1378)	1468 (1530)
Creatinine Clearance (mL/mL)	>30-50 mL/min	>50-80 mL/min	>80-110 mL/min	>110 mL/min
	1466 (1283)	1387 (1345)	1536 (1504)	1457 (1422)
MIC (ng/mL)	<= 0.015	0.03	0.06	>=0.12
	1587 (1418)	1483 (1316)	1517 (1490)	1412 (1266)
Gender	Male		Female	
	1403 (1374)		1600 (1605)	

[1]: The categorical divisions for body weight, age, BMI, and BSA represent quartiles

1.1.2: Are the proposed *S. aureus* and *S. pyogenes* in vitro susceptibility criteria for oritavancin supported based on the available clinical and nonclinical data?

Yes, the provided information was sufficient for the reviewer to determine in vitro susceptibility criteria (breakpoints) for oritavancin based on both the clinical and nonclinical data. Briefly, both the reviewer and sponsor conducted several analyses to support possible *S. aureus* breakpoints for oritavancin. These analyses included:

i) determining the probability of target attainment for achieving AUC_{0-72}/MIC relationships in patients corresponding to nonclinical PK/PD targets that were associated with bacteriostasis and 1-log kill
ii) univariate analyses based on categorical (two-group with a single cut off) and continuous AUC_{0-72}/MIC to predict clinical response for endpoints of early clinical efficacy at day 3, >20% lesion size reduction at day 3, and post-therapy evaluation.

Nonclinical probability of target attainment

AUC/MIC was previously determined by the sponsor to be the PK/PD parameter of relevance for oritavancin in animal models of infection. The nonclinical AUC_{0-72}/MIC targets for oritavancin against *S. aureus* were determined to be 3941 and 4581 for net bacterial stasis and 1-log reduction from baseline. Both the sponsor and the reviewer used the above target values as well as simulated AUC_{0-72} values for patients receiving a single 1200 mg IV dose of oritavancin based on a population PK model for oritavancin. The percent probability of attaining the nonclinical AUC_{0-72}/MIC targets for *S. aureus* was then calculated for the simulated patients for fixed MIC values from 0.016 to 1 mcg/mL. A graphic representation of the reviewer's nonclinical probability of target attainment results are shown in Figure 1.2.1. The left column of the graphs corresponds to all patients in the microbiologically evaluable (MicroE) subset with PK data available, and the right column corresponds to same population but subset to those subjects with *S. aureus* at baseline. A summary of the predictions from the sponsor's and the reviewer's analysis are provided in Table 1.2.1. Using the Reviewer's analysis, a breakpoint of up to 0.25 mcg/mL for *S. aureus* could be supported as the probability of attaining the nonclinical bacteriostatic target at an MIC of 0.25 mcg/mL is above 90%. Using the same benchmark for the Sponsor's analyses, a breakpoint of up to 0.125 mcg/mL would be supported for *S. aureus.* It should be noted that both of the methods predict a substantial drop off at an MIC of 0.25 mcg/mL and that the probability of target attainment predictions are relatively similar for an MIC of 0.125 mcg/mL, though the Reviewer's predictions exceeds 90% (95.6%) whereas the Sponsor's prediction is less than 90% (85.1%). One potential reason for these slightly different predictions is that the simulated AUC_{0-72} values from the Reviewer's population PK model had a narrower distribution than the Sponsor's.

Figure 1.2.1: Graphical summary of reviewer's analyses for probability of target attainment based on nonclinical data

Population: MicroE with PK | **Population: MicroE with PK, *S. aureus* only**

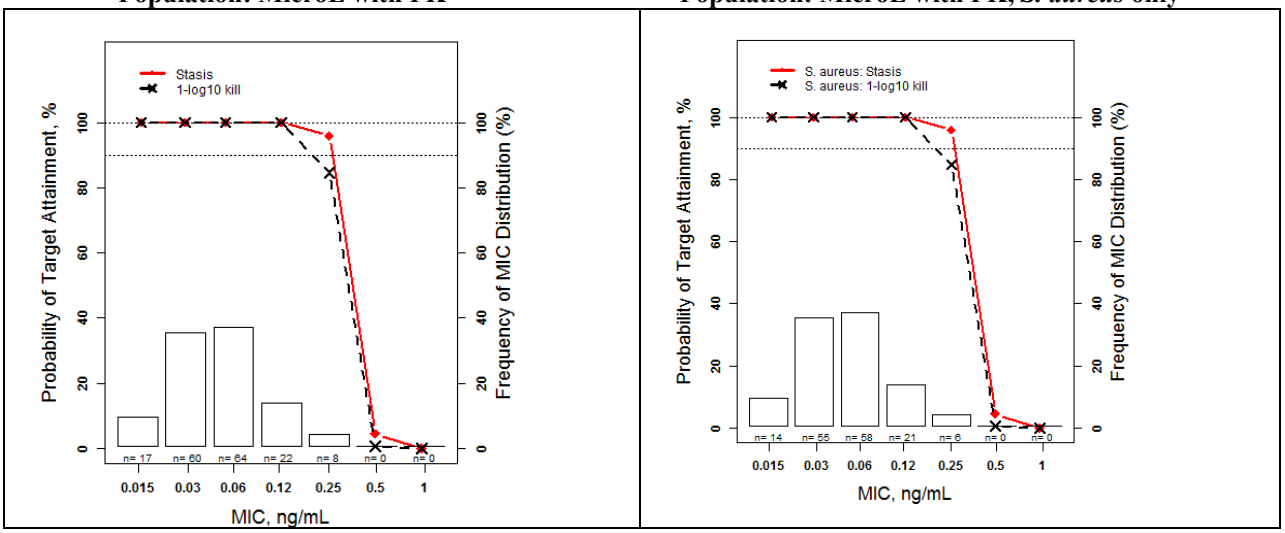


Table 1.2.1: Reviewer and sponsor analyses for probability of PK/PD target attainment (nonclinical targets)

	Reviewer Analyses		Sponsor Analyses	
MIC	Stasis	1-log kill	Stasis	1-log kill
0.016	100	100	Not reported	Not reported
0.031	100	100	Not reported	Not reported
0.062	100	100	100	100
0.125	100	100	99.8	99.4
0.25	95.6	83.7	85.1	74.8
0.5	5.2	0.8	20.0	10.0
1	0	0	Not reported	Not reported

Clinical PK/PD Analysis

The sponsor conducted univariate analysis based on categorical (two-group with a single cut off) and continuous AUC_{0-72}/MIC. The categorical analysis identified an AUC_{0-72}/MIC target of 11,982 at PTE, which in turn, was used in a probability of target attainment analysis by MIC for the clinical PK/PD target (11,982), as well as the mean probability of clinical response by MIC (see Table 3.2.10). The reviewer also conducted categorical analyses similar to the sponsor, and a comparison of the targets identified by the reviewer and sponsor are summarized below in Table 1.2.2. In addition, the reviewer conducted independent univariate analyses that evaluated continuous PK/PD relationships at ECE, >20% reduction in lesion size, and PTE (see Table 1.2.2 for reviewer targets). Similar to the nonclinical PTA analysis, predictions of treatment outcome were performed using the identified clinical PK/PD relationships, simulated oritavancin AUC_{0-72} values for patients administered 1200 mg i.v. based on the developed population PK model, and fixed MIC values from 0.016 to 1 mcg/mL.

Table 1.2.2: AUC_{0-72}/MIC ratio thresholds for univariate relationships between the probability of achieving dichotomous efficacy endpoints and AUC_{0-72}/MIC ratio evaluated as a two-group variable based on data from all patients and patients with *S. aureus*

	Reviewer Target – All Patients	Reviewer Target – *S. aureus* Patients	Sponsor Target – All Patients	Sponsor Target – *S. aureus* Patients
ECE	33,737	33,711	38,951	24,574
>20% reduction in lesion size	15,093	38,691	Not reported	Not reported
PTE	11,517	11,517	11,982	11,982

Figure 1.2.2 is a graphical summary of the analyses conducted by the reviewer and show model-predicted clinical response for ECE, >20% lesion size reduction, and PTE. Table 1.2.3 displays the data in Figure 1.2.2 in tabular form and displays it next to the sponsor's analysis based on a categorical (two-group with a single cut off) AUC_{0-72}/MIC, which was the clinical PK/PD analysis used by the sponsor to inform their proposed breakpoint. Since breakpoints are defined on an organism level, only the data for the *S. aureus* population is included. For a target endpoint response of 90%, the >20% lesion size reduction and PTE continuous PK/PD analyses conducted by the reviewer would support a breakpoint of 0.125 mcg/mL. Similarly, the sponsor's categorical PK/PD analysis for PTE supports a breakpoint of 0.125 mcg/mL. The analysis based on ECE suggests a lower breakpoint would be necessary to achieve ~90% response rate, though it should be noted that the ECE response in the Phase III trials, which demonstrated non-inferiority to the active comparator, was only 83%. Therefore,, a target of 90% based on ECE may be too conservative of a threshold. As such, a breakpoint of 0.125 mcg/mL appears to be supported by both the reviewer's and the sponsor's clinical PK/PD analyses.

Figure 1.2.2: Graphical summary of reviewer analyses

Population: MicroE with PK | **Population: MicroE with PK, *S. aureus* only**

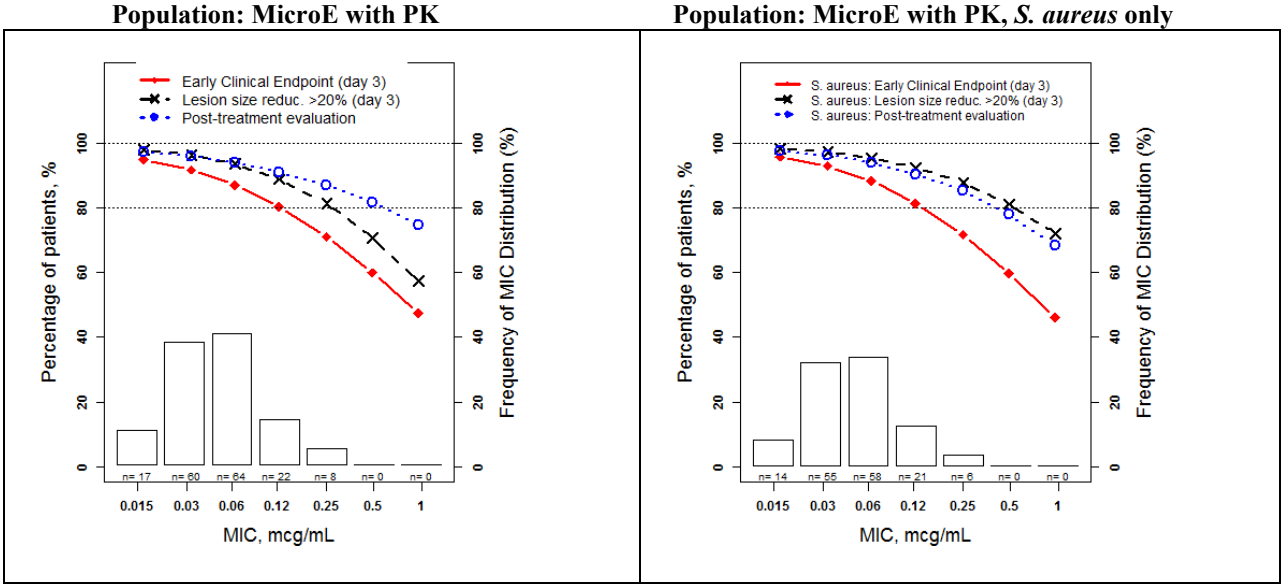


Table 1.2.3: Reviewer and sponsor analyses for mean model-predicted probability of clinical success

	Reviewer Analyses (Continuous PK/PD Analysis)			Sponsor Analysis (Categorical, Two-group Analysis)
MIC	ECE	>20% reduction	PTE	PTE
0.016	95.7	98.2	97.6	Not reported
0.031	92.8	97.1	96.1	Not reported
0.062	88.2	95.2	93.8	95.8
0.125	81.3	92.3	90.3	89.7
0.25	71.7	87.8	85.1	82.9
0.5	59.7	81.1	77.8	82.6
1	46.3	72	68.3	Not reported

Summary

The probability of clinical response analysis by endpoints is an exploratory analysis with no pre-established cutoffs for acceptability. However, it is interesting to note that the different clinical endpoints examined resulted in different model-predicted probabilities of response. The clinical PK/PD analyses conducted by both the reviewer and the sponsor would lead to the selection of a breakpoint of 0.125 mcg/mL. The nonclinical PK/PD analyses would lead to a breakpoint of 0.125 (sponsor) or 0.25 (reviewer) when applying the traditional 90% PTA for net bacterial stasis. There were very few *S. aureus* organisms with an MIC of 0.25 mcg/mL or over in the trial, so setting the breakpoint there would likely be extrapolating too much. Weighing the totality of the evidence, a breakpoint of 0.125 mcg/mL seems to be the most appropriate. The sponsor has suggested a *S. aureus* breakpoint of 0.125 mcg/mL (b) (4) and the reviewer agrees that this is an appropriate choice.

