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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	206-334
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Applicant's letter date:	12/6/13
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Product:	ORBACTIV (oritavancin diphosphate)
Indication:	For treatment of ABSSI
Applicant:	The Medicines Company Parsippany, New Jersey
Review Division:	DAIP
Reviewer:	Amy Nostrandt
Supervisor/Team Leader:	Wendelyn Schmidt
Division Director:	Sumathi Nambiar
Project Manager:	Naseya Minor

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1 Executive Summary

1.1 Introduction

Oritavancin is described as a lipoglycopeptide antibiotic that will be administered as a single intravenous (IV) dose for the treatment of ABSSSI caused by susceptible isolates of Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA). The application states that the oritavancin diphosphate drug substance is obtained by (b) (4) of a fermentation product from *Kibdelosporangium aridum* (formerly referred to as *Amycolatopsis orientalis*).

The application states that the pharmacokinetic (PK) and pharmacodynamic (PD) profile of oritavancin includes concentration-dependent killing and a long half-life which allows for single dose treatment. The Sponsor states that oritavancin exerts in vitro activity against Gram-positive bacteria and has multiple mechanisms of action which may reduce its propensity to select for resistance.

1.2 Brief Discussion of Nonclinical Findings

From the pharmacology/toxicology review of NDA 22-153:

"The toxicities seen in the rat and dog were similar. In the dog, emesis, histamine release (manifested as facial reddening, welts, increased blood pressure), and stool changes were noted. In rats, death (moribund sacrifice) during the toxicity studies was much more common (partially due to injection site issues). Otherwise, both species showed decreases in red blood cells, increases in BUN, AST/ALT, histiocytosis (macrophages) with eosinophilic/acidophilic granules in liver, kidney, spleen, injection site, and lymph nodes. The histiocytosis did not resolve over the 1-2 month recovery period and correlates well with the persistent levels of oritavancin in the liver and carcass."

Four new studies were conducted. A study intended to qualify impurities utilized multiple batches of test article, all at a dose of 60 mg/kg. Lethality was seen in one test batch. Doses in that study were still only half the equivalent of the intended clinical dose, so this study was not sufficient to qualify all impurities in a manner relevant to clinical dosing. Two new fertility studies were conducted; these were again negative for adverse effects on fertility. A study to examine macrophage function concluded that effects on innate macrophage functions would be unlikely to occur following treatment with a single 1200 mg dose of oritavancin.

It should be noted that single doses administered by IV bolus or infusion over 1 hour were associated with lethality at doses lower than the proposed clinical dose. Safety of the proposed clinical dose and of the associated impurities has not been demonstrated in nonclinical studies. Development has proceeded on the basis of safety determined in clinical trials.

1.3 Recommendations

1.3.1 Approvability

The application is approvable from a pharmacology/toxicology standpoint.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Interspecies comparisons are made on the basis of (b) (4) but should be in terms of body surface area normalized doses or human equivalent doses.

8.1 Pregnancy

Pregnancy Category (b) (4) C

Reproduction studies performed in rats and rabbits have revealed no evidence of (b) (4) harm to the fetus due to oritavancin at the highest concentrations administered, 30 mg/kg/day and 15 mg/kg/day, respectively. Those daily doses would be equivalent to a human dose of 300 mg, or 25% of the single clinical dose of 1200 mg. Higher doses were not evaluated in nonclinical developmental and reproductive toxicology studies.

There are no adequate and well-controlled trials in pregnant women. ORBACTIV should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals have not been conducted to determine the carcinogenic potential of oritavancin.

No mutagenic or clastogenic potential or oritavancin was found in a battery of tests, including an Ames assay, *in vitro* chromosome aberration assay in Chinese hamster ovary cells, *in vitro* forward mutation assay in mouse lymphoma cells and an *in vivo* mouse micronucleus assay.

Oritavancin did not affect the fertility or reproductive performance of male rats (exposed to daily doses up to 30 mg/kg for at least 4 weeks) and female rats (exposed to daily doses up to 30 mg/kg for at least 2 weeks prior to mating). Those daily doses would be equivalent to a human dose of 300 mg, or 25% of the clinical dose.

2 Drug Information

2.1 Drug

Generic Name

Oritavancin

Chemical Name

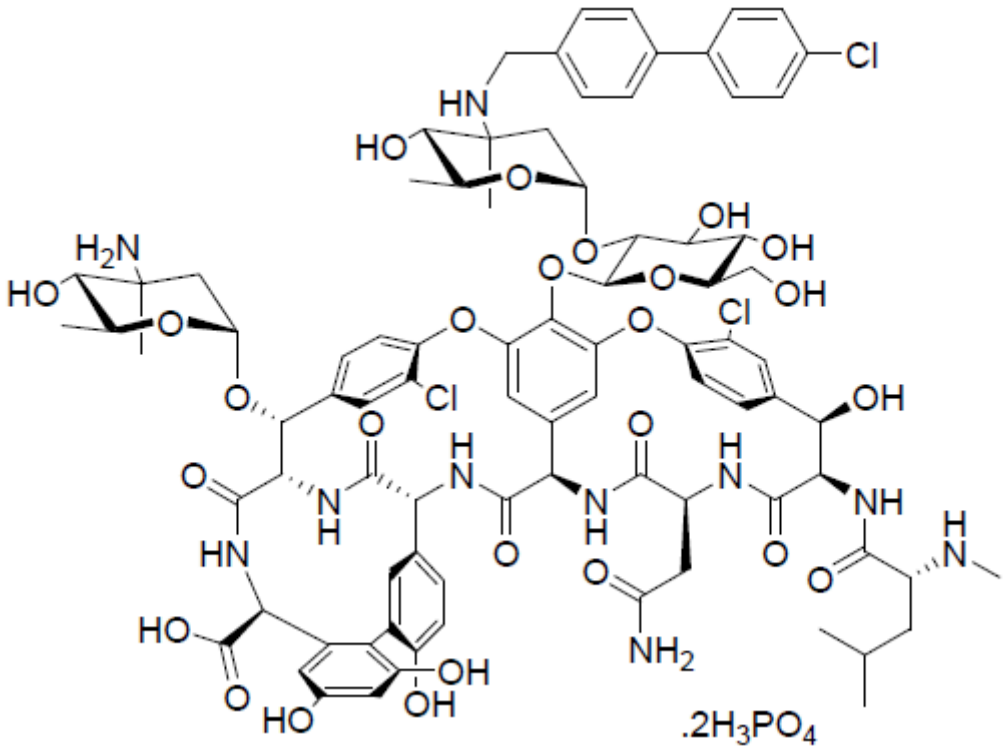
[4"*R*]-22-*O*-(3-amino-2,3,6-trideoxy-3-*C*-methyl-α-L*arabino*-hexopyranosyl)-*N*3''-[(4'-chloro[1,1'-biphenyl]-4-yl)methyl]vancomycin phosphate [1:2] [salt]

Molecular Formula/Molecular Weight

$C_{86}H_{97}N_{10}O_{26}Cl_3 \bullet 2H_3PO_4$

MW = 1989.09

Structure or Biochemical Description



Pharmacologic Class

Lipoglycopeptide antibiotic

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 51,292

NDA 22-153

2.3 Drug Formulation

The application states that the drug product, Oritavancin for Injection, is a sterile, lyophilized white to off-white [redacted] (b) (4) powder for IV infusion. Each 50 mL vial contains 400 mg of oritavancin (free base equivalent). Each vial is reconstituted with 40 mL sterile water for injection. This solution is further diluted only into sterile 5% dextrose

(D5W) for IV infusion. Both the reconstituted solution and the diluted solution for infusion are clear and colorless.

The formulation is a (b) (4) ratio of drug (405 mg, a 1.25% overfill to ensure 400 mg can be withdrawn) to mannitol (b) (4) with phosphoric acid used to adjust the pH. The application states that the excipients have been tested according to the USP/NF and Ph.Eur. prior to use, and the primary packaging components have met specifications.

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

The application states, "Pivotal toxicology studies conducted in support of this submission utilized material representative of that evaluated in the clinical program. It should be noted that the toxicology studies were conducted with material prepared by various laboratory and commercial-scale processes and contain impurities many of which are present at higher levels than in the drug product intended for market. The toxicity profile of oritavancin was consistent across the range of various toxicity studies. As such, the safety profile generated with these materials supports the commercial formulated drug product."

One new toxicology study was conducted to qualify impurities, but the dose was too low to qualify many of the impurities present at the clinical dose.

2.6 Proposed Clinical Population and Dosing Regimen

Two independent pivotal Phase 3 studies were performed to compare the efficacy and safety of a single 1200 mg IV dose of oritavancin to 7 to 10 days of IV vancomycin (1 g or 15 mg/kg twice daily), a standard of care, for the treatment of ABSSSI. The application states that a single dose of oritavancin was clinically non-inferior to vancomycin from the standpoint of efficacy and had a similar safety profile to 7 to 10 days of vancomycin treatment (1 g or 15 mg/kg twice daily) over a 60-day follow-up period. The application also states that no therapeutic drug monitoring was required for oritavancin, and no oritavancin dosage adjustments were required for patients with renal or hepatic impairment or in other subpopulations.

2.7 Regulatory Background

Oritavancin was the subject of NDA 22-153, which was not approved.

3 Studies Submitted

3.1 Studies Reviewed

General Toxicology studies:

1. Study no. 1991-001: Oritavancin: A Two Phase Single Dose Intravenous Toxicity Study in Rats with a 7-Day Treatment Free Period

Reproductive Toxicology studies:

1. Study no. AB05352: Fertility toxicity study by 1-hour intravenous infusion in the male rat (Segment I)
2. Study no. AB17380: Fertility toxicity study by 1-hour intravenous infusion in the female rat (Segment I)

Special Toxicology studies:

1. Study no. MDCO-ORI-M014: Impact of Oritavancin on Macrophage Functions in vitro

3.2 Studies Not Reviewed

Remaining pivotal toxicology studies have been previously reviewed under NDA 22-513 and IND 51,292

3.3 Previous Reviews Referenced

Pharmacology/Toxicology review of NDA 22-513

4 Pharmacology

4.1 Primary Pharmacology

The application states that studies demonstrated the activity of oritavancin in animal models of systemic infection. It states that the spectrum of oritavancin activity includes the Gram-positive organisms that cause ABSSSI, including staphylococci (MSSA, MRSA, hVISA, VISA, VRSA and linezolid and daptomycin-nonsusceptible strains), streptococci (including penicillin- and macrolide-resistant strains), and enterococci (VSE and VRE with VanA and VanB phenotypes).