Additional Considerations

It should be noted that the response rates for the PK population used in the analysis (ECE: 89%, PTE: 94%; 20% lesion size reduction: 94%) were higher than the response rates observed in the MRSA mITT population (ECE: 81%; PTE: 83%; 20% lesion size reduction: 93%). These differences suggest that the PK population may differ somewhat from the trial MRSA mITT population, likely due to the exclusion of subjects with insufficient temperature data at the ECE visit (primary analysis imputed them as failures, but these subjects were excluded from the above analysis) and PTE visit (patients who were treatment failures due to lost to follow-up or who discontinued due to adverse events were excluded from this analysis). As all of these removed subjects were treatment failures, it is likely that inclusion of these subjects would have resulted in decreases in the response rates from the models of mean-predicted probability of clinical success. This would be another reason why the results from these models should not be utilized as a primary source of evidence for the selection of a breakpoint with the current submission.

Breakpoints for *S. pyogenes*

The reviewer's breakpoint assessment for *S. pyogenes* noted that there were no failures in patients included in the PK/PD dataset. As such, the reviewer could not identify any relationships between oritavancin exposures and clinical response. The reviewer's analyses were limited to a probability of target attainment analysis based on nonclinical information. As the AUC_{0-72}/MIC cut off for *S. pyogenes* was at least 1/20ththan that of *S. aureus* based on the animal model data, the reviewer's probability of target attainment analysis predicted a 100% response rate for *S. pyogenes* for MIC values up to 0.5 mg/L. Based on this observation, the reviewer proposes a breakpoint of 0.5 mg/L based on the available surveillance data and agrees with the sponsor that the available data can support a breakpoint of 0.5 mg/L for *S. pyogenes*.

1.2 Recommendations

The Division of Pharmacometrics (Office of Clinical Pharmacology) has reviewed this application from a clinical pharmacology perspective and recommends approval of 1200 mg oritavancin as a once-only intravenous dose. The Reviewer agrees with the Sponsor's conclusions from the population PK analyses that no dose adjustments are necessary for oritavancin on the basis of age, sex, race, body weight, or renal function status in adult patients. Based on initial review of the nonclinical and clinical oritavancin data, the reviewer recommends a *S. aureus* breakpoint of 0.12 mcg/mL. However, it should be noted that the determination of breakpoints involves multiple disciplines providing clinical and microbial interpretations in addition to the above nonclinical and PK-PD observations. The ultimate determination of the oritavancin breakpoint should depend on the totality of information provided by each discipline and continues to be assessed as of the completion of this review

2 Pertinent regulatory background

Oritavancin is a lipoglycopeptide antibiotic that is currently being developed to treat acute bacterial skin and skin structure infections (ABSSSI) due to susceptible Gram-positive bacteria. The original oritavancin NDA (22-153) was submitted on 2/8/08; the original clinical pharmacology (and pharmacometric) review was entered into DARRTS on 12/1/08, and the application received a complete response (CR) letter on 12/8/08. The primary reason for the CR letter was that" the application did not contain sufficient evidence to demonstrate the safety and efficacy of oritavancin." The dosing regimen of oritavancin proposed in the original NDA was 200 mg QD, or 300 mg QD for patient's $\geq$ 110 kg.

Following receipt of the CR letter, the Sponsor re-evaluated their dosing strategy and decided to conduct a Phase 2 trial which evaluated a 1200 mg single dose of oritavancin to take advantage of oritavancin' s long half-life and concentration-dependent antibacterial activity. After performing well in the Phase 2 trial, the 1200 mg once-only dose was selected for further development. Two new identically-designed Phase 3 trials (SOLO I and SOLO II) were conducted in support of the new dosing regimen. The oritavancin resubmission was given a new NDA number (206-334). Pharmacokinetic sampling was included in a subset of patients in SOLO I and SOLO II; this sampling forms the basis of the population PK analysis and contributes to PK/PD analyses exploring efficacy endpoints and potential breakpoints.

3 Results of Sponsor's Analysis

Reviewer comment: Unless otherwise noted, the figures and tables displayed in section 3 reflect the sponsor's analyses. This section covers both the sponsor's population PK analysis and their proposed susceptibility test interpretive criteria.

3.1 Population PK Analysis

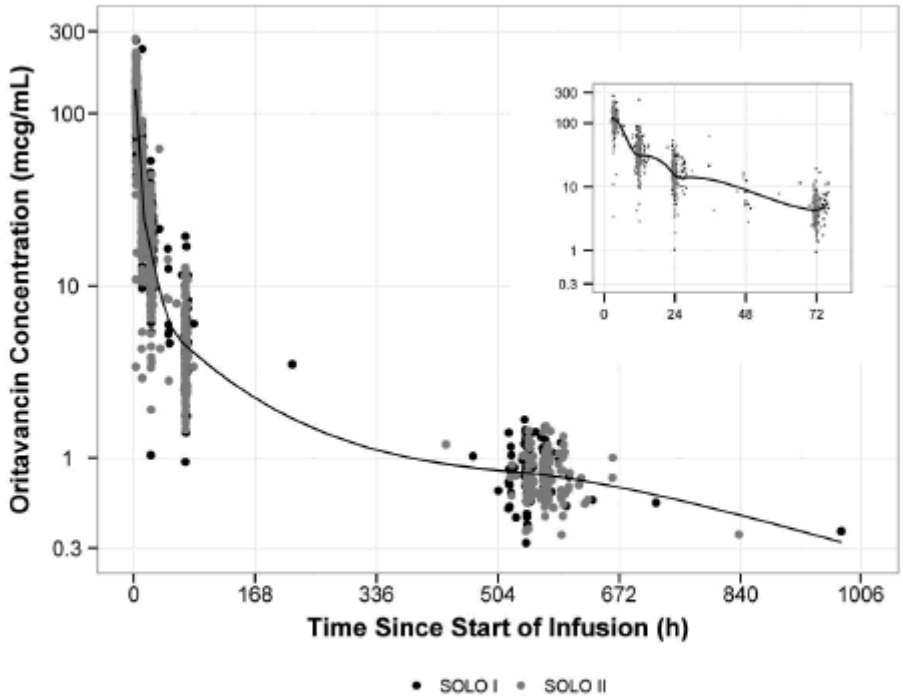
Objectives:

- To characterize oritavancin plasma PK in patient enrolled in SOLO I and SOLO II by updating the existing population PK model for oritavancin
- To assess the impact of subject demographic and disease characteristics on inter-individual variability (IIV) for selected PK parameters
- To generate individual predicted oritavancin plasma concentration-time profiles and calculated exposure measures for use in subsequent efficacy PK/PD analyses

Studies included in the Population PK Analysis:

The final PK analysis dataset was constructed using data from the two Phase 3 trials (SOLO 1 and SOLO 2) in patients with ABSSSI administered a 1200 mg single dose of oritavancin. This dataset included 485 oritavancin plasma concentrations from 110 patients from SOLO I and 852 oritavancin plasma concentrations from 187 patients in SOLO II. The log of the observed oritavancin concentrations are plotted over time in Figure 3.1.1. A summary of the categorical (Table 3.1.1) and continuous (Table 3.1.2) demographic information for SOLO I and SOLO II are also shown below.

Figure 3.1.1: Semi-log scatterplot of oritavancin plasma concentrations versus time since start of infusion (n=1337 oritavancin concentrations for analysis overall)



Note: The inset shows the first 80 hours of the post-dose period.
The solid lines through the data are nonparametric smoothers.

Table 3.1.1: Summary [n (%)] of categorical subject demographics of the PK analysis population (n=297)

	Variable	SOLO I	SOLO II	Pooled
Sex	Male	67 (60.9%)	134 (71.7%)	201 (67.7%)
	Female	43 (39.1%)	53 (28.3%)	96 (32.3%)
Race	White	73 (66.4%)	154 (82.4%)	227 (76.4%)
	Black	10 (9.09%)	7 (3.74%)	17 (5.72%)
	Asian	24 (21.8%)	20 (10.7%)	44 (14.8%)
	American Indian/Alaska Native	2 (1.81%)	3 (1.60%)	5 (1.68%)
	Native Hawaiian or Pacific Islander	1 (0.909%)	3 (1.60%)	4 (1.35%)

Table 3.1.2: Summary statistics [Mean (CV%), Median (Min-Max)] of the continuous subject demographic characteristics of the PK analysis population

Variable	SOLO I (n = 110)	SOLO II (n = 187)	Pooled (n = 297)
Age (yr)	48.2 (29.9%) 48.0 (18.0 – 89.0)	44.6 (27.9) 45.0 (19.0 – 79.0)	45.9 (29.4) 47.0 (18.0 – 89.0)
Weight (kg)	83.1 (32.2%) 78.0 (47.6 – 178)	77.9 (25.4) 74.8 (42.7 – 148)	79.9 (28.8) 75.6 (42.7 – 178)
Height (cm)	169 (6.70%) 170 (129 – 196)	170 (6.56) 170 (125 – 203)	170 (6.59) 170 (125 – 203)
BSA (m^2)	1.93 (15.2%) 1.89 (1.31 – 2.79)	1.88 (13.3) 1.89 (1.33 – 2.71)	1.90 (14.1) 1.89 (1.31 – 2.79)
BMI (kg/m^2)	28.9 (30.6%) 27.0 (17.0 – 67.4)	26.9 (23.2) 25.5 (15.9 – 55.5)	27.7 (27.0) 26.2 (15.9 – 67.4)
CLcr ($mL/min/1.73m^2$)	102 (32.4%) 102 (29.8 – 216)	108 (28.7) 109 (37.7 – 189)	106 (29.7) 106 (29.8 – 216)

Abbreviations:
BSA = Body surface area, BMI = Body mass index, CLcr = Creatinine clearance, %CV = Coefficient of variation (percent coefficient of variation)

Reviewer comment: The demographics of the patients in the population PK subset were similar to the demographics of the overall population, with the possible exception of race. Specifically, the overall population had a higher representation for Asians (28.1% overall) and a lower representation of Whites (64.4% overall).

Base Model:

Initial structural model development involved the fitting of the previous population PK model (a three-compartment model with a zero-order intravenous infusion and first-order elimination) to the oritavancin concentration-time data from SOLO I. The population PK parameter estimates for the model applied to SOLO I data were consistent with those from the previous population PK model which utilized only Phase 2/3 data (other study than SOLO I or SOLO 2). Of note, the population mean CL in the updated analysis was slightly higher and the population mean volume terms were generally smaller using data from SOLO I.

The model was then fit to the pooled data from SOLO I and SOLO II. The population PK parameter estimates and associated standard errors for the model are provided in Table 3.1.3. The population mean parameter estimates were similar to those obtained from the fit of the model to the SOLO I data alone and are relatively consistent with those from the previous population PK model.

In general, the magnitude of the inter-individual variability (IIV) was also consistent with that seen in the fit of the SOLO I data alone and with the values seen in the original population PK analysis.

Table 3.1.3: Base structural population PK model applied to the pooled data from SOLO I and SOLO II – Parameter estimates and standard errors

Parameter	Population mean			Magnitude of IIV (%CV)		
	Final estimate		%SEM	Final estimate		%SEM
	SOLO	*Previous*[a]		SOLO	*Previous*[a]	
CL (L/h)	0.454	*0.544*	1.95	26.9	*38.2*	12.3
Vc (L)	4.33	*6.32*	6.50	38.9	*42.8*	63.1
Q2 (L/h)	0.523	*0.363*	4.25	46.7	*88.7*	10.7
V2 (L)	67.3	*124*	3.59	50.0	*33.5*	12.3
Q3 (L/h)	1.35	*1.11*	9.02	48.2	*61.5*	38.4
V3 (L)	6.10	*20.5*	7.22	38.9	*64.7*	40.0
SD_{in}	0.22	*0.22*	—	—	—	—
SD_{sl}	0.216	*0.298*	3.73	—	—	—
Minimum value of the objective function = 2681						

a. Values in the "Previous" column are the estimates from the previous base structural model [2, 3] applied to the data from Studies H4Q-MC-ARRM, H4Q-MC-ARRL, and H4Q-MC-ARRD only [3].

Abbreviations:

CL = Total clearance, Vc = Volume of distribution of the central compartment, Q2, Q3 = Distributional clearances, V2, V3 = Volume of distribution of the peripheral compartments, SD_{in} = Intercept (additive) term for residual variability model for plasma concentrations, SD_{sl} = Slope (proportional) term for residual variability model, SEM = Standard error of the mean (percent standard error of the mean), IIV = Interindividual variability, CV = Coefficient of variation (percent coefficient of variation)

Final Model with Covariate Effects

The final population PK model for the pooled data from SOLO I and II was a three-compartment model with zero-order infusion and first-order (linear) elimination. Power-law covariates of age and height were included on V_c and CL, respectively. The population PK parameter estimates and associated standard errors for the model are provided in Table 3.1.5. In general, the magnitude of the IIV was relatively low (maximum of 62.4% for V3) with the exception of Q3, which had an IIV of 87.2%. These results are consistent with the values seen in the original population PK analysis.

Table 3.1.5: Final population PK model using pooled data from SOLO I and SOLO II – Parameter estimates and standard errors

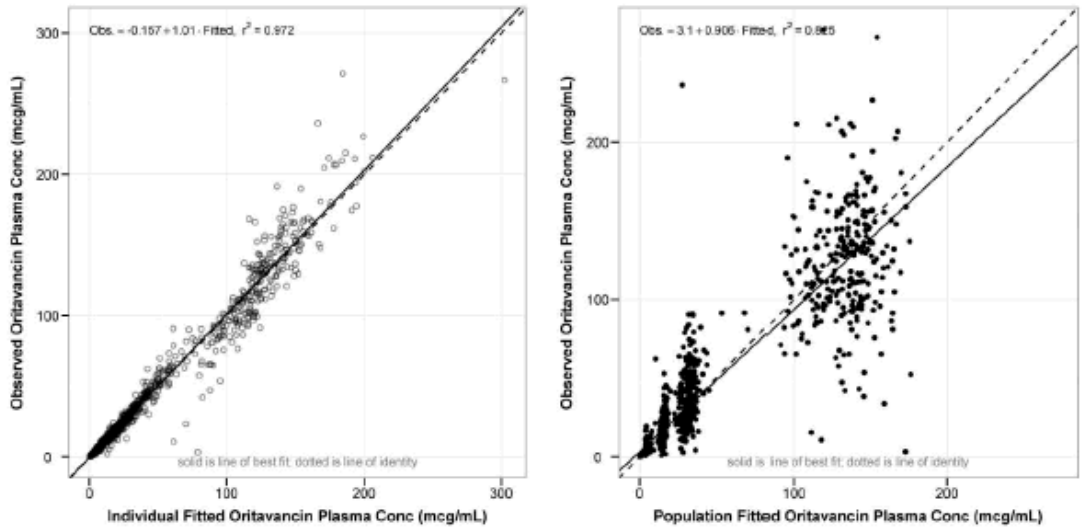
Parameter	Population mean		Magnitude of IIV (%CV)	
	Final estimate	%SEM	Final estimate	%SEM
CL (L/h)	0.445	—	27.2	21.6
Vc (L)	5.79	—	34.3	24.5
Q2 (L/h)	0.469	3.68	50.7	15.7
V2 (L)	75.5	5.63	48.3	14.5
Q3 (L/h)	0.666	4.78	87.2	22.9
V3 (L)	6.29	5.61	62.4	15.7
Vc-AGE Coefficient (L)	5.54	3.98	—	—
Vc-AGE Power	-0.641	11.0	—	—
CL-HTCM Coefficient (L/h)	0.446	2.57	—	—
CL-HTCM Power	0.695	84.8	—	—
SD_{in}	0.22	—	—	—
SD_{sl}	0.182	3.82	—	—
Minimum value of the objective function = 2636				

Abbreviations:

CL = Total clearance, Vc = Volume of distribution of the central compartment, Q2, Q3 = Distributional clearances, V2, V3 = Volume of distribution of the peripheral compartments, AGE = Patient age in years, HTCM = Patient height in cm, SD_{in} = Intercept (additive) term for residual variability model for plasma concentrations, SD_{sl} = Slope (proportional) term for residual variability model, %SEM = Standard error of the mean (percent standard error of the mean), IIV = Interindividual variability, %CV = Coefficient of variation (percent coefficient of variation)

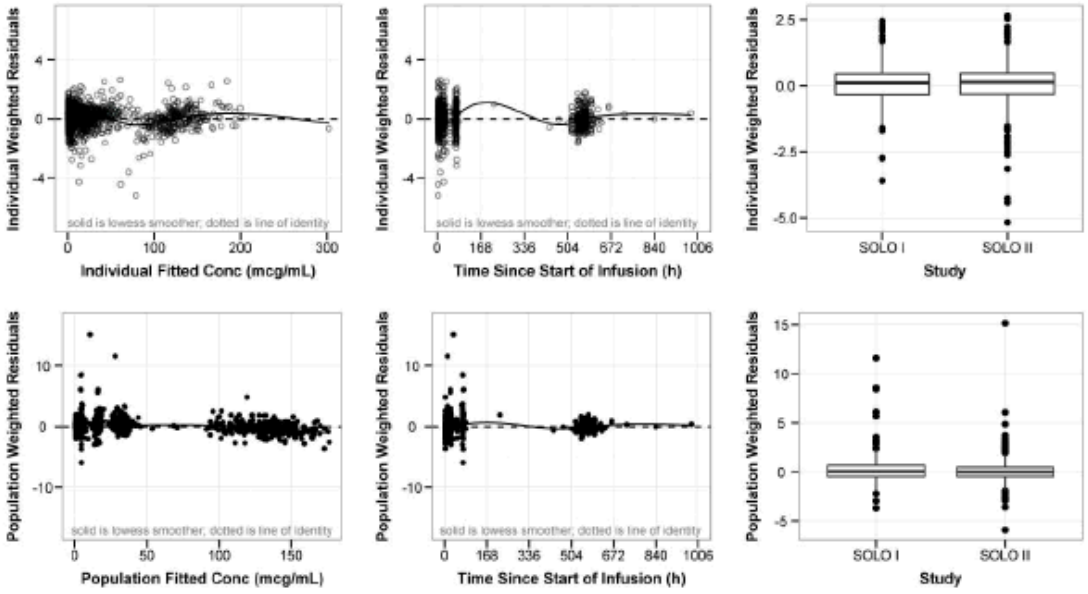
The goodness-of-fit plots for this model are provided in Figure 3.1.5 and Figure 3.1.6. In general, the plots in Figure 3.1.6 show consistent scatter about zero indicating that there are no significant biases in the fit of the data across the range of fitted concentrations over time. Of note, the box-and-whisker plots of individual and population weighted residuals (far right column of Figure 3.1.6), indicate that the fit of the model is similar between the two studies as would be expected given that the studies employed identical designs.

Figure 3.1.5: Goodness-of-fit plots for the final population PK model – Individual and population fitted concentrations



Abbreviations: Conc=Concentration, Obs. = Observed, r^2 = Coefficient of determination (r-squared)

Figure 3.1.6: Goodness-of-fit plots for the final population PK model – Individual and population weighted residuals

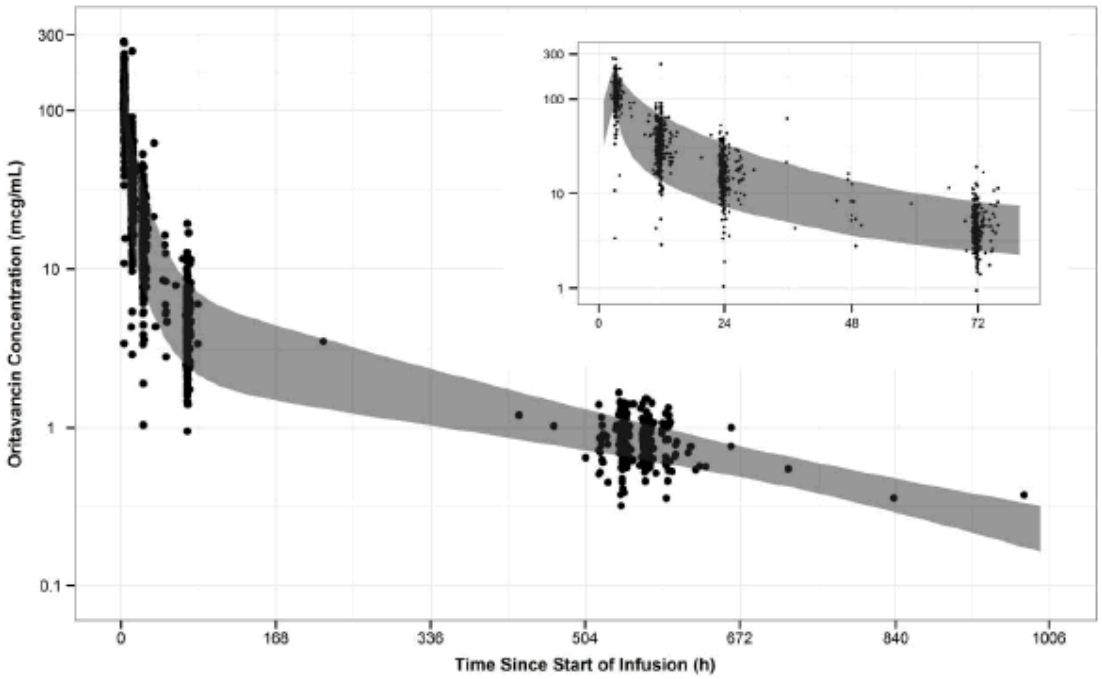


Abbreviations: Conc = Concentration

A visual predictive check (VPC), a simulation-based model diagnostic and qualification tool, was used to evaluate the ability of the model to adequately describe the observed PK data (see Figure 3.1.7). The process involved the simulation of 2000 subjects using the final population PK model (to obtain simulated PK parameters), and bootstrapping of the patients in the final population PK dataset (to obtain relevant demographic characteristics for the simulated population). The majority of the observed data fall within the 90% CI from the simulation, with 17% of the observed concentrations outside of that CI. The number of observed concentrations

above and below the CI was consistent (103 below and 127 above). Overall, this model is expected to provide robust and reliable estimates of oritavancin plasma exposure when used for PK/PD analyses for efficacy, which will be reported separately.

Figure 3.1.7: Visual predictive check for the final oritavancin population PK model using pooled data from SOLO I and SOLO II (n=1337 total oritavancin concentrations obtained in the population PK analysis)



Note: solid circles are observed data; shaded region is 90% CI from stochastic simulation
Abbreviations: CI = Confidence interval

The summary statistics for oritavancin plasma exposure and secondary PK parameters are provided in Table 3.1.6. The mean steady-state volume of distribution (Vss) of 100 L suggests that oritavancin is widely distributed after IV administration. The half-lives associated with the three compartment nature of oritavancin PK indicate a rapid initial distribution (mean $t_{1/2\alpha}$ of 2.29 hours) followed by a slower secondary distribution phase (mean $t_{1/2\beta}$ of 13.4 hours) and a slow terminal elimination (mean $t_{1/2\gamma}$ of 245 hours). Note that the exposure-related parameters were obtained from the fitted profile while the half-life estimates were obtained using the individual post-hoc parameter estimates and accepted equations.

Table 3.1.6: Summary statistics for individual, model-derived oritavancin plasma exposure and secondary PK parameters for all patients included in the PK population (n=297). Note that the C_{min} presented in the table corresponds to the last time point where oritavancin concentration was detectable

	Mean (CV%)	Median	Min	5th	25th	75th	95th	Max
V_{ss} (L)	97.8 (56.4%)	90.2	15.1	47.3	69.1	115	158	615
C_{max} (µg/mL)	138 (23.0%)	135	11.1	93.9	120	154	187	319
C_{min} (µg/mL)	2.06 (195%)	0.881	0.264	0.645	0.764	1.04	7.69	42.8
T_{min} (h)	482 (39.8%)	555	11.4	71	542	571	597	979
AUC_{0-24} (µg•h/mL)	1110 (33.9%)	1050	109	686	885	1300	1720	4060
AUC_{0-48} (µg•h/mL)	1390 (36.5%)	1310	172	836	1080	1630	2160	5370
AUC_{0-72} (µg•h/mL)	1530 (36.9%)	1430	223	910	1190	1790	2420	5900
AUC_{0-576} (µg•h/mL)	2510 (31.4%)	2350	607	1590	2000	2920	3750	7750
$AUC_{0-\infty}$ (µg•h/mL)	2800 (28.6%)	2640	832	1860	2270	3200	4070	8070
$T_{1/2,\alpha}$ (h)	2.29 (49.8%)	2.01	0.0192	1.01	1.55	2.78	4.43	6.97
$T_{1/2,\beta}$ (h)	13.4 (10.5%)	13.1	7.75	12.0	12.6	14.0	16.2	20.3
$T_{1/2,\gamma}$ (h)	245 (14.9%)	242	139	192	222	262	308	435