Oritavancin is described as having three mechanisms of action that target the cell envelope of Gram-positive bacteria. Oritavancin inhibits the

1. transglycosylation and
2. transpeptidation steps of cell wall synthesis and
3. disrupts bacterial membrane integrity, leading to membrane depolarization and permeabilization.

The application states that oritavancin has rapid, concentration-dependent bactericidal activity and that multiple mechanisms of action should limit the development of resistance to the drug.

The Sponsor states that combinations of oritavancin with gentamicin, linezolid and rifampin are synergistic in vitro against MRSA strains with hVISA and VISA phenotypes, and that oritavancin is synergistic with with gentamicin in vivo in animal models of infection.

4.2 Secondary Pharmacology

From the Sponsor's summary:

In secondary pharmacodynamic studies, oritavancin competed with radioligand binding to dopaminergic D_1 and D_2 receptors in rat brain homogenates with affinity constants (K_i) of 2.25 µM and 3.46 µM, respectively. However, in behavioral and central

nervous system (CNS) studies conducted in mice and in toxicity studies conducted in rats and dogs, oritavancin administration was not associated with clinical signs characteristic of dopamine agonist or antagonist activity.

Oritavancin exhibited a slight inhibition on the force of acetylcholine induced contractions of guinea pig ileum tissue at concentrations ≥1 μM. However, studies in mice showed that oritavancin did not affect charcoal meal transit time suggesting that oritavancin did not have an impact on ileum contractions in vivo.

4.3 Safety Pharmacology

From the Pharmacology/Toxicology review of NDA 22-153:

Neurological effects:

In mice at 50 mg/kg i.v. (the highest dose tested), hexobarbital sleep time was slightly increased, and body temperature was decreased. No changes in activity were noted.

Cardiovascular effects:

Oritavancin was tested for ion channel effects on human myocytes. IC50 values ranged from 0.5 uM (1.0 ug/mL) for the sodium channel to 22 uM (43 ug/mL for the potassium channel). Similar results were seen with cells transfected with hERG. Plasma levels in humans Cmax in phase 2 and 3 studies with a 200 mg dose were 27 ug/mL. Clinical monitoring has addressed this concern. In a cardiac study conducted in conscious dogs, doses of 5, 10, and 25 mg/kg given intravenously over 1 hour resulted in no changes in ECG. But, there were significant histaminic responses at the high dose including an increase in blood pressure and heart rate. Similar responses were seen in a 2 week dog toxicology study at doses up to 15 mg/kg. Rats showed an increase in blood pressure at 50 mg/kg i.v.

Pulmonary effects: Not conducted.
(*Reviewer's comment: Pulmonary safety pharmacology is part of the required core battery of studies. It is unclear why the Sponsor did not conduct this study or address pulmonary function in general toxicology studies.)*

Renal effects:

A slight decrease in creatinine and sodium clearance were noted at the highest dose tested, 50 mg/kg i.v. in female rats.

Gastrointestinal effects:

No changes in gastrointestinal transit time were noted in mice after a dose of 50 mg/kg i.v. of oritavancin.

Reviewer's comment: The above NOAEL/LOAEL doses, 50 mg/kg in mice, 50 mg/kg in rats, 10 mg/kg in dogs, when normalized for total body surface area, would be equivalent to human doses of approximately 4.2 mg/kg, 8.3 mg/kg, and 5 mg/kg, respectively, or 252, 498, and 300 mg, respectively, for a 60 kg patient. None of these doses is high enough to support safety of the single proposed 1200 mg dose.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Pharmacokinetics studies have been previously reviewed. Based on the review of NDA 22-153, single dose pharmacokinetics studies were conducted in mice, rats, and dogs. Toxicokinetic monitoring was also performed in repeated dose toxicology studies.

Detection and quantitation methods are described in the application as follows: The original methods used solid phase extraction followed by reverse phase liquid chromatography coupled with fluorescence detection (LC/UV method) to quantitate oritavancin in rat, rabbit and dog plasma, rabbit serum, and dog liver. Subsequently, a more sensitive and specific method involving LC/MS/MS was developed to measure oritavancin concentrations in rat and dog plasma, rat liver, and dog feces. Liquid scintillation counting (LSC) methodology was used for mass balance studies to quantitate ^{14}C-oritavancin in different matrices from mice, rats, and dogs.

Absorption

The application states that oritavancin exhibits linear, dose proportional plasma kinetics with maximal levels attained at the first sampling time point after the end of infusion. There were no gender differences in the PK among the different species. The application states that there was no plasma accumulation of oritavancin following multiple dosing, however this seems inconsistent with the long terminal half-lives described. The application states that there was little, if any, systemic exposure in oral toxicokinetic studies in rats and dogs.

The terminal plasma half-life ranged from 8 to 33 hours in mice, from 4 to 14 hours in rats and 66.9 hours in dogs. Sampling time points were over a shorter period of time post-infusion than they were in pharmacokinetics studies in humans, and that period of time varied from study to study. This may have resulted in inaccurately determined terminal half lives in those species. The terminal half-life of oritavancin in humans is 245 h.

The application states that plasma exposures and half-lives were similar in pregnant and non-pregnant rats. Oritavancin is secreted into the milk of lactating dams and is orally absorbed and widely distributed in the tissues of nursing pups. Pharmacokinetic profiles were similar in neutropenic and non-neutropenic mice administered oritavancin by the IV route.

Distribution

Studies of radiolabeled test article were studied in rats and dogs that suggested that oritavancin is widely distributed throughout the body with long tissue retention times.

Two weeks after a single IV dose of ^{14}C-oritavancin, 37% of the radioactive dose was recovered from rats and 16% from dogs. The long retention times in animals are consistent with observations in humans where <6% of the administered dose is recovered in urine and feces after 14 days of dose administration.

The application states that quantitative whole body autoradiography studies in rats showed that oritavancin is distributed to most tissues throughout the body with peak levels attained within 1-6 h of IV administration. Highest concentrations of radiocarbon

were observed in liver and intestinal wall, with moderate concentrations of radioactivity at the early time points in the adrenal gland, bone marrow, cecal wall, kidney, lung, salivary gland, and spleen. Low or background levels of radioactivity indicated poor distribution to brain, eye and testes. The application states that, in general, the half-life of oritavancin ranged between 100 and 200 h in the majority of tissues. The previous reviewer noted that the radiolabel studies did not distinguish whether or not the label was still associated with the parent compound.

The application states that oritavancin was observed to accumulate in the liver of dogs following multiple dosing, and that this finding correlated with histopathological findings from toxicity studies in which macrophages containing eosinophilic granules, presumably from oritavancin uptake, were seen in liver and tissues throughout the body even following treatment free periods. The application further states that fetal tissues were not exposed to oritavancin following administration of a single IV dose to pregnant rats at GD 18, indicating that oritavancin does not cross the placenta (*Reviewer's comment: It is unclear whether or not the analysis was timed to best make that determination)*.

The serum protein binding of oritavancin was determined in the mouse, rat, dog, and human. The application states that the extent of binding was relatively similar (~85%) between species, ranging from a low of 81.9% in human to a high of 87.1% in dog plasma. The previous reviewer noted that there were issues with test article binding to glassware and filters.

Metabolism

There does not appear to be any evidence from in vitro or in vivo animal experiments to show that oritavancin is metabolized. The application states that nonclinical findings were consistent with an in vitro human liver microsome study that also did not reveal evidence of oritavancin metabolism.

Oritavancin does appear to inhibit hepatic drug metabolizing cytochrome P450 activity. Several enzymes, including CYP1A1/2, CYP2B and CYP3A4/5, were observed to have decreased activity in rat and dog studies at dose levels ≥ 5 mg/kg. The inhibition was partially reversible following recovery periods. These results were said to be consistent with in vitro studies in human liver microsomes where oritavancin showed weak inhibitory activity toward all CYPs assayed including, CYP3A4, CYP2D6, CYP2C9, CYP2C19, CYP2B6, and CYP1A2.

Excretion

The application states that studies in mice, rats, and dogs indicate that the primary route of elimination of oritavancin is via bile into the feces. The elimination of oritavancin was markedly slower in dogs than in rodents with 6.1 % of the radioactive dose present in feces at 96 h. The application states that the long retention times in animals are consistent with observations in humans where about 6% of the administered dose is recovered in urine and feces after 14 days of dose administration (*Reviewer's comment: Elimination appears to be markedly slower in humans than in dogs*.). In contrast to animals where feces is the primary route of excretion, in humans the majority of the recovered dose is in urine (~5%) and the rest in feces (<1%).

The application also states that studies in lactating rats indicated that oritavancin is excreted in milk and absorbed orally by nursing pups. Radiolabel was detected in most pup tissues.

6 General Toxicology

From the Pharmacology/Toxicology review of NDA 22-153:

"The non-clinical testing program for oritavancin includes rat and dog studies of up to 13 weeks duration. Several bridging studies were also conducted, most recently with the drug product from (b) (4) and batches with increased impurities. Both rats and dogs showed remarkably similar pathology with the major finding of histiocytosis in the kidney, liver, lymph nodes, spleen, thymus, bone marrow, and injection site, along with significant reductions in RBC number (and associated parameters). No new toxicities were noted when the duration of administration was increased from 1 month to 3 months.

Single dose studies with up to 160 mg/kg in mice and 120 mg/kg in the rat showed maximal non-lethal doses of 40 mg/kg (lethality at 80 mg/kg). In a separate rat single dose toxicity study, bolus doses of 0, 50, or 30 mg/kg were administered; no differences in clinical signs, hematology, clinical chemistry, or microscopic observations were noted between control and oritavancin-treated animals.

A summary of the doses used in the subchronic studies are shown below, along with the major toxicities observed. In the dogs, a histaminic response was seen in the first few days of dosing, tolerance was noted after the first week or two. Later studies compensated by administering anti-histamines. Gastrointestinal changes (emesis, diarrhea, mucoid stools or loose stools) were also noted in the dogs. In the rats, lethality was seen in the studies of at least 2 weeks duration. Dosing was limited by injection site issues, which then led to venous catheterization. It is not clear whether some of the deaths in the 13 week study were due to drug damage or catheter infections. In both rats and dogs, periodic changes (not seen in every study) included decrements in body weight and food consumption, increases in APTT, and increased organ weights in the liver, kidney, and spleen. Decreases in red blood cell parameters (RBC #, hematocrit, hemoglobin etc) were seen in almost all studies. Increases in BUN and liver enzymes (AST/ALT/frequently ALP) were also noted in nearly all studies. These changes were accompanied by histiocytosis (i.e. macrophages in connective tissue). The histiocytes contained eosinophilic or acidophilic material, depending on the pathologist's word choice. Histiocytes were also found in the sinusoids of the lymph nodes and spleen as well as near the injection site and accounted for the frequent gross observation of "masses". The histiocytes were still present (although a lesser extent) at the end of the recovery period.

No significant differences in toxicity profile were observed when oritavancin was spiked with impurities or after a drug product manufacturing switch.

Rat and dog subchronic studies with daily doses of oritavancin				
Species	Duration	Doses mg/kg	NOAEL/LLD mg/kg	Observations
Rat	2 wk	1, 5, 15	NOAEL = 1 No deaths	↓RBC #, body weight, ↑AST/ALT; Eosinophilic granules in renal cortical epithelium, Kupffer cells, and granules in macrophages of spleen, thymus and lymph nodes
	2 weeks[@]	1, 5, 15	NOAEL = 5 No deaths	↓RBC #, WBC #; ↑AST/ALT; Eosinophilic granules in Kupffer cells, LN, bone marrow at all doses
	2 week[%]	5, 30, 60	NOAEL = 30 No deaths	↓ body weight, food consumption ↑AST/ALT; liver weight, hepatocellular necrosis and inflammation. Heart: myocardial degeneration and inflammation; gross changes in spleen, kidney, LN.
	2 weeks[$]	1, 5, 15	NOAEL = 5 LLD = 15	↓RBC #; ↑AST/ALT; Kupffer cell degeneration, PAS + material in hepatocytes/Kupffer cells and spleen, lymph nodes, marrow
	1 month	5, 10, 15, 40, 30	NOAEL= 5 LLD = 15	↓ body weight, ↓RBC #, ↑AST/ALT/ALP, BUN; Liver, spleen, thymus, lymph nodes: eosinophilic granules in macrophages
	1 month*	5, 10, 15	NOAEL = 5, no deaths	↑AST/ALT; periportal liver degeneration, injection site inflammation and fibrosis; lymphoid hyperplasia in lymph nodes, spleen (also congestion)
	13 weeks	5, 15, 45/30	No NOAEL Deaths in all groups	Deaths in 15 C, 30 L, 25 M, and 39 H; Signs= swellings, masses, paralysis, limp; ↓body weight, food consumption; ↑AST/ALT/ALP; hepatic necrosis, inflammation, accumulation of histiocytes with eosinophilic granules in liver, spleen, lymph nodes, thymus, lung catheter site, and ovaries; masses at injection site.
Dog	2 weeks	1, 5, 15	NOAEL = 5 No deaths	↑ histamine, face reddened, loose stools, emesis; ↑BUN, AST/ALT; eosinophilic granules in hepatocytes, renal cortical cells and macrophages
	2 week infusion[%]	5, 30, 60	NOAEL = 30 No deaths	↓body weight, food consumption; ↑ AST/ALT; hepatocellular degeneration and necrosis, renal tubular degeneration and mineralization; macrophages with cytoplasmic acidophilic granules near sinusoid spaces

	4 weeks	5, 10, 30	NOAEL = 5 No deaths	Signs: redness, welts, emesis, stool changes; ↑APTT, BUN, AST/ALT eosinophilic granules in liver, kidney, lymph nodes, spleen
	13 weeks	5, 15, 45	NOAEL = 5 No deaths	Emesis, stool changes; ↓body weight; ↑AST/ALT, BUN, APTT; ↑organ weight of liver, spleen, kidney; eosinophilic histiocytes in sinusoids of liver, lymph nodes, alveoli, submucosa of kidney and injection site.

(b) (4)

L= low dose, M= mid dose, H= High

% 1 hour infusion instead of 30 minutes

$ bridging study to (b) (4) formulation

LLD = lowest lethal dose

*spiked with new impurities"

6.1 Single-Dose Toxicity

1. Study title: Oritavancin: A Two Phase Single Dose Intravenous Toxicity Study in Rats with a 7-Day Treatment Free Period

Study no.:	1991-001
Study report location:	Module 4
Conducting laboratory and location:	(b) (4)
Date of study initiation:	12/4/12
GLP compliance:	Yes, except that documentation of stability of each lot of the test article was not provided
QA statement:	Yes
Drug, lot #, and % purity:	Oritavancin diphosphate, Lot #124RM5 (Phase A - Group 2, Phase B – Group 4), Lot # 23480-134 (Phase B - Group 5), and Lot #1169-142 (Phase B - Groups 6 and 7), assay 56.9-75% (free base)

Key Study Findings

This study was conducted to qualify impurities present at different levels in different lots of the test article, Oritavancin. In Phase A, the toxicity was determined following a single intravenous administration of Oritavancin lot # 124RM5 (said to have been was used in prior toxicity studies) in order to determine a dose for use in Phase B. In Phase B, the toxicity of Oritavancin lot numbers 124RM5, 23480-134 and 1169-142 were determined following a single intravenous administration. Seven treatment groups of ten male Crl:CDR(SD) rats were administered the vehicle (5% Dextrose for Injection, USP) or test article at a dose level of 60 mg/kg, plus an additional group in Phase B treated with 28 mg/kg of lot # 1169-142. Vehicle or test article was administered to all

groups as a single 1-hour intravenous infusion into the tail vein at a volume of 10 mL/kg. Animals were observed for 7 days post-dose.

In Phase A, findings at 60 mg/kg of lot #124RM5 were limited to minimal reductions in erythrocyte parameters and minimal increases in AST and ALT on Day 2 which resolved by Day 8. Increased reticulocytes at Day 8 were indicative of a regenerative response. Microscopic findings at the infusion site were the only findings considered by the Sponsor to be "adverse."

In Phase B, two animals dosed at 60 mg/kg (lot #1169-142) were found dead on Day 1; the cause of death was not determined, but may have been related to treatment. Clinical observations in surviving animals in that group on Day 1 included decreased activity, swelling, and rapid breathing that may have been indicative of a histaminergic response that was resolved by Day 2. In general, clinical findings consisted of red skin discoloration of the tail for all lots, and rigid, black and/or purple discoloration of the tail, clear and/or red discharge from the injection site, and swelling of the nose/muzzle for lot #23480-134 (60 mg/kg). Findings had generally resolved prior to termination at Day 8, with the exception of black tail discoloration.

Reductions in erythrocyte parameters were again seen on Day 2 in all treated animals. Minimal increases in total bilirubin on Day 2 were suggestive of hemolysis. Red cell findings were resolved by Day 8. Additionally, on Day 2, mild to moderate increases in neutrophils and/or monocytes were observed in all treated animals, suggestive of an inflammatory response. On Day 8, partially recovered increases in neutrophils persisted in groups treated with 60 mg/kg of lot #23480-134 and lot #1169-142). Mild reductions in lymphocytes were also observed in animals at 28 mg/kg (lot #1169-142) and 60 mg/kg (all lots) on Day 2, however a rebound was observed in all treatment groups at the Day 8 collection.

At the Day 2 and/or Day 8 collections, mild increases in AST and ALT were observed in animals at 60 mg/kg (all lots), relative to controls. Animals receiving Oritavancin (all lots) had mild decreases in albumin and albumin/globulin ratio on Day 2, compared to control, which had resolved by Day 8 except in the group treated with 60 mg/kg of lot # 1169-142. Mild decreases in alkaline phosphatase (ALP) were reported in groups treated with all lots of Oritavancin, but this parameter trended towards recovery on Day 8.

Post-mortem macroscopic findings were limited to discoloration described in clinical observations for animals treated with 60 mg/kg of lot numbers 23480-134 and 1169-142, although microscopic findings at the infusion site in the tail were described in all Oritavancin treated animals (all lots). Spleen weights were increased in all Oritavancin treated animals (all lots), correlating with extramedullary hematopoiesis.

The only findings that the Sponsor considered to be adverse were the microscopic findings seen locally at the infusion site for animals treated at 60 mg/kg of lot #124RM5 and lot #23480-134. Mortality may have been related to treatment with 60 mg/kg of lot # 1169-142, so a NOAEL for the impurities in that lot could not be determined. Otherwise, systemic effects appeared to be mild and reversible. It is unclear how differences in effects seen between groups treated with different lots of test article may have been related to differences in impurity profile. It should be noted that the 60 mg/kg dose in the rat would be equivalent to a 600 mg dose to a 60 kg patient, or half the proposed clinical dose. The dose was not high enough to be relevant to the

clinical dose, and the doses of individual impurities were not all high enough to qualify the impurities at the clinical dose.