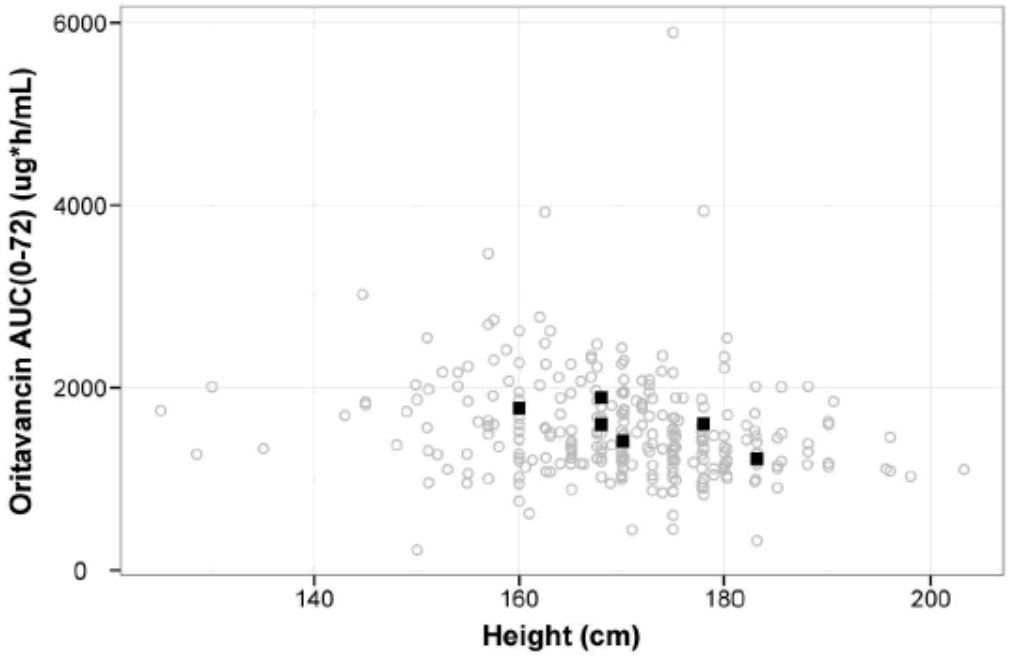
Abbreviations:

Vss = Steady-state volume of distribution, C_{max} = Maximum plasma concentration; peak plasma concentration, C_{min} = Minimum plasma concentration, T_{min} = Time of minimum drug concentration, AUC_{0-24} = Area under the plasma concentration-time curve from time zero to 24 hours, AUC_{0-48} = Area under the plasma concentration-time curve from time zero to 48 hours, AUC_{0-72} = Area under the plasma concentration-time curve from time zero to 72 hours, AUC_{0-576} = Area under the plasma concentration-time curve from time zero to 576 hours, $T_{1/2}$ = Half-life, $T_{1/2,\alpha}$ = Half-life for the alpha phase, $T_{1/2,\beta}$ = Half-life for the beta phase, $T_{1/2,\gamma}$ = Half-life for the gamma phase, CV% = Coefficient of variation (percent coefficient of variation)

LFT abnormalities as a function of exposure

As shown in Figure 3.1.8, there was no apparent relationship between AUC_{0-72} and the occurrence of elevation in ALT. Similar results are obtained when examining the AST and bilirubin. Note that height was chosen for the x-axis of the plots as a graphing convention in order to provide a spread of the data with LFT abnormalities.

Figure 3.1.8: Scatterplot of oritavancin AUC_{0-72} versus height for all patients included in the pooled, SOLO I and SOLO II PK population, stratified by occurrence of a Grade 3 or higher elevation in ALT (n=297)



Note: Black, filled squares represent patients with a Grade 3 or higher elevation in ALT (n=6); grey, open circles represent patients that did not have a Grade 3 or higher elevation in ALT (n=291)

Sponsor's Conclusions

- The structure of the previous population PK model (a three-compartment model with zero order IV input and linear elimination) provided an excellent fit to the pooled oritavancin concentration-time data from SOLO I and SOLO II.
- The population PK analysis identified two significant covariates that influenced oritavancin exposure: a relationship between age and Vc where central volume of distribution (Vc) decreased with increasing age and a relationship between height and clearance (CL) where CL increased with increasing height. These relationships explained a relatively small amount of the IIV in oritavancin (0% of the IIV for CL and 4.5% of the IIV for V_c).
- Patient age and height were only modestly related to more clinically relevant PK parameters (i.e. C_{max} and AUC_{0-72}). Therefore, dose modifications are not warranted on the basis of patient age or height.
- Dose modifications are also not warranted on the basis of any of the other patient covariates evaluated (gender, body weight, race, renal function, or diabetes) as none of these patient factors were found to be related to oritavancin pharmacokinetics
- The results of the exploratory analysis suggests that the occurrence of LFT abnormalities (Grade 3 or higher elevation in AST or ALT, total bilirubin greater than 15-times the upper limit of normal) was independent of oritavancin AUC_{0-72}.

Reviewer comments: The reviewer conducted an independent assessment of the sponsor's population PK model and identified a similar model structure (three compartment model). The reviewer's independent analysis (described in section 4), utilized log-transformed data (sponsor's analysis was based on untransformed concentration data) but was otherwise similar to the approach used by the sponsor. The reviewer was unable to obtain model convergence when random-effect parameters were included on all fixed-effects, though this was reconciled when the random-effect was removed from Q3. The random-effect for V3 was also highly variable and suggests that the available data from SOLO 1 and SOLO 2 may not be sufficient to inform individual variability on the third compartment (V3 and Q3) due to the sparse sampling approach. However, the available data clearly demonstrates a need for a third compartment given the precision in the fixed-effect estimates for V3 and Q3 and detectable oritavancin concentrations at 576 hours following administration of a single dose.
The reviewer's evaluation of covariates did not identify any clinically significant covariates (see below). This is in agreement with the sponsor's covariate analysis which identified numerically significant covariates of age on Vc and height on CL; however, these covariate effects were not identified as appreciably impacting oritavancin exposures and no dose adjustments are recommended based on these covariates. The reviewer agrees that no clinically significant impact of sex, race, body weight, and renal function status were identified from the available data; however, it should be noted that the initial population PK data based on Phase 2/3 data (not SOLO 1 or SOLO 2) identified body weight as a significant covariate. That analysis included patients with more frequent PK sampling, and it is uncertain if the covariate conclusions from the current analysis may have been influenced by the inclusion of only sparse sampling in the current analysis.

3.2 Susceptibility Test Interpretive Criteria

Introduction/Objectives

The pharmacokinetic data collected during SOLO I and SOLO II were used to evaluate PK/PD relationships for efficacy and to confirm predictions for dose selection made during the course of drug development. Using a population PK model based on the SOLO PK data and both non-clinical and clinical PK/PD targets for efficacy, analyses evaluating PK/PD target attainment and predicted clinical response were performed to support establishing interpretive criteria for in vitro susceptibility testing of oritavancin against *S. aureus* and *S. pyogenes*. The objectives of these analyses were:

- To characterize PK/PD relationships for efficacy using data from oritavancin-treated patients with ABSSSI, baseline Gram-positive ABSSSI pathogens, and sufficient PK data who were enrolled in SOLO I and SOLO II
- To evaluate PK/PD target attainment and predicted clinical response in support of establishing interpretive criteria for in vitro susceptibility testing of oritavancin against *S. aureus* and *S. pyogenes*

Methods

- **Analysis Population**

The analysis population consisted of patients with ABSSSI enrolled in SOLO I and II who received oritavancin, were in the microbiologically evaluable (MicroE) population for each

study, and for whom sufficient PK data were available. The MicroE population included all patients who met the criteria for inclusion in the MicroITT and clinically evaluable (CE) populations. The microbial intent-to-treat (MicroITT) population included all patients in the modified intent-to-treat (mITT) population (i.e. all patients randomized into the trial and receiving any study drug) and who had a Gram-positive baseline bacterial pathogen known to cause ABSSSI against which the test study drug has antibacterial activity. The CE population included patients in the mITT population who met the inclusion/exclusion criteria, received the full course of study treatment for 7 to 10 days, and had investigator assessment of clinical cure at PTE.

For both analysis populations, data for patients for whom the primary outcome at the early clinical efficacy (ECE) visit or clinical response at the end-of-treatment (EOT), Day 10, or post-therapy evaluation (PTE) visits was determined to be a failure not due to study drug were excluded from analyses of these endpoints. For the assessment of primary outcome at the ECE visit, if patients had insufficient temperature data, a failure was declared. Data for such patients were excluded from the analyses of primary outcome at the ECE visit. **Efficacy Endpoints** Table 3.2.1 provides a listing of the efficacy endpoints assessed in the univariable PK/PD analyses for efficacy.

Table 3.2.1: Listing of univariable PK/PD analyses for efficacy

Efficacy endpoints	Efficacy endpoint type	Evaluation time point
Primary outcome	Dichotomous	ECE
Clinical response[a]	Dichotomous	EOT, Day 10, PTE
Sustained clinical response	Dichotomous	PTE
Microbiological response	Dichotomous	EOT, Day 10, PTE
Change in the area of infection relative to baseline	Dichotomous, time-to-event, and continuous	ECE, Days 1 to 9, EOT, Day 10, PTE
Temperature	Time-to-event or continuous[b]	Days 1 to 9

a. Clinical response was based on the investigator-assessed clinical cure at the EOT, Day 10, and PTE visits.
b. Analyses for fever resolution were undertaken if there were sufficient numbers of patients that were febrile at baseline. If all patients had fever resolution during the observation period, fever resolution was evaluated as a continuous rather than a time-to-event endpoint.

Reviewer's comment: The reviewer's analysis of PK/PD relationships and probability of target attainment based on the clinical data from SOLO I and SOLO II was limited to endpoints of ECE, clinical response at PTE, and change in lesion size of >20% at the ECE visit, all of which are dichotomous efficacy assessments. The latter assessment is consistent with the endpoint described in the FDA guidance for ABSSSI.

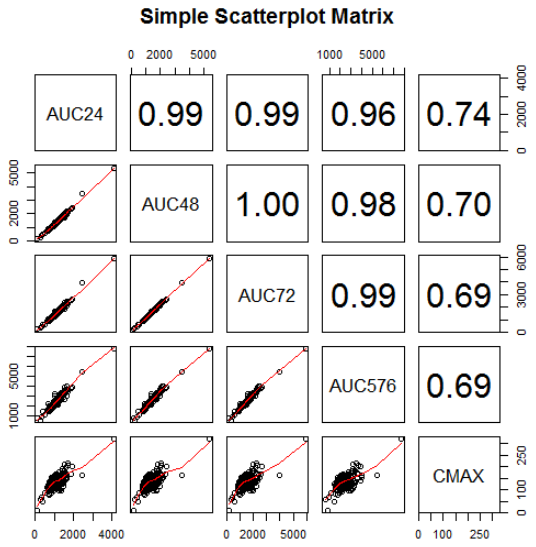
- Pharmacokinetic/Pharmacodynamic Analyses

Generation of Oritavancin AUC_{0-72}/MIC Ratio Values

Using the population PK model, individual fitted oritavancin concentration-time profiles were generated for each patient in the analysis populations using post-hoc PK parameter estimates from the population PK analysis. The AUC_{0-72} was calculated from the first 72 hours of the

profile using the linear trapezoidal rule. AUC_{0-72}/MIC ratio was calculated by dividing total drug AUC_{0-72} by the oritavancin MIC value for the baseline infecting pathogen. For those patients who had more than one pathogen isolated at baseline, the pathogen, specimen type, and baseline oritavancin MIC value were considered when selecting the MIC value to use to calculate the AUC_{0-72}/MIC ratio. The pathogen with the higher MIC value was generally selected. *S. aureus*, which typically manifests higher MIC values, was considered preferentially over other Gram-positive pathogens. Given the potential for greater clinical relevance, more weight was given to isolates recovered from blood cultures as compared to the ABSSSI infection site.

Reviewer's comment: The reviewer conducted an analysis of concordance between oritavancin exposure measures at different time points (24 hours, 48 hours, 72 hours, 576 hours, C_{max}, see below). The results are shown below and demonstrate good correlation between all of the exposure measures. As the nonclinical assessments are based on oritavancin AUC_{0-72}/MIC and as the primary endpoint (and legion size reduction) is obtained at day 3, the reviewer agrees with the sponsor's selection of AUC_{0-72}/MIC and also used AUC_{0-72} as the oritavancin PK parameter for exposure-response analyses.



Exploratory PK/PD Analyses (Univariable and Multivariable PK/PD Analyses)

Exploratory analyses for dichotomous and continuous efficacy endpoints were conducted to identify relationships between the probability of achieving each efficacy endpoint and oritavancin AUC_{0-72}/MIC ratio, AUC_{0-72}, and MIC value. In addition to the evaluation of independent variables, AUC_{0-72}/MIC ratio, AUC_{0-72}, and MIC, patient demographic and disease-related characteristics and underlying comorbidities were considered. A listing of the additional independent continuous and categorical variables that were considered is provided in Table 3.2.2.

Univariate relationships for dichotomous efficacy endpoints were examined using Chi-square or Fisher's exact tests for categorical independent variables and logistic regression for continuous independent variables. Univariate relationships for continuous efficacy endpoints were evaluated on Days 1 to 10, EOT, and PTE using linear regression or Spearman correlation and corresponding tests for associations.

Table 3.2.2: Listing of independent variables evaluated

Demographic	Disease-related or underlying comorbidities
Age (yr)	ABSSSI type
AUC_{0-72} (mg•h/L)	Gram-negative pathogen isolated at baseline
AUC_{0-72}:MIC ratio	Concomitant aztreonam administration
Body mass index (BMI) (kg/m^2)	Concomitant metronidazole administration
CLcr (mL/min/1.73 m^2)	Hepatitis or other hepatic condition
Ethnicity-Hispanic	IV drug use
Height (cm)	Presence of diabetes mellitus
MIC (mg/L)	Presence of polymicrobial infection
Race/Ethnicity	Presence of MRSA at baseline[a]
Sex	Presence of severe peripheral vascular disease
Weight (kg)	Specimen type

a. Evaluated only for the analysis population containing patients with *S. aureus*.

Multivariable analysis was considered for each efficacy endpoint if a statistically significant ($p<0.05$) or borderline significant ($p=0.05$ to 0.1) univariate relationship between the probability of achieving the efficacy endpoint and AUC_{0-72}/MIC ratio, AUC_{0-72}, or MIC value was identified. Multivariable models were developed using the forward inclusion of independent variables with an entry criterion of largest improvement of Akaike's Information (AIC), if any. Model-predicted results for a given efficacy endpoint were also assessed on the subset of patients with *S. aureus* and *S. pyogenes* pathogens at baseline.

Probability of Target Attainment and PK-PD Simulation Analysis

Nonclinical PTA

Using S-ADAPT, a population of 5000 simulated patients was generated. Patient demographic characteristics were sampled with replacement from the age and height of the patients included in the SOLO I and II population PK analysis dataset as these were the significant covariates identified from the initial population PK analysis. Oritavancin concentration-time profiles after administration of a single 1200 mg dose administered over 3 hours were simulated for these 5000 patients. AUC_{0-72} values were then calculated for each simulated patient by numerical integration of the concentration-time profiles. Oritavancin is ~85% protein bound across species, so total AUC was used rather than free AUC. Using the AUC_{0-72} values for simulated patients, the percent probability of attaining the non-clinical AUC_{0-72}/MIC ratio targets for *S. aureus* and *S. pyogenes* was determined. The nonclinical PK/PD targets for oritavancin efficacy are shown in Table 3.2.3.

Table 3.2.3: Summary of nonclinical PK/PD targets for oritavancin efficacy against *S. aureus* and *S. pyogenes* based on total drug concentration

Pathogen [reference]	Median (min – max) AUC_{0-72}:MIC ratio associated with the bacterial reduction endpoint	
	Net bacterial stasis	1-log_{10} CFU reduction from baseline
S. aureus [11]	3,941 (265 - 30,255)	4,581 (305 - 35,348)
S. pyogenes [12]	120 (10.2 - 963)	198 (16.2 – 1,376)

CFU = Colony forming units.

11. Institute for Clinical Pharmacodynamics. Pharmacokinetic-pharmacodynamic analyses of oritavancin against *Staphylococcus aureus* using data from a murine-thigh infection model. Final Report, ICPD 00236, November 4, 2011.
12. Institute for Clinical Pharmacodynamics. Analysis of pharmacokinetics and pharmacokinetics-pharmacodynamics of oritavancin against *Streptococcus pyogenes* using data from a murine-thigh infection model. Final Report, ICPD 00180, October 6, 2008.

Percent probabilities of PK/PD target attainment were assessed at individual fixed MIC values spanning the MIC distribution for oritavancin against both *S. aureus* and *S. pyogenes* based on recent surveillance data (see Table 3.2.4). Overall percent probabilities for *S. aureus* and *S. pyogenes* were determined using these two MIC distributions.

Table 3.2.4: MIC distributions for *S. aureus* and *S. pyogenes*

Pathogen (no. of isolates tested)	Number of occurrences (cumulative % inhibited) by MIC (mg/L)								
	≤ 0.008	0.015	0.03	0.06	0.12	0.25	0.5	MIC_{50}	MIC_{90}
S. aureus (n=13,336)[a]	352 (2.6)	3181 (26.5)	5436 (67.3)	3201 (91.3)	968 (98.5)	198 (100)	0	0.03	0.06
S. pyogenes (n=960)[a]	106 (11.0)	198 (31.7)	248 (57.5)	204 (78.8)	135 (92.8)	63 (99.4)	6 (100)	0.03	0.12

a. As described in reference 17, data were collected from the US and Europe during 2010-2012 as part of the [redacted](b) (4) Protocol 12-TMC-02.

[redacted](b) (4)

[redacted](b) (4)

Clinical PTA

Using the AUC_{0-72}/MIC ratio thresholds based on univariable PK/PD relationships for *S. aureus*, the percent probability of PK/PD target attainment was also determined for oritavancin against *S. aureus*, average mean model-predicted percent probability of PK/PD target attainment were determined.

Model-predicted clinical response

Using the AUC_{0-72} values for simulated patients receiving a single 1200 mg IV dose of oritavancin, the percent probability of attaining the above-described non-clinical AUC_{0-72}/MIC ratio targets for S. aureus was determined. Percent probabilities of PK/PD target attainment were assessed at individual fixed MIC values spanning the MIC distribution for oritavancin against *S. aureus* based on recent surveillance data. Overall, percent probabilities of PK/PD target attainment for each set of AUC_{0-72}/MIC ratio targets for *S. aureus* were determined using the MIC distribution.

Clinical PK/PD relationships for efficacy endpoints were derived from analyses of data from patients with *S. aureus* which were conducted as described above. Using univariable relationships between a given dichotomous efficacy endpoint and AUC_{0-72}/MIC ratio, a model-predicted percent probability of achieving clinical success was determined at each fixed MIC value for each simulated subject. Averaging across the simulated patients yielded a mean model-predicted percent probability of clinical success for each fixed MIC value. For univariable relationships for which AUC_{0-72}/MIC ratio was evaluated as a two-group variable, mean model-predicted percent probabilities of clinical success translated to a weighted average of the two response probabilities with weights representing the frequencies of simulated patients below and above the threshold. For continuous efficacy endpoints, model-predicted mean clinical success and likelihoods of events at selected time points, respectively, were determined rather than percent probability of clinical success.

Using the AUC_{0-72}/MIC ratio thresholds based on univariable PK/PD relationships for *S. aureus*, the percent probability of PK/PD target attainment was also determined for fixed MIC values. Using the above-described MIC distribution for oritavancin against *S. aureus*, average mean model-predicted percent probabilities of clinical success and the overall (i.e., the weighted average) percent probability of PK/PD target attainment were determined.

Results

Analysis Population

A total of 529 patients (244 from SOLO I and 285 from SOLO II) were treated with oritavancin and had baseline pathogen and MIC information, thereby constituting the oritavancin-treated subset of the MicroITT population. Of these 529 patients, 175 (53 from SOLO I and 122 from SOLO II) were in the MicroE population and had sufficient PK data. Of these 175 patients, 154 (50 from SOLO I and 104 from SOLO II) had *S. aureus* isolated at baseline.

Assessment of Efficacy

Percentages of patients designated as successes for the primary outcome and clinical, sustained clinical, and microbiological response by visit based on data from all patients with *S. aureus* are shown in Table 3.2.5. The percentage of all patients and patients with *S. aureus* infection achieving each of the dichotomous area of infection endpoints, cessation of spread or ≥ 10, 20, 30, 50, and 70% reduction from baseline in the area of infection at the ECE, EOT, Day 10, or PTE visits is shown in Table 3.2.6.

Table 3.2.5: Summary of response efficacy endpoints by visit for all patients with PK and a confirmed Gram positive organism and patients with *S. aureus*

Analysis population	Visit	% Success (n/N)			
		Primary outcome	Clinical response	Sustained clinical response	Microbiological response
All patients	ECE	89.0 (154/173)	-	-	-
	EOT	-	98.3 (172/175)	-	98.3 (171/174)
	Day 10	-	97.7 (171/175)	-	97.7 (170/174)
	PTE	-	94.3 (165/175)	90.3 (158/175)	94.3 (164/174)
Patients with *S. aureus*	ECE	90.1 (137/152)	-	-	-
	EOT	-	98.7 (152/154)	-	98.7 (152/154)
	Day 10	-	98.1 (151/154)	-	98.1 (151/154)
	PTE	-	94.2 (145/154)	91.6 (141/154)	94.2 (145/154)

Table 3.2.6: Summary of dichotomous area of infection efficacy endpoints by visit for all patients and patients with *S. aureus*

Analysis population	Visit	N	Dichotomous area of infection efficacy endpoints % (n)					
			Cessation of spread	Endpoints for reduction from baseline in the area of infection				
				≥ 10%	≥ 20%	≥ 30%	≥ 50%	≥ 70%
All patients	ECE	175	98.9 (173)	95.4 (167)	93.7 (164)	87.4 (153)	69.1 (121)	36.0 (63)
	EOT	175	100 (175)	100 (175)	100 (175)	100 (175)	98.9 (173)	87.4 (153)
	Day 10	172	100 (172)	100 (172)	100 (172)	100 (172)	98.8 (170)	95.9 (165)
	PTE	174	100 (174)	100 (174)	99.4 (173)	99.4 (173)	99.4 (173)	98.3 (171)
Patients with *S. aureus*	ECE	154	100 (154)	97.4 (150)	95.5 (147)	89.0 (137)	70.1 (108)	36.4 (56)
	EOT	154	100 (154)	100 (154)	100 (154)	100 (154)	98.7 (152)	87.7 (135)
	Day 10	151	100 (151)	100 (151)	100 (151)	100 (151)	98.7 (149)	96.0 (145)
	PTE	153	100 (153)	100 (153)	99.3 (152)	99.3 (152)	99.3 (152)	98.0 (150)

Reviewer comment: The response rates for the PK population used in this analysis (ECE: 89%, PTE: 94%; 20% lesion size reduction: 94%) was higher than the response rates observed in the MRSA mITT population (ECE: 81%; PTE: 83%; 20% lesion size reduction: 93%). These differences suggest that the PK population may differ somewhat from the overall MRSA mITT population, and that the relationships identified from this population may overestimate the response at different MIC values.

Summary of Exposure Measures

Summary statistics for $AUC_{0\text{-}72}$, baseline MIC, and $AUC_{0\text{-}72}$/MIC ratio based on data from all patients and patients with *S. aureus* alone are provided in Table 3.2.7.

Table 3.2.7: Summary statistics for AUC_{0-72}, baseline MIC, and AUC_{0-72}/MIC ratio for all patients and patients with *S. aureus*

Analysis population	Variable	AUC_{0-72} (mg•h/L)	MIC (mg/L)	AUC_{0-72}:MIC ratio
All patients (N=175)	Mean (%CV)	1,494 (38.5)	-	56,401 (248)
	Median or $MIC_{50/90}$ (min - max)	1,417 (223 – 5,895)	0.06/0.12 (0.001 - 0.25)	33,208 (3,393 – 1,417,272)
	5^{th} – 95^{th} percentile	874.6 – 2,306	-	7,106 – 113,471
	25^{th} – 75^{th} percentile	1,169 – 1,751	-	19,284 – 49,757
Patients with *S. aureus* (N=154)	Mean (%CV)	1,495 (39.0)	-	38,771 (84.0)
	Median or $MIC_{50/90}$ (min - max)	1,424 (325 – 5,895)	0.06/0.12 (0.015 - 0.25)	32,875 (3,393 – 262,629)
	5^{th} – 95^{th} percentile	875 – 2,263	-	7,387 – 90,924
	25^{th} – 75^{th} percentile	1,157 – 1,723	-	18,942 – 48,831

Exploratory PK/PD Analyses (Univariable and Multivariable PK/PD Analyses)

Univariable

AUC_{0-72}/MIC ratio thresholds for univariable relationships between the probability of achieving dichotomous efficacy endpoints and AUC_{0-72}/MIC ratio evaluated as a two-group variable based on data from all patients and patients with *S. aureus* are shown in Table 3.2.8.

Table 3.2.8: AUC_{0-72}/MIC ratio thresholds for univariable relationships between the probability of achieving dichotomous efficacy endpoints and AUC_{0-72}/MIC ratio evaluated as a two-group variable based on data from all patients and patients with *S. aureus*

Efficacy endpoint	All patients				Patients with *S. aureus*			
	AUC_{0-72}:MIC ratio threshold	Percent of patients < or ≥ AUC_{0-72}:MIC ratio threshold achieving efficacy endpoint		P-value	AUC_{0-72}:MIC ratio threshold	Percent of patients < or ≥ AUC_{0-72}:MIC ratio threshold achieving efficacy endpoint		P-value
		< threshold % (n/N)	≥ threshold % (n/N)			< threshold % (n/N)	≥ threshold % (n/N)	
Primary outcome at ECE	38,951	82.2 (83/101)	98.6 (71/72)	<0.001	24,574	79.6 (43/54)	95.9 (94/98)	0.001
Clinical response at EOT	32,375	96.5 (82/85)	100 (90/90)	0.11	19,111	94.9 (37/39)	100 (115/115)	0.06
Clinical response at Day 10	19,111	92.9 (39/42)	99.2 (132/133)	0.043	19,111	92.3 (36/39)	100 (115/115)	0.015
Clinical response at PTE	11,982	84.6 (22/26)	96.0 (143/149)	0.043	11,982	82.6 (19/23)	96.2 (126/131)	0.029
Sustained clinical response at PTE	23,924	80.0 (48/60)	95.7 (110/115)	<0.001	19,459	80.5 (33/41)	95.6 (108/113)	0.006

Given that for other antibiotics, the magnitude of the PK/PD index associated with net bacterial stasis in a murine-thigh infection model has been found to be associated with good outcomes in patients with ABSSSI for outcomes assessed at the test of cure visit, focus was given to the comparison of this non-clinical AUC_{0-72}/MIC ratio target to the AUC_{0-72}/MIC ratio threshold identified for clinical response at PTE. An AUC_{0-72}/MIC threshold of 11,982 was found to distinguish clinical responders from clinical non-responders at PTE based on data from all patients and from patients with *S. aureus*. The previously-derived median (min-max) AUC_{0-72}/MIC for net bacterial stasis of *S. aureus* was 3,941 (265 - 30,255). Examining these data, one can see that the AUC_{0-72}/MIC ratio threshold of 11,982 is within the non-clinical AUC_{0-72}/MIC ratio range of 265 to 30,255. Given the high percentage of patients with *S. aureus* who had AUC_{0-72}/MIC ratio thresholds ≥11,982, this finding was supportive of the 1200 mg oritavancin dose.