Methods

Doses:	See table below
Frequency of dosing:	Single dose
Route of administration:	IV, by one hour infusion
Dose volume:	10 mL/kg
Formulation/Vehicle:	5% Dextrose for Injection, USP
Species/Strain:	male Crl:CD$_R$(SD) rats
Number/Sex/Group:	10 males
Age:	approximately 6.5 to 8 weeks of age
Weight:	275 to 326 g
Satellite groups:	None
Unique study design:	See table below. The dose for Phase A was based on previous acute toxicity studies of Oritavancin in rats. In these studies, 40 mg/kg administered as a bolus was described as causing no signs of toxicity, while 80 mg/kg was associated with several early deaths. Therefore, in Phase A, 60 mg/kg of Oritavancin was chosen for administration as a 1-hour intravenous infusion. The findings at this dose level were used to establish the dose level used in Phase B. The report states that Oritavancin Lot #124RM5 has been used in prior toxicity studies. Findings in Phase A were considered to be minor and localized to the injection site, so 60 mg/kg was selected as the dose level in Phase B, and was not expected to have major adverse effects.
Deviation from study protocol:	None that were thought to affect the integrity of the study

Group Assignments				
Group Number	Dose Level (mg/kg)	Test Article Lot Number	Number of Male Animals	Animal Numbers
Phase A				
1	0	NA	10	1001-1010
2	60	124RM5	10	2001-2010
Phase B				
3	0	NA	10	3001-3010
4	60	124RM5	10	4001-4010
5	60	23480-134	10	5001-5010
6	28	1169-142[a]	10	6001-6010
7	60	1169-142	10	7001-7010

NA – Not applicable
[a] A correction factor for the free base was not applied.

A correction factor was not initially used in the preparation of Lot #1169-142 for Phase B, (Group 6); however, a correction factor was used in a second preparation of Lot #1169-142 (Group 7) for Phase B. Consequently, Lot #1169-142 was studied at doses of 28 and 60 mg/kg.

Reviewer's comment: Although this table indicates that there were 10 animals in Group 7, data tables indicate that, after 2 animals died, there were only 7 surviving for later evaluation.

Formulations of the test article were prepared in the vehicle on the day of dosing at a nominal concentration of 6 mg/mL (or 2.8 mg/mL when correction factor was not applied). The measured pH prior to filtration was 4.64 to 5.13. The prepared formulations were filtered through a (b) (4) filter and stored at room temperature until administration.

Reviewer's comment: Specific information regarding the preparation of dosing solutions is not provided. The drug substance lots were all of relatively low purity and contained a large number of impurities. The correction factors used for preparation of dosing solutions were not provided. It is unclear what the specific amounts of each individual impurity present in the dosing solutions were or how differences in study findings related to differences in impurity profiles between lots. The impurities present in the clinical lots, their acceptance criteria, and their relationship to the impurities present in these nonclinical lots are not specified in the report.

The following table contains information regarding impurities, residual solvents, and contaminants provided by the CMC reviewer:

Attribute	Units	Nonclinical Batch Number			Clinical drug substance specifications
		124RM5	23480-134	1169-142	
Assay, free base, anhydrous	(w/w%)	82.8	57.1	56.9	80-95
[redacted]					(b) (4)

(b) (4)

NMT – not more than
ND – none detected
NT – not tested

Reviewer's comment: Since the dose administered in this study was only half the equivalent of the clinical dose, impurities would have to be present at twice the

concentration allowed in the clinical drug substance at the NOAEL level in order to qualify them at the clinical dose.

Observations and Results

Mortality

All animals were observed for morbidity, mortality, injury, and the availability of food and water twice daily.

In Phase A, on Day 2, one control and one treated animal (60 mg/kg, Lot #124RM5) died during sample collection. This was considered to be procedure-related and not test article-related.

In phase B, immediately following dosing on Day 1, two treated animals (Group 7, 60 mg/kg, Lot #1169-142) were found dead. No cause of death was determined, but relationship to treatment cannot be ruled out.

Also in Phase B, animal number 7010 at 60 mg/kg (Lot #1169-142) was not dosed, due to "test article limitations." That animal was euthanized on Day 8 and the carcass was discarded without evaluation.

Clinical Signs

All animals were observed twice daily. Detailed clinical observations were performed on some animals at receipt and on all animals on Day -1, at approximately 6 hours after the end of infusion on Day 1, and daily thereafter.

No test article-related signs were reported for Phase A.

In Phase B, following administration of Lot #23480-134, purple discoloration of the tail was observed in 6/10 animals on Day 1 through Day 6. Black discoloration of the tail was observed in 5/10 animals on Days 7 and 8. Rigid tail was observed in 3/10 animals starting on Day 3 and continued through Day 6. The latter observation was reported to have resolved by Day 7 in two of the animals, but persisted until termination on Day 8 in the third. Clear and/or red discharge from the injection site was observed in 3/10 animals between Days 2 and 5. On Days 1 and 2, a single animal exhibited swelling of the nose/muzzle, which resolved by Day 3. Salivation was observed in 1/10 animal on Day 1, but was considered to be an incidental finding.

In Phase B, following administration of Lot #1169-142 at 60 mg/kg on Day 1, test article-related observations of rapid breathing, swelling of the body, swelling of the fore/hind feet were observed in one or 2 of the surviving 7 animals. Decreased activity was observed in all 7 surviving animals. All observations were reported to have resolved by Day 2. Red skin discoloration of the tail was noted for 1-2 animals on Days 4-8.

Body Weights

Body weights for all animals were measured and recorded at receipt, prior to randomization (Day -1), and at termination on Day 8.

No test article-related effects were reported.

Feed Consumption

Not evaluated

Ophthalmoscopy

Not performed

ECG

Not performed

Hematology

Clinical pathology evaluations were conducted on all surviving animals at approximately 24 hours after the end of infusion on Day 2 and at the terminal necropsy. Three to four mL of blood were sampled from overnight-fasted animals from the jugular or sublingual vein on Day 2 and from the vena cava after carbon dioxide inhalation at necropsy.

Phase A:

Reductions (2 to 4%) in red cell mass (erythrocytes, hemoglobin and hematocrit) were seen on Day 2 in animals administered Oritavancin Lot #124RM5, relative to controls, but had resolved by the Day 8. Increased reticulocyte counts were evidence of a regenerative response.

Also at the Day 2 collection, treated animals had statistically significant increases in neutrophils (31%), monocytes (68%) and eosinophils (78%), and decreased lymphocytes (27%), relative to controls. Those findings were consistent with an inflammatory response, correlating with microscopic findings at the infusion site. Effects on leukocytes were also resolved by the Day 8 collection.

A statistically significant decrease in platelets (22%) was observed in treated animals relative to controls, that was considered to have been associated with thrombus formation at the infusion site. Reductions in platelet counts resolved by the Day 8 collection.

Phase B:

At the Day 2 collection, there were statistically significant reductions in red cell mass (erythrocytes, hemoglobin and hematocrit; 7% to 12%) in all Oritavancin treated groups, relative to controls. These reductions were of similar magnitude in all treatment groups, and had resolved by the Day 8 collection. Minimal to mild increases in absolute reticulocytes (11% to 26%) on Day 8, relative to controls were indicative of a regenerative response. Increases in absolute reticulocytes tended to be more pronounced in animals administered Oritavancin Lot #124RM5 and Lot #1169-142 (60 mg/kg), and correlated with the presence of extramedullary hematopoiesis in the spleen.

At the Day 2 collection, mild to moderate increases in neutrophils and monocytes were noted in animals administered Oritavancin Lot #124RM5 (36% and 132%, respectively), Lot #23480-134 (191% and 124%, respectively) and Lot #1169-142 at 60 mg/kg (171% and 175%, respectively), relative to controls. An increase in monocytes was also noted in animals receiving Oritavancin Lot #1169-142 at 28 mg/kg (153%), relative to controls. These findings were considered to be typical of an inflammatory response, correlating with inflammatory changes at the infusion site. Partial recovery

was noted , but neutrophils remained increased at the Day 8 collection in animals administered Lot #23480-134 (55%) and Lot #1169-142 at 60 mg/kg (20%).

Decreased lymphocytes were also observed in animals administered Lot #124RM5 (23%), Lot #23480-134 (37%), and Lot #1169-142 at 28 mg/kg (19%) and 60 mg/kg (13%), relative to controls. This finding had reversed by the Day 8 collection, where lymphocytes were increased 20% to 71%, relative to controls.

At the Day 8 collection, mild statistically significant increases in platelets were observed in animals administered Lot #23480-134 (35%) and Lot #1169-142 at 60 mg/kg (27%), relative to controls. In contrast to the Phase A platelet findings, these increases were considered to be secondary to the combined effects of the regenerative erythroid response and inflammatory response (reactive thrombocytosis).
No test article-related effects on coagulation were reported.

Clinical Chemistry

Phase A:

At the Day 2 collection, statistically significant increases in aspartate aminotransferase (AST) (30%) and alanine aminotransferase (ALT) (21%) were observed in animals receiving Lot #124RM5, relative to controls. Increases in AST and ALT were resolved by the Day 8 collection.

At the Day 2 collection, animals had a statistically significant decrease in albumin (6%), which resulted in a decreased albumin/globulin ratio (12%), relative to controls. These changes were considered to be secondary to an inflammatory response and associated with inflammation at the injection site. These changes were resolved by the Day 8 collection.

At the Day 2 collection, an increase in total bilirubin (29%) was noted relative to controls. Taking into consideration the effects on red blood cell hematology parameters, this increase in total bilirubin is suggestive of hemolysis.

Phase B:

At the Day 2 and/or Day 8 collections, increases in AST and ALT were observed in animals administered Lot #124RM5 (up to 26%, and 47%, respectively), Lot #23480-134 (up to 63% and 98%, respectively) and Lot #1169-142 at 60 mg/kg (up to 104% and 62%, respectively), relative to controls. The report states that changes in AST and ALT were not associated with microscopic hepatocellular effects in any treatment group.

At the Day 2 collection, animals administered Oritavancin (all lots) had statistically significant decreases in alkaline phosphatase (ALP) (21% to 31%), relative to controls. These values were partially recovered at the Day 8 collection. The significance of a reduction in serum levels of this enzyme are unclear.