Multivariable

Given the lack of consistent results for the univariate analyses of the area of infection efficacy endpoints and certain limitations that arise from assessing efficacy endpoints early in therapy, including the high percentage of patients that achieve such endpoints, multivariable analyses were only performed to evaluate factors associated with clinical response at PTE. As a first step to conducting multivariable analyses for clinical response at PTE, univariable relationships between the probability of achieving this efficacy endpoint and other independent variables were evaluated.

Given the limited number of failures for clinical response at PTE for both analysis populations (10/175 and 9/154 failures among all patients and patients with *S. aureus*, respectively) it was evident that multivariate models could only support retention of two independent variables.

The final model for clinical response at PTE based on data from patients with *S. aureus* is shown in Table 3.2.9.

Table 3.2.9: Final multivariable model for clinical response at PTE based on data from patients with *S. aureus*

Independent variable	Parameter estimate (SE)[a]	Odds ratio (95% confidence interval)	P-value[b]
AUC_{0-72}:MIC ratio ≥ 11,982[c]	1.75 (0.764)	5.75 (1.28 – 25.7)	0.028
BMI ≥ 24.8 to < 29.1 kg/m^2[d, e]	Positive value[e]	> 1[e]	0.010
BMI ≥ 29.1 kg/ m^2[d]	-0.976 (0.745)	0.377 (0.087 – 1.63)	

a. The parameter (SE, standard error) for the intercept is 1.58 (0.645).
b. Likelihood ratio p-value.
c. Reference group = patients with AUC_{0-72}:MIC ratio < 11,982.
d. Reference group = patients with BMI < 24.8 kg/m^2.
e. Direction of relationship is indicated but the parameter estimate and odds ratio could not be estimated due to 100% observed success in this BMI range.

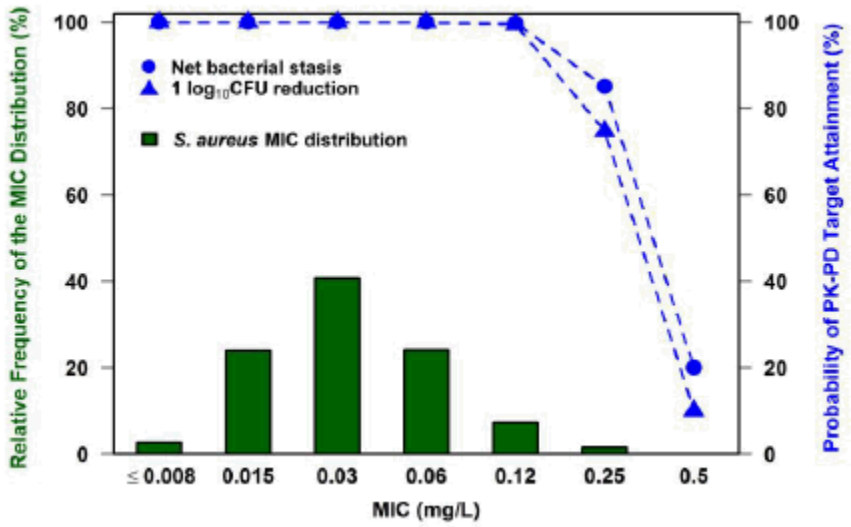
Reviewer comment: The low number of treatment failures for all of the efficacy assessments hinders identification of relevant covariates for treatment response, including PTE. It is not clear why the sponsor selected this measure for further evaluation. The reviewer evaluated other efficacy variables, including early clinical efficacy and lesion size reduction at day 3, the latter of which is in agreement with the FDA Guidance for ABSSSI.

Probability of Target Attainment and PK-PD Simulation Analysis

Nonclinical PTA

The percent probabilities of PK/PD target attainment by MIC value for non-clinical AUC_{0-72}/MIC ratio targets for net bacterial stasis and 1-$\log_{10}$ CFU reduction from baseline for *S. aureus* is shown in Figure 3.2.1. Overlaid on the figure is the oritavancin MIC distribution against *S. aureus* from recent surveillance of clinical isolates in the US and Europe.

Figure 3.2.1: Percent probabilities of PK/PD target attainment by MIC for *S. aureus* based on a non-clinical PK/PD relationship

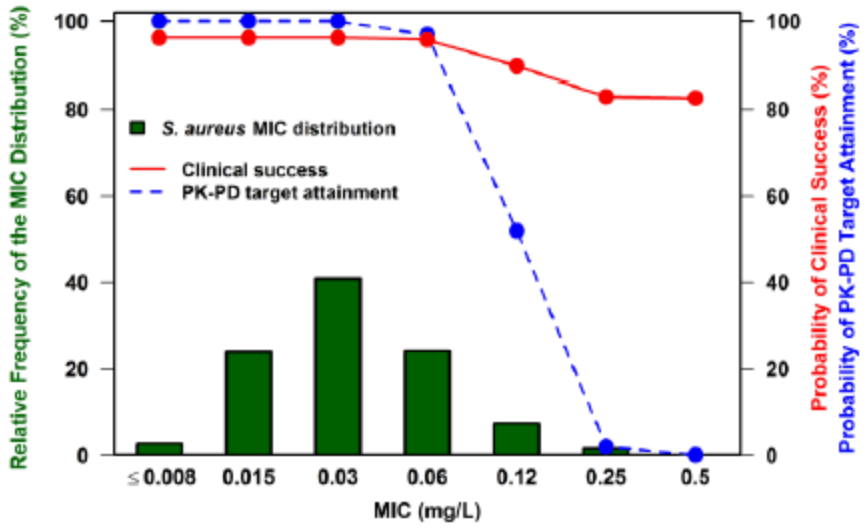


Clinical PTA and Model-Predicted Clinical Response

At a fixed MIC value and using parameter estimates from the univariable relationship between clinical response at PTE and AUC_{0-72}/MIC ratio evaluated as two-group variable based on data from patients with *S. aureus*, each simulated patient was assigned one of the two model-

identified percent probabilities of clinical success. Across simulated patients, the mean model-predicted percent probabilities of clinical success by MIC were determined. Additionally, using the AUC_{0-72}/MIC ratio threshold based on this univariable relationship (AUC_{0-72}/MIC ratio = 11,982) percent probabilities of PK/PD target attainment by MIC were also determined. Mean percent probabilities of clinical success and percent probabilities of PK/PD target attainment overlaid on the MIC distribution for oritavancin against *S. aureus* is shown in Figure 3.2.2.

Figure 3.2.2: Mean percent probabilities of clinical success and percent probabilities of PK/PD target attainment by MIC for *S. aureus* based on the PK/PD relationship for clinical response at PTE



Summary

A tabular summary of the percent probabilities by MIC is provided in Table 3.2.10. In addition, the overall percent probability of PK/PD target attainment and the average mean percent probability of clinical success weighted across the MIC distribution for oritavancin against *S. aureus* is also shown.

At an MIC value of 0.12 and 0.25 mg/L, the percent probability of achieving the AUC_{0-72}/MIC ratio target associated with net bacterial stasis was 99.8 and 85.1%, respectively. At an MIC value of 0.12 mg/L, the percent probability of achieving the AUC_{0-72}/MIC ratio threshold of 11,982 was 51.9% whereas the mean model-predicted percent probability of clinical success was 89.7%. At an MIC value of 0.25 mg/L, the percent probability of achieving the AUC_{0-72}/MIC ratio threshold of 11,982 was 1.9%; the mean model-predicted percent probability of clinical success at this MIC value was 82.9%.

Table 3.2.10: Percent probabilities of PK/PD target attainment and mean percent probabilities of clinical success by oritavancin MIC and overall across the MIC distributions for *S. aureus*

Oritavancin MIC (mg/L)	Results based on non-clinical PK-PD data[a]		Results based on clinical PK-PD data[b]	
	Probability of PK-PD target attainment (%)		Probability of PK-PD target attainment (%)	Mean model-predicted probability of clinical success (%)
	Net bacterial stasis	1-$\log_{10}$ CFU reduction		
0.06	100	100	96.9	95.8
0.12	99.8	99.4	51.9	89.7
0.25	85.1	74.8	1.9	82.9
0.5	20.0	10.0	0	82.6
Overall[c]	99.8	99.6	94.3	95.4

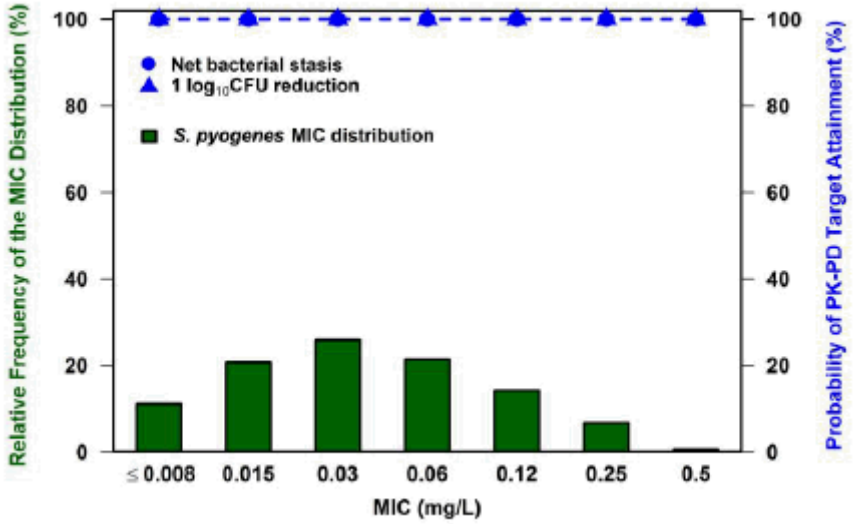
a. Based on non-clinical PK-PD targets for *S. aureus* described in reference 11.
b. Based on univariable PK-PD relationship for clinical response at PTE for patients with *S. aureus*.
c. Represents the overall (i.e., weighted average) percent probability of PK-PD target attainment or the average mean model-predicted percent probabilities of clinical success over the MIC distribution for oritavancin against *S. aureus*.

Reviewer comment: The reviewer disagrees with the sponsor's selection of a two-group variable for AUC_{0-72}/MIC in simulations for predicting the probability of clinical success based on the clinical PK-PD data. The implications of this dichotomous PK-PD relationship are that response rates from the simulations are bounded based on the observed response rate in subjects above and below the threshold value. This is depicted above in the Table 3.2.10 where the mean model-predicted percent probability of response for clinical success was 95.8% and 82.6% for an MIC of 0.06 mg/L and 0.5 mg/L, respectively. These predicted response rates correspond to the observed response rates in subjects above and below the respective threshold values provided by the Sponsor in Table 3.2.8. Therefore, interpreting these simulation results based on when the response rate decreases below a specific percentage may be inappropriate.

<u>*S. pyogenes* Probability of target attainment (nonclinical)</u>

Percent probabilities of PK/PD target attainment by MIC for *S. pyogenes* are shown in Figure 3.2.3. The percent probability of PK/PD target attainment by MIC was 100% up to the highest MIC evaluated, 0.5 mg/L, for AUC_{0-72}/MIC ratio targets associated with both net bacterial stasis and a 1-$\log_{10}$ CFU reduction from baseline. Accordingly, the overall percent probability of PK/PD target across the MIC distribution was 100% for both AUC_{0-72}/MIC ratio targets.