At the Day 2 collection, increases in total bilirubin were noted in Lot #124RM5 (21%), Lot #23480-134 (43%) and Lot #1169-142 at 60 mg/kg (36%), relative to controls. This finding was considered to be likely due to hemolysis, and had resolved by the Day 8 collection.

At the Day 2 collection, animals administered Oritavancin (all lots) had statistically significant decreases in albumin (8% to 11%), which resulted in a decreased albumin/globulin ratio (5% to 16%), relative to controls. These changes were considered to be secondary to an inflammatory response. These findings were

resolved in most animals by Day 8, but decreased albumin persisted in animals administered Lot #1169-142 at 60 mg/kg.

Urinalysis

The animals were housed in stainless steel metabolism cages and urine was collected for at least 12 hours for urinalysis.

No test article-related effects were noted in Phase A. In phase B, increased urine volume with corresponding decreased specific gravity were seen in animals administered lots #23480-134 and #1169-142 at 60 mg/kg on Day 2, but had resolved by Day 8.

Gross Pathology

Postmortem study evaluations were performed on all animals found dead or euthanized at the terminal necropsy.

No macroscopic findings were reported in Phase A. In Phase B, Oritavancin-related macroscopic findings were restricted to the infusion site area of the tail and included mild to moderate discoloration. The report states that the black discoloration of the tails in 3/10 animals administered Lot #23480-134 correlated with mild to moderate myofiber degeneration/necrosis and/or squamous epithelium degeneration/necrosis, which was occasionally mixed with epidermal crusts and debris. The red discoloration of the tail of animals administered Lot #1169-142 (60 mg/kg) was localized to the infusion site and correlated with mild myofiber degeneration/necrosis.

Organ Weights

Organs weighed were: adrenals, brain, epididymis, testes, heart, kidneys, liver, lung, pituitary, salivary gland (mandibular), spleen, thymus, and thyroid/parathyroids. Paired organs were weighed together.

In Phase A, thymus weights were lower and spleen weights were slightly higher in treated animals than in controls. In Phase B, spleen weights were increased for all lots tested, although the changes were nonsignificant for Lot 124RM5 in both Phases A and B. Increased spleen weight was said to correlate to increases in extramedullary hematopoiesis in that organ. Also in Phase B, for Lot 1169-142, liver weights were increased at 28 mg/kg, but not at 60 mg/kg, while increased brain, kidney, lung and thyroid weights and decreased testis and epididymis weights were seen at 60 mg/kg.

Histopathology

Adequate Battery

A full set of tissues were collected. Bone marrow smears were collected at necropsy and held, but do not appear to have been examined.

Peer Review

No

Histological Findings

In Phase A and B, Oritavancin-related microscopic findings were observed at the tail infusion site. In phase B, Oritavancin-related microscopic findings were also seen in the spleen of animals administered Lot #124RM5 and Lot #1169-142 at 60 mg/kg.

Oritavancin-related tail infusion site changes included minimal subacute to chronic, predominately perivascular inflammation; minimal to mild focal degeneration/necrosis of the vascular wall at the infusion site; minimal to moderate degeneration/necrosis of myofiber, mild to moderate degeneration of squamous epithelium; minimal hyperostosis of the caudal vertebrae; and minimal to mild thrombi. These were seen in all animals in all treatment groups.

Microscopic changes in the spleen of animals administered Lot #124RM5 and Lot #1169-142 in Phase B consisted of increases in extramedullary hematopoiesis, which correlated with increases in absolute reticulocyte counts and with increases in spleen weight. Additionally, extramedullary hematopoiesis was reported in the liver, but not the spleen, of animals treated with Lot #124RM5 in Phase A.

Toxicokinetics

Not performed

Dosing Solution Analysis

Dosing formulations prepared for the study were evaluated for concentration. Samples (1 mL) were collected after filtration of the prepared formulation, and 0.25 mL samples were collected from the infusion line of the first four animals/group at the end of infusion.

Dosing Formulation Analysis Sample Collection

Sample Type	Concentration Sampled (mg/mL)	Number of Samples per Concentration			Sample Volume (mL)	Interval
		Collected	Analyzed	Backup		
Concentration Analyses[a]	Phase A – 0, 6 Phase B – 0, 6[b]	2	1	1	1	dose preparation
Concentration Analyses[a]	Phase A – 0, 6 Phase B – 0, 6[b]	4	2	2	0.25	at EOI

[a] The samples, including backup samples, were stored frozen (-50 to -90°C) pending analyses or final disposition.
[b] Samples were collected from each test article lot used in Phase B.

The Sponsor did not perform stability analysis, stating that documentation that the test article is stable as a solution at study concentrations for at least 48 hours at room temperature has been previously provided.

The dosing solution concentrations were within ± 10%, and were considered to have met acceptance criteria.

7 Genetic Toxicology

From the Pharmacology/Toxicology review of NDA 22-153:

"In vitro (Ames, mouse lymphoma, chromosomal aberrations) and in vivo (mouse micronucleus) genetic toxicity testing has been adequately conducted. All of the studies were negative."

8 Carcinogenicity

Carcinogenicity studies were not performed, nor were they required based on the short duration of use.

9 Reproductive and Developmental Toxicology

From the Pharmacology/Toxicology review of NDA 22-153:

"The potential for reproductive toxicity was studied in rats and rabbits. The studies were all negative at the highest doses tested. Dosing in these studies was adequate based on maternal toxicity. The studies are summarized in the following table. The AUC levels were collected from the 1 month rat toxicology studies (Day 14 values) for the Segment I studies, and from an accompanying PK study for the rat Segment II study. No PK data in pregnant rabbits or in the multigenerational rats was collected.

Reproductive Toxicity studies conducted with oritavancin				
Study	Species	Doses tested (mg/kg/day)	NOAEL (mg/kg)	AUC @ NOAEL
Male Fertility (Seg I)	Rat	0, 5, 15, 30	30	407 ug.h/mL
Female fertility (Seg I)	Rat	0, 5, 15, 30	30	343 ug.h/mL
Preimplantation	Rat	0, 5, 15, 30	30	---
Developmental (Seg II)	Rat	0, 5, 15, 30	30	522 ug.h/mL
Developmental (Seg II)	Rabbit	0, 1, 5, 15	15	---
Pre and Post-natal (Seg	Rat	0, 5, 15, 30	30	---

Reviewer's comments: In the absence of suitable comparative pharmacokinetic data (the AUC value for the rat developmental study is only based on 24 hours rather than infinity), these NOAEL doses would be equivalent to a 5 mg/kg/day clinical dose, or 300 mg/day for a 60 kg patient, considerably lower than the single 1200 mg dose now under consideration.

Fertility studies were repeated. The Sponsor states that the original studies did not meet current ICH guidelines. The repeated studies, reviewed below, also reported negative findings at the high dose of 30 mg/kg/day.

While data from single bolus dose toxicology studies suggest that a single dose equivalent to the proposed clinical dose would likely result in lethality, the high doses used in embryo-fetal toxicity studies were not sufficiently maternally toxic. The reports indicated that the "maternal toxicity" at the high doses consisted of slightly decreased corrected body weight gain and increased splenic weight due to extramedullary hematopoiesis in the spleen. The former is not sufficient as a dose-limiting toxicity, and the latter was represented by the Sponsor in general toxicology study reports as "not adverse." Accumulation of eosinophilic material in various organs was also seen in the rabbit study, but has not been considered dose-limiting in general toxicology studies.

The Sponsor has proposed a Pregnancy category (b) (4) *however, given that the highest dose is 25% of the therapeutic dose (24 hour AUC is approximately 33% of the clinical AUC), and that the test article was not tested to maternal toxicity, Category C would be more appropriate.*

9.1 Fertility and Early Embryonic Development

Two new fertility studies were submitted to the current NDA. The previously submitted studies included treatment of males for 2 weeks prior to mating; the application states that these studies are not consistent with current ICH guidelines. The new studies included 4 weeks treatment of males prior to mating.

1. Study title: Fertility toxicity study by 1-hour intravenous infusion in the male rat (Segment I)

Study no.:	AB05352
Study report location:	Module 4
Conducting laboratory and location:	(b) (4)
Date of study initiation:	25 February 2013
GLP compliance:	Yes (OECD)
QA statement:	Yes
Drug, lot #, and % purity:	Oritavancin Bis Phosphate Salt, batch no. 87556IL00, purity is stated in the test to be 92.2 % (Study Sponsor information), but the appended certificate of analysis indicates that the assay was 85.9% (volatile free basis), which was used to calculate the % free base as 83.07%.

Key Study Findings

Intravenous infusion of Oritavancin for 1-hour to male Sprague Dawley rats at doses of 5, 15 and 30 mg/kg/day throughout a 4-week pre-mating period, during mating (with groups of untreated females) and through to the day before necropsy (after at least 8 weeks of treatment) was associated with reductions in mean body weight gain and food consumption, red coloured urine, increased urinary volume, and changes in serum or urinary clinical chemistry parameters at all dose levels. Necropsy revealed pale liver at 15 and 30 mg/kg/day and enlarged spleen at 30 mg/kg/day. There were also test item-related microscopic lesions of the kidney at 15 and 30 mg/kg/day comprising eosinophilic inclusions and cell degeneration in the cortical tubular epithelium, nuclear pyknosis/tubular basophilia of the renal medulla, as well as cellular cast(s) and/or multifocal tubular dilatation secondary to the corticotubular changes. There was no adverse effect of treatment in any group on male gonadal function, mating performance, or fertility as assessed by evaluation of the reproductive indices, sperm counts and motility, macroscopic findings and reproductive organ weights. There was no evidence of a male-mediated effect on early gestation of untreated females in any group when administered to males during spermatogenesis and mating. The NOAEL for fertility including gonadal function, mating behavior, reproductive performance and early gestation in the male Sprague Dawley rat was concluded to be 30 mg/kg/day (HED = 5 mg/kg/day, or 300 mg/day for a 60 kg patient).