Figure 3.2.3: Percent probabilities of PK/PD target attainment by MIC for *S. pyogenes* based on a non-clinical PK/PD relationship



Reviewer comment: The MICs in the above plot are likely from surveillance studies, although that was not specified in the report as it was for the comparable S. aureus *plot. The reviewer similarly observed that there were no failures in subjects with* S. pyogenes *at baseline in the PK/PD dataset. As such, the reviewer could not identify any relationships between oritavancin exposures and clinical response. The reviewer's analysis was limited to probability of target attainment based on nonclinical information. As the AUC_{0-72}/MIC cut off for* S. pyogenes *was at least 20-fold lower than that of* S. aureus *based on the animal model data (see Table 3.2.3), the reviewer's analysis similarly predicted a 100% response rate for* S. pyogenes *for MIC values up to 0.5 mg/L. The reviewer limited the analysis to MIC values of 0.5 mg/L based on surveillance data and agrees with the sponsor that the available PK/PD data can support a breakpoint of up to 0.5 mg/L for* S. pyogenes*. However, it should be noted that the proposed* S. pyogenes *breakpoint* (b) (4) *is ≤0.25 mcg/mL, which is also supported by the reviewer's analysis.*

Sponsor's Conclusions

- Results of univariable analyses based on data from SOLO I and II demonstrated statistically significant PK/PD relationships for a number of efficacy endpoints, including clinical response at PTE.
    - The high percentage of patients achieving such efficacy endpoints and the limited number of failures, made it difficult to fully characterize the PK/PD relationships
    - Given the majority of all patients and patients with *S. aureus* achieved the AUC_{0-72}/MIC ratio threshold of 11,982 for the univariable relationship for clinical response at PTE and the relatively higher percentages of successful responses for those with higher versus lower AUC_{0-72}/MIC ratios (96.0 versus 84.6% for all patients; 96.2 versus 82.6% for patients with *S. aureus*), results of this evaluation provide support for the single 1200 mg oritavancin dosing regimen that was studied in SOLO I and II

- The PK/PD target attainment and model predicted clinical response analyses based on non-clinical and clinical PK/PD data provide support for establishing in vitro interpretive criteria for oritavancin against *S. aureus* and *S. pyogenes*.
    - Overall percent probabilities of PK/PD target attainment based on non-clinical $AUC_{0\text{-}72}$/MIC ratio targets for both net bacterial stasis and a 1-$\log_{10}$ CFU reduction from baseline were ≥99.6% for both *S. aureus* and *S. pyogenes*
    - The average model-predicted percent probability of clinical success at PTE for patients with *S. aureus* was 95.4%
    - For *S. aureus*, susceptibility breakpoints of 0.12 to 0.25 mg/L can be supported
    - For *S. pyogenes*, susceptibility breakpoints as high as 0.5 mg/L can be supported

4 Reviewer's Analysis

4.1 Objectives

The reviewer conducted independent analyses for the following objectives:

1) To evaluate the adequacy of the Sponsor's population PK model
2) To evaluate the effect of covariates of interest on oritavancin exposure
3) To evaluate *in vitro* susceptibility test interpretive criteria for oritavancin against *Staphylococcus aureus* by using the PK-PD relationships developed from all available efficacy endpoints in the ABSSSI patients with *S. aureus* infection.

4.2 Methods

4.2.1 Data Sets

Data sets used are summarized in Table 4.1.1.

Table 4.1.1. Analysis Data Sets

Study Number	Name	Link to EDR
Population PK	pksolo.xpt; (no population PK control streams were provided with the submission)	\\cdsesub1\evsprodNDA206334\0000\icpd-00247-1
PK/PD Analyses	pkpdall.xpt, tteall.xpt	\\cdsesub1\evsprodNDA206334\0000\icpd-00247-2

4.2.2 Software

Logistic regression, probability calculation, and plotting were performed using R version 3.0.0.

4.2.3 Models

4.2.4 Population PK

The sponsor's final population PK model was used as the starting point for the reviewer's analysis. The structure was a 3-compartment open model with first-order elimination. Inter-individual variability was estimated with an exponential error structure on clearance (CL),

central volume of distribution (V_c), both peripheral volumes of distribution (V_2 and V_3) and both inter-compartmental clearances (Q_2 and Q_3). Residual variability was expressed as a proportional error model and the dependent variable was log-transformed for the reviewer's analysis.

Covariates identified by the sponsor were not included in the reviewer's evaluation. The reviewer agrees that height was numerically significant for the sponsor's analysis but was uncertain regarding the biological plausibility of height as a covariate. The reviewer evaluated similar covariates to the sponsor with the exception of height.

4.2.5 PK-PD Breakpoint Analysis

A repetition analysis was performed to confirm the parameters estimated in the Sponsor's PK-PD analysis. A similar methodology to that utilized by the sponsor and described in section 3 was used, with the exception that the reviewer utilized only continuous logistic regression analyses for predicting clinical response at different fixed MIC values. Similar to the sponsor, the reviewer used both nonclinical information and two-group cut points identified based on a classification regression tree analysis to identify AUC_{0-72}/MIC cut points for probability of target attainment analyses.
The AUC_{0-72}/MIC ratio was the only independent variable explored by the reviewer as it was highly correlated with all other oritavancin exposure metrics (see Section 3) and was considered best correlated with selected efficacy endpoints in the PK-PD analysis. The reviewer's analysis evaluates the suitability of PK/PD relationships for early clinical efficacy, clinical response post treatment, and lesion size reduction at day 3 as the efficacy endpoints in the determination of the S. aureus breakpoint for oritavancin. The developed PK/PD relationships are subsequently used for calculation of probability of responses at each MIC value.

4.3 Results

Population PK model and covariates of interest
The sponsor's population pharmacokinetic model was generally found to be acceptable. However, one of the covariate relationships that they identified was a relationship between height and clearance. In the reviewer's analyses height was replaced by more biologically plausible covariates such as BMI or BSA since height is likely acting as a surrogate for weight. However, the reviewer's alterations to the model did not result in differences in the parameter estimates which would be of clinical relevance. Therefore, the population PK model proposed by the sponsor is acceptable.

The reviewer's population pharmacokinetic parameter estimates for the final PK model are shown in Table 4.4.1. These parameters are similar to those obtained from the sponsor (refer to Table 3.1.6). It should be noted, however, that the parameter estimates from the reviewer's analysis were more similar to those identified by the sponsor's original analysis (based on previous Phase I/II data) than the updated parameters from the SOLO I and SOLO II trials. In addition, that initial analysis identified covariate effects of body weight on CL and BSA on V_c. That initial data set, which consisted of rich PK sampling, may be more appropriate for precisely identifying numerical covariates for oritavancin. However, the available data from the SOLO

trials do not suggest that any of the covariates evaluated based on the Phase III data have a major impact on oritavancin PK.

Table 4.4.1: Population PK parameter estimates based on the reviewer's final model (log-transformed dependent variable)

Parameter	**Estimate**	**RSE(%)**	**CI95**
Fixed-Effects Parameter Estimates			
CL (L/hr)	0.451	1.8	(0.435-0.467)
V1(L)	6.83	3.7	(6.33-7.33)
Q2 (L/h)	0.382	3.5	(0.356-0.408)
V2 (L)	117	8.8	(97-137)
Q3 (L/h)	0.686	10.1	(0.551-0.821)
V3 (L)	8.71	4.4	(7.96-9.46)
Inter-Individual Variability Estimates (CV%)	**Estimate**	**RSE(%)**	**Shrinkage**
Omega(CL)	25.7	8.9	16
Omega(V1)	46.2	24.9	26
Omega(Q2)	50.5	8.7	16
Omega (V2)	34.5	28.1	61
Omega (Q3)	0	-	-
Omega (V3)	12.9	260	76
Residual Variability Estimate	**Estimate**	**RSE (%)**	**CI95**
Proportional Error	0.27	13.13	(0.20-0.34)

This is further explored in Table 4.4.2, which shows the mean (median) AUC_{0-72} values of oritavancin by subsets of different possible covariates. The AUC_{0-72} of oritavancin did not demonstrate significant variation across quartiles of body weight, age, BMI, or BSA. There also did not appear to be a relationship between oritavancin exposure and patient race or baseline MIC value. Based on the reviewer's assessment of the oritavancin population PK model and exploration of oritavancin exposures by different covariates, the reviewer agrees that no dosage adjustment for oritavancin is required on the basis of sex, age, race, body weight, or renal function status. The population pharmacokinetic values that are reported in the label will be updated based on the values identified from the reviewer's analysis.

Table 4.4.2: Predicted AUC_{0-72} based on post-hoc parameter estimates from the reviewer's population PK analysis and integration of oritavancin exposures over 72 hours for a subset of covariates[1]

	Oritavancin AUC72 (ng·h/mL): Mean (median)			
Body weight (kg)	>= 43 & <64	>= 64 & <76	>= 76 & <89	>= 89 & <=178
	1470 (1406)	1534 (1497)	1434 (1419)	1428 (1387)
Age (years)	>= 18 & <36	>= 36 & <47	>= 47 & <55	>= 55 & <=89
	1646 (1677)	1482 (1452)	1369 (1342)	1375 (1306)
BMI (kg/m^2)	>= 15.9 & <22.8	>= 22.8 &	>= 26.2 &	>= 30.4 &

		<26.2	<30.4	<=67.4
	1433 (1351)	1464 (1413)	1491 (1459)	1478 (1433)
BSA (m^2)	>= 1.31 & <1.73	>= 1.73 & <1.89	>= 1.89 & <2.04	>= 2.04 & <=2.79
	1514 (1490)	1532 (1511)	1423 (1413)	1404 (1378)
Race	Asian	African American	White	Other
	1578 (1555)	1581 (1511)	1436 (1378)	1468 (1530)
Creatinine Clearance (mL/mL)	>30-50 mL/min	>50-80 mL/min	>80-110 mL/min	>110 mL/min
	1466 (1283)	1387 (1345)	1536 (1504)	1457 (1422)
MIC (ng/mL)	<= 0.015	0.03	0.06	>=0.12
	1587 (1418)	1483 (1316)	1517 (1490)	1412 (1266)
Gender	Male		Female	
	1403 (1374)		1600 (1605)	

[1]: The categorical divisions for body weight, age, BMI, and BSA represent quartiles

Evaluation of In Vitro Susceptibility Test Interpretive Criteria for Oritavancin (Breakpoint)
As presented above (see Table 3.2.10), the sponsor conducted several analyses to support possible *S. aureus* breakpoints for oritavancin. They presented the probability of target PK/PD target attainment for achieving the following: an AUC_{0-72}/MIC of 3,941 corresponding with a bacteriostatic effect in the animal model, an AUC_{0-72}/MIC of 4,581 corresponding with a 1-log kill in the animal model, the probability of achieving an AUC_{0-72}/MIC of 11,982 which corresponds to the AUC/MIC threshold identified for the univariate relationship for achieving a dichotomous efficacy endpoint at PTE. The sponsor also included the probability of achieving model-predicted clinical success by MIC. The sponsor concludes that an oritavancin breakpoint of 0.12 or 0.25 mcg/mL could be supported for *S. aureus* based on these data. (b) (4) the sponsor proposes a breakpoint of 0.12 mcg/mL.

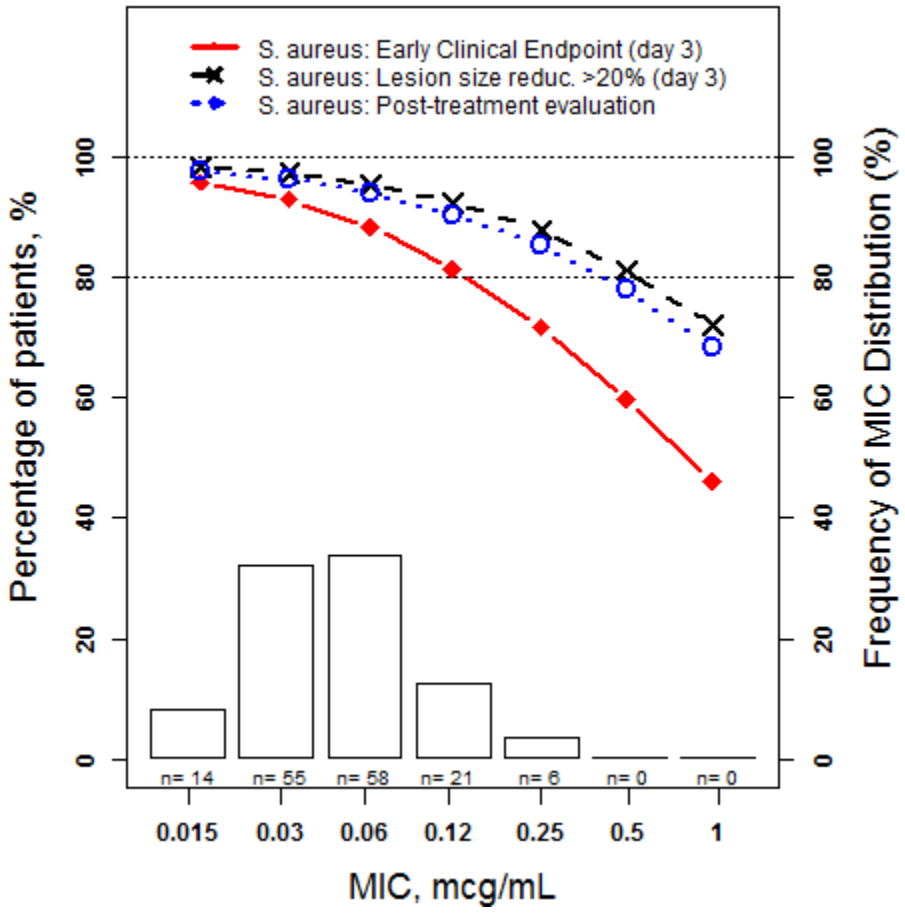
In the reviewer's analysis, the predicted PK/PD relationships for the following selected efficacy endpoints are used for the probability of response by MIC value: ECE, >20% reduction in lesion size, and PTE. The ECE endpoint was included because it was the primary endpoint of the SOLO I and SOLO II trials. The >20% reduction endpoint was included because it is recommended in the current FDA guidance for ABSSSI treatment as the primary efficacy endpoint in lesion size at 48 and 72 hours compared to baseline. The PTE endpoint was included because it is a point of emphasis for the sponsor's PK/PD analysis described above.