Methods

Doses:	0, 5, 15, and 30 mg/kg/day
Frequency of dosing:	Once daily
Dose volume:	10 mL/kg/hour
Route of administration:	IV infusion over one hour
Formulation/Vehicle:	5 % Dextrose Injection, USP (D5W) Dosing solutions were prepared daily and kept refrigerated. A correction factor for the active ingredient of 1.204 was used for preparation of the dosing solutions.
Species/Strain:	Sprague-Dawley rats, Crl: OFA (SD)
Number/Sex/Group:	20 males per group 20 females per group were untreated.
Satellite groups:	None
Study design:	Rats were acclimated for 2 weeks. At least 5 days before the start of treatment, a polyurethane catheter was implanted into the posterior vena cava via the left femoral vein of the males. Following implantation, the animals were maintained on continuous infusion with physiological saline prior to the start of treatment and between daily treatments. Males were treated for 28 days before mating, throughout mating and up to the day before necropsy. Animals were paired on the basis of one male and one female from the same group for a maximum of 11 days. Vaginal smears were taken daily from females during cohabitation. The day of mating was confirmed by the presence of sperm in a vaginal smear or a vaginal plug was recorded and taken as Day 0 of gestation (G0). Mated females were separated from the males once mating had been confirmed.
Deviation from study protocol:	None that were considered to have affected the outcome of the study

Observations and Results

Mortality

Animals were observed at the beginning and end of each working day. No compound-related deaths were reported. Two males in the control group and one male in the 15 mg/kg/day group were found dead during the study (Days 6, 56, and 56, respectively). These deaths were considered incidental and not treatment related. The

15 mg/kg/day treated male had froth in the trachea with all lung lobes uncollapsed and dark, but the cause of death was not determined.

Clinical Signs

Clinical condition was monitored during the study for males and untreated females. During the treatment period, observations were made before and at least once after daily treatment. Additionally, a full clinical examination was performed daily for males and daily during gestation for females. From Day 8 onwards, attention was paid twice weekly to urine color for males.

Blood and urine were collected from all males on the day of sacrifice (Day 56 or 57) for clinical laboratory determinations. Blood was collected from the retro-orbital sinus, under anesthesia, from fasted animals. Urine was collected on ice in metabolism cages for approximately 16 hours from males while food and water were withheld.

Sporadic occurrences of red colored urine were reported in animals in all dose groups. Incidences were highest during the first four weeks of treatment, but no dose-relationship was reported.

After 8 weeks of treatment, dose-related increases in mean alkaline phosphatase, aspartate aminotransferase (up to 6-fold) and alanine aminotransferase (up to 8-fold) concentrations were observed in all treated groups compared with the control. Those values were reported to be outside of the historical control range only for the high dose group, and may be indicative of adverse effects on the liver at that dose. Similar dose-related trends were reported for mean glucose, BUN, creatinine, and cholesterol concentrations in all treated groups relative to control, but values for all but cholesterol were reported to be within the historical control range. Reduction in mean sodium and increase in mean potassium concentrations in the 15 and 30 mg/kg/day groups relative to control were reported, but were said to be close to the limits of the historical control range, and were therefore unlikely to be biologically significant.

After 8 weeks of treatment, there was a dose related increase of urine volume for all treated animals relative to controls. Blood was present in the urine in most samples. Urine pH was slightly lower in the 15 and 30 mg/kg/day groups than in the control. Mean urinary excreted concentration of sodium, chloride, calcium, phosphorus and glucose were higher at all dose levels. Mean urinary excreted concentrations of potassium and N-acetyl-beta-D glucosaminidase (NAG) were also higher in the 30 mg/kg/day group attaining statistical significance when compared with controls.

Body Weight

Body weight was recorded twice weekly for males. For females, body weight was recorded once pre-mating, weekly during mating, and on Days 0, 4, 8, 10, and 13 of gestation.

There was a dose-related reduction in body weight gain in males from Day 0 to 55 for the treated groups relative to control. Terminal mean body weight was 9 % lower in the 15 and 30 mg/kg/day dose groups than in the control group and was consistent with reduced food consumption.

Feed Consumption

Food consumption was measured weekly for males during the pre-mating period. It was also recorded for untreated females during gestation over Days 0-4, 4-8, 8-10, and 10-13.

Decreased food consumption from Day 0 to 28 was reported for all treated groups, relative to control. Mean food consumption was statistically significantly ($p<0.05$) reduced by 12% in the 30 mg/kg/day group during the last 2 weeks of the pre-mating period compared with control, while a 6 % statistically significant ($p<0.05$) reduction in food consumption was noted for the 15 mg/kg/day group during the last week of the pre-mating period.

Toxicokinetics

Not performed

Dosing Solution Analysis

Duplicate samples were taken from each formulation, after filtration, on the first day of dosing (Day 0) and during the last two weeks of dosing (Days 50 and 56), and from two dosing infusion lines per group on the first day of dosing (Day 0), during the first week of mating (Day 28) and on the last day of dosing (Day 56). The samples were stored frozen (between -15 and -25°C) and protected from light. The samples were analyzed within 1 to 9 weeks after preparation which was stated to be outside of the current stability period (two weeks). The report states that, since the achieved concentrations were within acceptance criteria, the samples were considered stable over different storage periods (at room temperature for a maximum of 7 hours, between +4 °C and +8 °C for a maximum of two days and between -15 and -25 °C for 1, 3, 4, 5 and 9 weeks). It was concluded that the delayed analysis had no impact on the study findings and conclusions.

The report states that the combined accepted results of the original and retest analysis indicate that all the dosing solutions were within the range of the target concentration.

Necropsy

Surviving animals were killed by CO_2 inhalation followed by exsanguination, then necropsied. Males were sacrificed after the end of the caesarean examinations of the females (during Week 9). Females underwent caesarean section on or near GD 13. The body weights of all surviving males were recorded before terminal necropsy. Kidneys (paired), testes and epididymides were weighed for all surviving males. All animals were given a full macroscopic examination. Abnormal tissues were sampled and preserved for possible histopathological examination. The kidneys of all males were fixed in 10 % formalin. Histopathological examinations were performed on kidneys for all males from all groups to determine if there was a histological correlation to the blood in urine.

One control male rat was found dead on Day 6, and dark fluid at the muzzle was noted on necropsy. The cause of death was not determined. Two additional male rats, one control and one mid-dose, were found dead one day before scheduled terminal sacrifice. The mid-dose animal showed froth in the trachea and dark and un-collapsed

lung. The cause of death of both animals was not determined. These findings were considered to be incidental.

At terminal necropsy, diffusely pale liver was recorded in a dose-related manner in treated males, with one animal affected at the low dose and 7/19 and 15/20, respectively, in the mid- and high dose groups. Splenic enlargement was noted in 16/20 high dose males and one mid-dose male. No histological evaluation of these organs was performed. Additionally, two male rats treated at 30 mg/kg/day each had a mass in the epididymis. These were not examined histologically, and were not considered likely to be treatment-related, although occurrence only in the high dose group makes this finding questionable.

Histological evaluation of the kidney revealed test item-related lesions in the mid- and high dose groups. Minimal or slight eosinophilic inclusions, associated with minimal single cell degeneration, were found in the cortical tubular epithelium of all males at 30 mg/kg/day. Minimal or slight nuclear pyknosis/tubular basophilia of the medulla was found in dose-related incidence and severity at 15 and 30 mg/kg/day. Minimal numbers of cellular cast(s) (2/20) and minimal or slight multifocal tubular dilatation (5/20) were seen in high dose males and were considered to be secondary to the observed cortical tubular changes. The report states that some of these changes were degenerative in nature and may have been the cause of the higher serum urea and creatinine and the reduced sodium and increased potassium noted in the clinical chemistry analysis. Additionally, absolute kidney weight was statistically significantly lower at 30 mg/kg/day.

In contrast to findings in general toxicology studies, macroscopic changes at the injection sites were “few and were not considered sufficient evidence of a test item-related effect.”

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)

Sperm counts and motility were assessed using automated equipment. The left cauda epididymis was sampled and used for the assessment of sperm motility. Sperm counts were performed using the left testis. The seminal vesicles, prostate gland, right testis, right epididymidis and left caput epididymidis of all males were fixed in modified Davidson’s fluid.

The inseminated untreated females were submitted to a caesarean examination on or close to GD 13, examined macroscopically and litter parameters were recorded. The ovaries and uterus of each female were removed and examined for determination of pregnancy status and evaluation of placentae, number of corpora lutea, number of live embryos, number of implantation sites, and number of resorption sites. All uteri were placed in ammonium sulfide solution to stain for undetected implantation sites. The vagina, uterus and ovaries of any female without uterine implantations were fixed in 10 % formalin.

There were no treatment-related effects on mean testicular sperm count or on the epididymal sperm motility parameters in any group.

Mean pre-coital interval was 2.6-3.00 days, with no significant differences between groups. The copulation index was 100% in all groups. The fertility indices were 95, 100, 100, and 90%, respectively, in the control, 5, 15, and 30 mg/kg/day groups. There were two females in the high dose group and one in the control group

that did not become pregnant; the report stated that these were considered to be incidental.

All pregnant females had viable embryos except one female in the 15 mg/kg/day dose group. She had only one corpus luteum corresponding to one resorbed implantation site. This isolated finding in the intermediate dose group was considered to be incidental.

Overall, females had a mean of 15.8, 15.8, 15.3 and 15.6 viable embryos, in the control, 5, 15 and 30 mg/kg/day dose groups, respectively. Mean numbers of corpora lutea (17.0 to 18.0), implantation sites (16.2 to 16.6) and the percentage pre-implantation loss (4.5 to 7.8 %) in the treated groups were considered to be similar to the control group or within the historical control range. The mean live litter size was comparable in all groups. The percentage of post-implantation loss was 4.2 %, 5.1 %, 5.9 % and 4.1 % in the control, 5, 15 and 30 mg/kg/day dose groups, respectively.

2. Study title: Fertility toxicity study by 1-hour intravenous infusion in the female rat (Segment I)

Study no.:	AB17380
Study report location:	Module 4
Conducting laboratory and location:	(b) (4)
Date of study initiation:	09 January 2013
GLP compliance:	Yes (OECD)
QA statement:	Yes
Drug, lot #, and % purity:	Oritavancin Bis Phosphate Salt, batch no. 87556IL00, purity is stated in the test to be 92.2 % (Study Sponsor information), but the appended certificate of analysis indicates that the assay was 85.9% (volatile free basis), which was used to calculate the % free base as 83.07%.

Key Study Findings

Intravenous infusion of Oritavancin for 1-hour to female Sprague Dawley rats at doses of 5, 15 and 30 mg/kg/day throughout a 2-week pre-mating period, during mating (with groups of untreated males) and through Day 7 of gestation revealed decreased body weight gain in the 30 mg/kg/day group during gestation Days 0-8 only, followed by a recovery. Food consumption was decreased in a dose-related manner in the mid- and high dose groups during the gestation period only.

There were no adverse effects of treatment on oestrus cycle, mating performance or fertility in any group. All females mated, fertility index was 90-95% in all groups, including control. The percentage post-implantation loss and the mean live litter size were comparable in all groups. Pre-implantion loss was greater in the low and mid-dose groups than in the control or high dose groups, however this was not considered to be an effect of treatment. The mean ovarian weight was slightly higher in all treated groups than in the control group, but was not dose-related in magnitude, and the difference from control was stated to have been within the historical control range. Non-

reproductive macroscopic necropsy findings in four females in the 30 mg/kg/day group consisted of enlarged spleen in two animals, a mass in the papillary process of the liver in another, and pale liver in another, which were possibly associated with treatment. It was concluded that there was no adverse effect of treatment in any group on mating performance, gonadal function, fertility or early gestation. Therefore, the No Observed Adverse Effect (NOAEL) for those parameters in the female Sprague Dawley rat was 30 mg/kg/day (HED = 5 mg/kg/day, or 300 mg/day for a 60 kg patient).

Methods

Doses:	0 (vehicle), 5, 15, and 30 mg/kg/day
Frequency of dosing:	Once daily
Dose volume:	10 mL/kg/hour
Route of administration:	IV infusion over one hour
Formulation/Vehicle:	5 % Dextrose Injection, USP (D5W) Dosing solutions were prepared daily and kept refrigerated. A correction factor for the active ingredient of 1.204 was used for preparation of the dosing solutions.
Species/Strain:	Sprague-Dawley rats: Crl: OFA (SD)
Number/Sex/Group:	20 Only females were treated. 16 additional females were required to ensure allocation based upon successful implantation of the catheter. Females were approximately 9 weeks old at the start of treatment, and males were approximately 13 weeks old at the start of pairing.
Satellite groups:	None
Study design:	Females underwent an acclimatization period of 14 days between arrival and the start of treatment. Males were acclimatized for 9 days between arrival and the start of mating. During the acclimatization period, i.e. at least 5 days before the start of treatment, the females were implanted. They were anaesthetised by continuous inhalation of isoflurane. A polyurethane catheter was implanted into the posterior vena cava via the left femoral vein. The catheter was attached to an infusion pump via a tether system and a swivel joint. The integrity of the system was verified daily. Animals were maintained on continuous infusion (0.4 mL/hour/animal) of physiological saline (0.9 % NaCl) between implantation and the start of treatment and between daily treatments. Females were treated for 14 days before mating, throughout mating and until Day 7 of gestation (inclusive). On the morning of Day 8 of gestation, the jacket was removed and the catheter cut off at the neck of the animal. Females for which mating was not detected were treated through to necropsy on the day after the end of the mating period.

	Animals were paired on the basis of one male and one female from the same group for a maximum of 21 days. Vaginal smears were taken daily from the females during cohabitation. The day of mating, confirmed by the presence of sperm in a vaginal smear or a vaginal plug, was recorded and taken as Day 0 of gestation. Mated females were separated from the males once mating had been confirmed and smearing ceased. Females with no evidence of mating after 14 days were re-paired for a maximum of 7 days with a proven fertile male from the same group.
Deviation from study protocol:	None that were considered to have affected the outcome of the study

Observations and Results

Mortality

All animals were observed at least twice daily. No mortality was reported.

Clinical Signs

All animals were observed daily for clinical signs. During the treatment period, the females were observed before and at least once after treatment. A full clinical examination was performed daily at the same time as the first daily clinical observation.

No test article-related observations were reported. However, one high dose female was cold to touch, pale, and had decreased activity on Day 15.

Body Weight

Body weights for males were recorded weekly from the first day of mating, but were not reported. For females, individual body weights were recorded twice weekly during the pre-mating and mating periods (only pre-mating data were reported), and on Days 0, 4, 8, 10 and 13 of gestation.

Mean body weights in the treated groups were comparable with controls during the pre-mating period. During gestation, mean body weight gain was statistically significantly lower (-33%) in high dose females from GD 0-8, relative to control. After that, body weight gain in the high dose group was comparable to controls. This finding correlated with reduced food consumption in the high dose group.

Feed Consumption

Food consumption of the females was measured weekly during the pre-mating period and over Days 0 to 4, 4 to 8, 8 to 10, and 10 to 13 of gestation.

There was no treatment-related effect on food consumption during the pre-mating period. Food consumption was lower for low dose animals in the second week

of the pre-mating period, but this was considered to be incidental since there was no dose-response.

During gestation, mean food consumption was statistically significantly reduced (by 11%) in the high dose group over GD 0-13, relative to control. In the mid-dose group, food consumption was decreased to a lesser degree (by 6%) between GD 4-8.

Toxicokinetics

Not performed

Dosing Solution Analysis

The report states that there are data to indicate that diluted solutions of the test article in D5W (5 % Dextrose Injection, USP) at 0.17 to 3.37 mg/mL are stable for two weeks when refrigerated (at +2 to +8 °C) or frozen at -70°C.

Duplicate samples (where possible) were taken from each formulation after filtration from one dosing infusion line per group, on the first day of dosing, and during the first and last weeks of mating (Days 16 and 34). The samples were stored frozen (between -15 and -25 °C) and protected from light. The samples were analyzed within 4 to 15 weeks after preparation which was outside the current stability period (two weeks). The report states that, since the achieved concentrations were within acceptance criteria, the samples were considered stable over different storage periods (at room temperature for a maximum of 7 hours, between +4 °C and +8 °C for a maximum of two days and between -15 and -25 °C for 4, 6, 8, 12, 13, 14 and 15 weeks). It was concluded that the delayed analysis had no impact on the study findings and conclusions.

The formulation samples were within the target concentration range ± 10% except for five samples collected on the first day of dosing. Of those, re-test results were in the targeted concentration range for four samples. The re-test of the 0.05 mg/mL formulation sampled on Day 0 after infusion was well below the target concentration (-18%); this was attributed to lack of homogeneity.

Necropsy

All females were killed by carbon dioxide inhalation and exsanguination, then necropsied. Untreated males were sacrificed without necropsy following completion of the majority of caesarean sections. Caesarean section was performed on Day 13 of gestation. The body weight of all females was recorded before necropsy. All females were given a macroscopic examination for structural or pathological changes. Any abnormalities observed were recorded. The report states that, since no abnormal organ or tissue was observed, there was no sampling for further histopathological examinations. The ovaries (paired) and empty uterus from each female were weighed. The vagina, uterus and ovaries of all females were fixed in 10 % neutral formalin. No histopathological examinations were performed.

Mean ovarian weight was slightly higher in all treated groups, but was not dose-related. The differences from control were within the historical control range, and were not considered to be toxicologically significant.

Findings were reported in four high dose females. Enlarged spleen was reported in two high dose females. One high dose female had a mass in the papillary process of the liver and another had a pale liver. These were considered to be possibly associated

with treatment and are consistent with findings in other studies, yet no histopathological examination was performed. No macroscopic findings were reported in the ovaries or uterus.

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)

Vaginal smears were taken daily in order to determine the stage of the oestrus cycle for each female from the first day of treatment until identification of mating or separation from the male. Mean cycle length, irregularity index, and percentage of days in oestrus were calculated for each female (excluding those that were acyclic or had more than five days without oestrus).

The percentage of females that were acyclic or had acyclic periods appeared to be increased in the mid- and high dose groups, relative to controls, but the values were said to be comparable to historical control data, so may not be treatment-related.

All females in each group mated (copulation index was 100%). The mean pre-coital interval for high dose females was slightly longer than concurrent and historical controls. The report states that this was due to three females that did not mate until after 12 days of pairing and were likely to have been pseudopregnant. If those animals were excluded, then the group mean pre-coital interval was similar to control. It is unclear whether or not this was an effect of treatment. Pseudopregnancy was reported for two females in the low dose group, but did not result in a longer pre-coital interval.

No adverse effect was reported on fertility. One or two mated females in each group did not become pregnant. Fertility indices in all groups, including control, were 90-95%, and fell within the historical control range.

The ovaries and uterus of each female were removed and examined at the time of caesarean section on GD 13, including examination of the placentae. Pregnancy status, number of corpora lutea, number of live embryos, number of intrauterine implantation sites, and number of intrauterine death (resorption sites) were recorded. The uterus of all females was placed in ammonium sulfide solution in order to stain any previously undetected implantation sites.

The numbers of corpora lutea per dam, implantations per dam and as a % of corpora lutea, and number of viable embryos were similar across groups. Post implantation loss, as a group total, was highest for the control group, with more dams affected than in treated groups. Pre-implantation loss was highest in the low and mid-dose groups, and appeared to exceed historical as well as concurrent controls. However, that in the high dose group was similar to controls, so the findings at the lower doses may have been incidental.

9 Special Toxicology Studies

From the Pharmacology/Toxicology review of NDA 22-153:

"Several special toxicology studies were conducted to investigate the effects of oritavancin on the immune system of rats and the effects of local administration in the rabbit. When administered to the eyes of rabbits (16 mg/eye, single dose), oritavancin caused mild iridal irritation and conjunctivitis. Similarly, when administered in the ear vein of rabbits once daily for 3 days at 60 mg/20 mL over 30 minutes, erythema and

edema were minimal. When placed on the skin of rabbits at 1000 mg/kg as a single exposure, moderate erythema was noted.