Model-predicted clinical response
Table 4.4.3 presents mean model predicted probabilities of response by MIC values for oritavancin against *S. aureus*, based on each of the three selected efficacy endpoints. Figure 4.4.1 graphically depicts the probabilities of these efficacy endpoints overlaid with the MIC distribution for *S. aureus*. Note that in this subset no patient had an MIC of greater than 0.25 mcg/mL and only six patients had a baseline MIC of 0.25 mcg/mL which could potentially bias predictions of the probability of achieving clinical success at higher MIC values.

Table 4.4.3. Mean model predicted probabilities of response by MIC values for oritavancin against *S. aureus*.

MIC (mcg/mL)	ECE	>20% lesion size reduction	PTE
0.016	95.7	98.2	97.6
0.031	92.8	97.1	96.1
0.062	88.2	95.2	93.8
0.125	81.3	92.3	90.3
0.25	71.7	87.8	85.1
0.5	59.7	81.1	77.8
1	46.3	72	68.3

Figure 4.4.1. Probabilities of efficacy endpoints overlaid with the MIC distribution for *S. aureus*

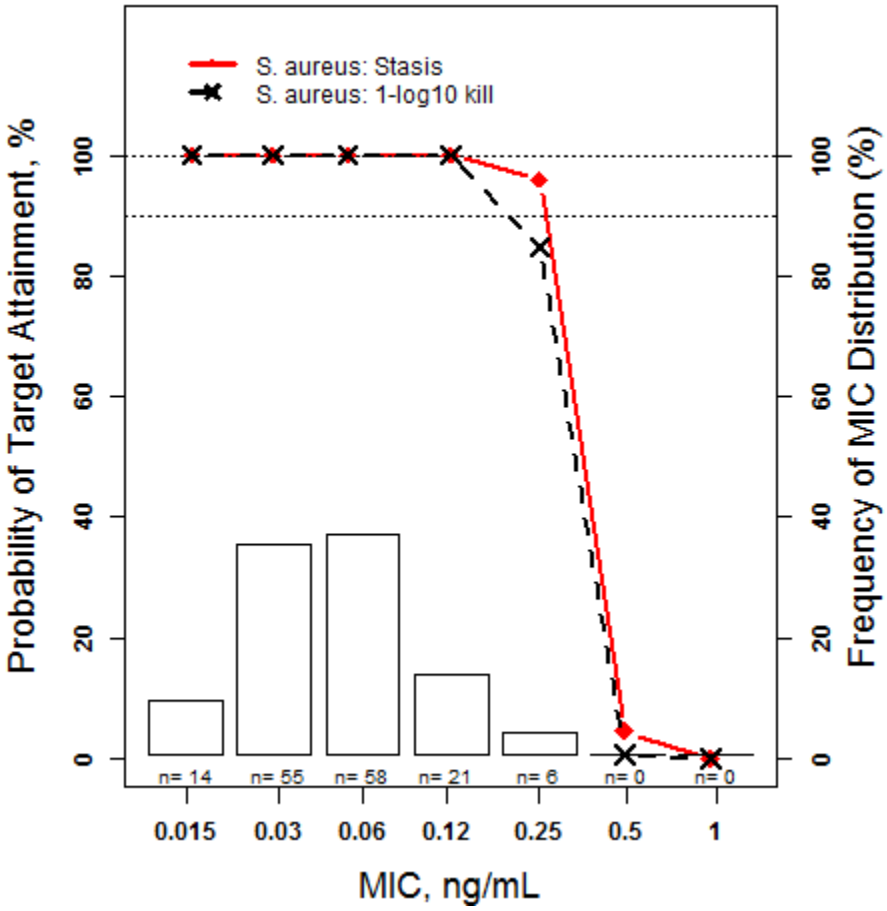


Similar patterns were observed in the predicted mean probabilities for all three efficacy endpoints.

Probability of Target Attainment - Nonclinical

The reviewer also conducted probability of target attainment analyses to determine whether the nonclinical *S. aureus* AUC/MIC targets corresponding with a static effect and a 1-log kill were met in patients using individual AUC_{0-72} values and baseline *S. aureus* MIC value (see Figure 4.4.2).

Figure 4.4.2: Probability of target attainment simulations for the nonclinical static and 1-log kill AUC_{0-72}/MIC targets for *S. aureus*



Probability of Target Attainment - Clinical

Figure 4.4.3 shows the probability of achieving the clinical AUC/MIC from the univariate analysis that corresponded with the Sponsor-defined cut point at PTE. Data from both nonclinical and clinical probability of target attainment are summarized in Table 4.4.4.

Figure 4.4.3: Probability of target attainment for the clinical PK/PD univariate AUC/MIC threshold

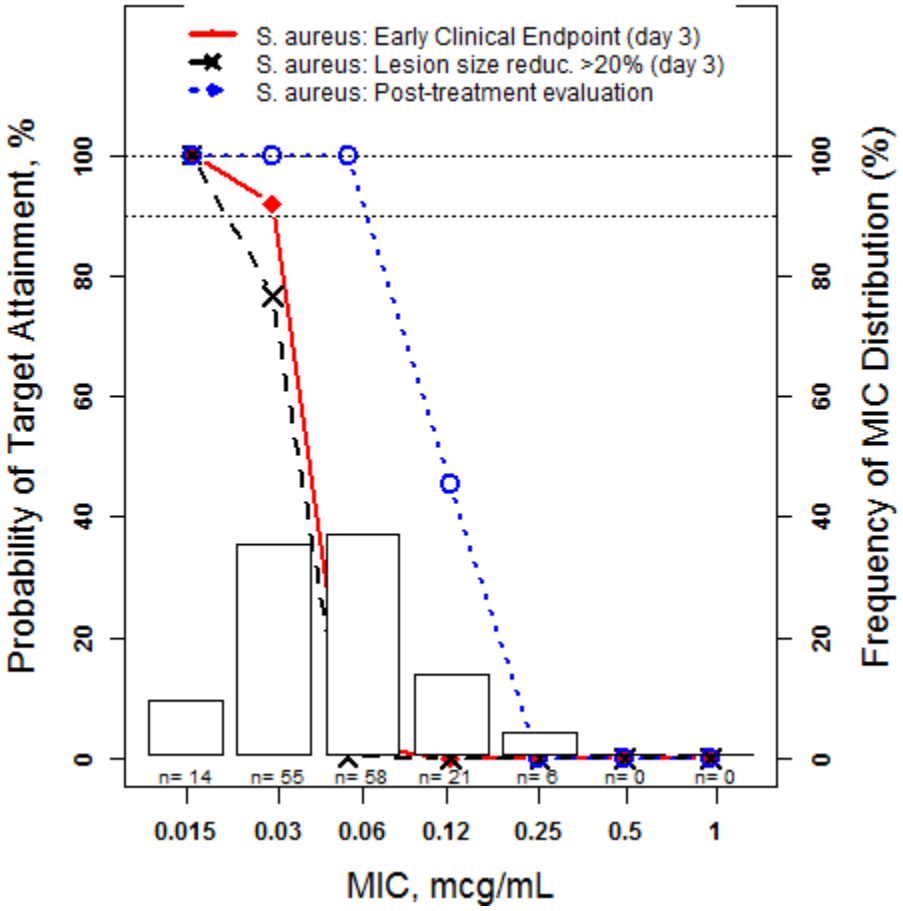


Table 4.4.4: Probability of target attainment based on the nonclinical targets defined in the animal model (stasis and 1-log kill) and the target clinical AUC_{0-72}/MIC defined in the univariate analysis by clinical endpoint

MIC	Stasis	1-log kill	PTE	>20% lesion size reduction
0.016	100	100	100	100
0.031	100	100	100	77
0.062	100	100	100	0.3

0.125	100	100	46.5	0
0.25	95.6	83.7	0	0
0.5	5.2	0.8	0	0
1	0	0	0	0

Summary

Table 4.4.5 is a combination of Tables 4.4.3 and 4.4.4 and will serve as a summary to discuss the results of the potential *S. aureus* breakpoints. Table 4.4.6 is a summary of oritavancin clinical response endpoints by MIC for *S. aureus* (observed from the SOLO I and SOLO II data).

Table 4.4.5: Summary of reviewer analyses on potential *S. aureus* breakpoints

	Model Predicted Probability of Clinical Response			PTA for Nonclinical and Clinical PK/PD Targets			
MIC	**ECE**	**>20% lesion size reduction**	**PTE**	**Stasis**	**1-log kill**	**PTE**	**>20% lesion size reduction**
0.016	95.7	98.2	97.6	100	100	100	100
0.031	92.8	97.1	96.1	100	100	100	77
0.062	88.2	95.2	93.8	100	100	100	0.3
0.125	81.3	92.3	90.3	100	100	46.5	0
0.25	71.7	87.8	85.1	95.6	83.7	0	0
0.5	59.7	81.1	77.8	5.2	0.8	0	0
1	46.3	72	68.3	0	0	0	0

Table 4.4.6: Primary Efficacy Outcome at ECE and Clinical Response at PTE by Oritavancin MIC for Oritavancin-Treated patients with *S. aureus* (MSSA and MRSA) at Baseline (MicroITT population; SOLO I and SOLO II pooled)

Oritavancin MIC (µg/mL)	Primary Efficacy Outcome at ECE[a]	Clinical Response at PTE
0.004	-	-
0.008	0/1 (0.0)	1/1 (100.0)
0.015	39/46 (84.8)	36/38 (94.7)
0.03	175/203 (86.2)	170/181 (93.9)
0.06	116/146 (79.5)	123/134 (91.8)
0.12	45/58 (77.6)	46/51 (90.2)
0.25	13/17 (76.5)	14/17 (82.4)
0.5	-	-
Total	**388/471 (82.4)**	**390/422 (92.4)**

[a] Primary efficacy outcome is from Table 5.9.5 in Appendix K.
[b] Clinical response at PTE is from Table 5.7.5 in Appendix K.
Source: Table 5.9.5 in Appendix K.; Table 5.7.5 in Appendix K.

The nonclinical PK/PD targets would suggest a breakpoint of 0.25 mcg/mL as the static target had a probability of target attainment of 95.6% at this MIC value. If the clinical PK/PD target were used to support a breakpoint, then a much more conservative value would be chosen, with different values depending on which clinical endpoint was selected. This approach is likely not advisable given the overall high cure rates for oritavancin that were observed in the pivotal trials. The model predicted probability of clinical response for different MIC values is another way to consider setting the breakpoint. The threshold for what is considered an acceptable response rate is not as well defined as the 90% probability of target attainment that is used as a rule of thumb. Given that the majority of the patients enrolled in the trials had MIC values of 0.06 mcg/mL or lower, and that oritavancin appears to be non-inferior to vancomycin, we can assume that the probability of response values that correspond with an MIC of 0.06 mcg/mL represent an acceptable threshold. However, there also appears to be sufficient data at an MIC of 0.125 mcg/mL to suggest that oritavancin is also efficacious at this MIC level. This suggests that approximate informal cutoffs for these endpoints would be approximately 80% for ECE, and 90% for >20% lesion size reduction and PTE. Although the ultimate determination of the oritavancin breakpoint will depend on the totality of information provided by each discipline, these analyses support a S. aureus breakpoint of up to 0.125 mcg/mL.

S. pyogenes breakpoint

The reviewer did not conduct similar analyses for the *S. pyogenes* breakpoint as the sponsor's analyses showed 100% target attainment at all MICs observed in the trial. The available data would therefore support a breakpoint of up to 0.5 mcg/mL.

5 Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
Oritavancin_ER_Analysis.R	Function for conducting exposure-response analyses for oritavancin based on SOLO 1 and SOLO 2 data in patients with S. aureus and S. pyogenes pathogens at baseline. Analyses include PK-PD evaluation based on clinical endpoints and probability of target attainment	\Reviews\Ongoing PM Reviews\Oritavancin_NDA206334_JAF\ER Analyses
Run12 mod, run12.lst, sdtab12, patab12, cotab12, catab12	Reviewer's final population PK model and output files	\Reviews\Ongoing PM Reviews\Oritavancin_NDA206334_JAF\PPK Analyses\Final Model
PKSOLO_ldv.csv	Population PK NONMEM dataset with log-transformed dependent variable	\Reviews\Ongoing PM Reviews\Oritavancin_NDA206334_JAF\PPK Analyses\Final Model

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/s/

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05/16/2014

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