Effects of oritavancin on the immune system were explored only in the rat; results were inconsistent. Two early studies in male Fischer 344 rats suggested a brief stimulatory effect on serum IgM levels following exposure to Freund's adjuvant conjugated sheep red blood cell antigen (SRBCA) at the end of a 2 week exposure to up to 15 mg/kg/day of oritavancin. However, if the rats were exposed to SRBCA at 1 month following a 2 week course of oritavancin, a dose-dependent decrease in serum IgM levels was seen. Serum IgG levels were unaffected in either arm of the study. A later study found almost no effect after exposure to SRBCA in the rat even with 30 mg/kg doses. A host-resistance study in rats (utilizing *Candida albicans*) showed increased mortality when *C. albicans* was administered immediately after daily X 14 day administration of up to 15 mg/kg oritavancin to Fischer 344 rats, suggesting a decrease in host resistance. If challenged after a 4 week recovery period, no changes in mortality were noted. In conclusion, acute exposure to oritavancin may diminish immune response in the rat."

The following new study was submitted to the current NDA:

1. Study no. MDCO-ORI-M014: Impact of Oritavancin on Macrophage Functions in vitro

Oritavancin has previously been shown to accumulate in cells and to cause morphological alterations of lysosomes and related vacuoles suggestive of a mixed-lipid storage disorder. In this study, the effects of oritavancin and comparators, vancomycin (a reference glycopeptide) and azithromycin (known for high cellular accumulation and capacity to cause a lysosomal storage disorder), on specific macrophage functions were tested in vitro in a series of experiments using murine J774 macrophages and differentiated human THP-1 cells.

First, the accumulation of oritavancin in the test cell lines was determined following incubation with concentrations of ^{14}C-labeled oritavancin that were said to be pharmacologically relevant. Treatment concentrations ranged from 5-50 mg/L, assessed at time points up to 24 hours.

Macrophages were incubated with oritavancin or the comparators at 37ºC for 3 hours, then washed with phosphate buffered saline (PBS) prior to use in the following assays for macrophage function.

Metabolic activity of the cells was evaluated by measuring the formation of purple formazan crystals from the yellow soluble dye, MTT, by cellular dehydrogenases. J774 cells were incubated with a range of concentrations of oritavancin for 3 hours, washed in PBS, and incubated for 1 hour with MTT. DMSO was added to dissolve the formazan crystals and absorbance was measured.

Results

Cellular accumulation of oritavancin proceeded over time in J774 macrophages and human THP-1 cells, increasing with time and higher extracellular concentration. Higher and earlier intracellular concentrations were achieved in the mouse cell line.

Data showed that the highest concentrations of oritavancin (20-50 mg/L) reduced phagocytosis of latex beads, but not of bacteria, in macrophage cell lines. Reduction in phagocytosis was most pronounced in the J774 cells, but occurred in both cell lines at concentrations that were identified in the report as clinically relevant. [The report states that peak oritavancin concentrations in human plasma following a single 1200 mg infusion were predicted to yield a free drug Cmax of 20 mg/L and a total drug Cmax of 129 mg/L.] Laser scanning confocal microscopy of J774 macrophages incubated for 3 hours in the presence of 25 mg/L oritavancin did not reveal any impairment of the ability of phagocytized latex beads to reach lysosomes.

Endocytosis or pinocytosis of FITC-dextran tended to decrease with increasing oritavancin concentration in J774 cells, but was not statistically significant. Lysosomal integrity and metabolic activity appeared to be unaffected by intracellular oritavancin.

A concentration-dependent increase of ROS production was observed in J774 cells pre-exposed to clinically relevant external concentrations of oritavancin. Higher ROS production was observed when cells were pre-incubated for longer periods of time to oritavancin. The increase in ROS production in THP-1 cells was not statistically significant and may have been related to findings that J774 cells accumulate the drug to a greater extent than do THP-1 cells.

In summary, oritavancin was found to impair latex bead phagocytosis and increase production of ROS in one or both macrophage cell lines following incubation

with clinically relevant concentrations of the drug. These findings were compared to experiments conducted using vancomycin and azithromycin. The only change reported for the comparators was that there was a slight increase in ROS production in cells exposed to 50 mg/L vancomycin. Lysosomal integrity and mitochondrial function did not appear to be impaired.

The report concluded that responses occurred at cellular concentrations of 10 µg/mg protein or higher (2000 mg/L) of oritavancin. It further states that healthy volunteers receiving a cumulative dose of 4 g (800 mg/day for 5 days) exhibited cellular concentrations of 560 µg/mL in alveolar macrophages, therefore, effects on innate macrophage functions would be unlikely to occur following treatment with a single 1200 mg dose of oritavancin.

11 Integrated Summary and Safety Evaluation

From the pharmacology/toxicology review of NDA 22-153:

"Oritavancin is a lipoglycopeptide which inhibits the formation of peptidoglycan, a component of bacterial cell walls. It has activity again Gram-positive bacteria, including methicillin-resistant *Staphalococcus aureus* (MRSA). Oritavancin as a single dose had minimal effects on the CNS, cardiovascular, renal or gastrointestinal systems. In toxicology studies in the dog, where ECGs were measured within 10 minutes of the end of infusion, no changes in ECGs were noted. However, in a patch clamp studies in human myocytes, the IC50 values ranged from 1 to 43 ug/mL. Human Cmax values were 27 ug/mL, suggesting that QT prolongation could be an issue in clinical use. Clinical monitoring was conducted.

Single dose pharmacokinetics as well as toxicokinetics were studied primarily in the rat and dog (with a few studies in the mouse). There were no remarkable differences in pharmacokinetics or toxicokinetics based on gender. No significant plasma accumulation of drug was noted. AUC, whether measured by radiolabel or HPLC did not differ greatly at the same doses, suggesting minimal metabolism. Further analysis of plasma and bile for oritavancin products confirmed this conclusion. Neither infection, neutropenia, nor pregnancy significantly changed the AUCs or Cmax levels of oritavancin in animal models. Clearance decreased over exposure time, leading to longer half-lives (initial plasma half-life for rats on day 1 was generally between 3 and 6 hours, while after multiple days of exposure, plasma half-life ranged from 5-10 hours). The half life in dogs was between 8 and 17 hours. In humans, the distribution half-life was approximately 31 hours, with the elimination half-life at 393 hours. The AUC in humans, normalized to a dose of 200 mg, was 139 ± 60 ug.h/mL. Elimination in both rats and dogs was low via the urine and feces (<5% urine, 10-30% fecal). Six weeks after a dose in the rat, approximately 70% of the dose was still associated with the carcass. In the 13 week dog and rat studies, levels of oritavancin in the liver 2 months after the cessation of dosing did not differ significantly from the levels immediately after the end of treatment. Levels of oritavancin in rat milk were roughly 1/5 of that in maternal plasma. Little distribution into the brain was seen. The highest concentrations of oritavancin were in the liver with significant amounts in the intestine (large and small), marrow, kidney, spleen and adrenals. With multiple administrations, liver levels rose at

a disproportionate extent. Protein binding in animals was low, but may have been associated with oritavancin binding to glassware used in the assay. Protein binding in the human was near 90%.

In the dog, emesis, histamine release (manifested as facial reddening, welts, increased blood pressure), and stool changes were noted. In rats, death during the toxicity studies was much more common. In the short term study, animals could not be dosed due to injection site (tail) damage. With the 13 week study, masses (usually histiocytic), and paralysis, as well as catheter-related infections were common at the high dose. Otherwise, the toxicities seen in the rat and dog were similar. Both species showed decreases in red blood cells, increases in BUN, AST/ALT, histiocytosis (macrophages) with eosinophilic/acidophilic granules in liver, kidney, spleen, injection site, and lymph nodes. The histiocytosis did not resolve over the 1-2 month recovery period and correlates well with the persistent levels of oritavancin in the liver and carcass. The ratio between the AUC at the NOAEL in the dog (13 week study) and the AUC at the clinical dose in humans was slightly greater than 3.

Oritavancin was negative in the genotoxicity studies conducted (Ames, mouse lymphoma, chromosomal aberrations and mouse micronucleus tests). Oritavancin did not affect fertility in the rat (doses up to 30 mg/kg), fetal development in the rat and rabbit (doses up to 30 and 15 mg/kg respectively), or pre and post-natal development in rats (doses up to 30 mg/kg). Given a human plasma AUC after a 200 mg dose of 139 ug.h/mL, and plasma AUCs in the rat of 340 to 520 ug.h/mL, a margin of safety of approximately 2.4 to 3.7 was seen. Immunotoxicity studies were contradictory, although oritavancin clearly induced histamine release in the dog."

It should be noted that comparison of dose multiples in the above text refers to a clinical multiple dosing regimen that was proposed in the previous NDA. Dosing for the current NDA is described as a single 1200 mg dose, infused over 3 hours. The Sponsor considers the cumulative dosing in repeated dose toxicology studies to support this dose, but this does not account for differences in the time course, and without actual tissue concentration data, that cannot be certain. Nevertheless, it does not seem necessary to repeat single dose toxicology studies at higher doses. Although the slower infusion rate should reduce toxicity, nonclinical safety data do not support a dose this high. Safety of the clinical regimen has been supported in development by previous clinical experience.

Four new studies were conducted. A study intended to qualify impurities utilized multiple batches of test article, all at a dose of 60 mg/kg. Lethality was seen in one test batch. Doses in that study were still only half the equivalent of the intended clinical dose, so this study was not sufficient to qualify all impurities in a manner relevant to clinical dosing. Two new fertility studies were conducted; these were again negative for adverse effects on fertility. A study to examine macrophage function concluded that effects on innate macrophage functions would be unlikely to occur following treatment with a single 1200 mg dose of oritavancin.

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/s/

AMY C NOSTRANDT
05/02/2014

WENDELYN J SCHMIDT
05/06/2014