A-1307 The Effects of Supratherapeutic Dose of Oritavancin on ECG Intervals: A Thorough QT Study in Healthy Volunteers

Contact Name
Al Bellibas
The Medicines Company
al.bellibas@themedco.com

S.E. Bellibas[1], N.Y Huang[1], B. Darpo[2], C. Sanabria[3], K. Fusaro[1], S. Good[1], J. Mason[4] [1]The Medicines Company, Parsippany, NJ, USA, [2]Karolinska Institute, Danderyd's Hospital, Div. of Cardiovascular Medicine, Stockholm, Sweden, [3]Spaulding Clinical, West Bend, WI, [4]Dept. of Medicine, Div. of Cardiology, University of Utah, Salt Lake City, Utah, USA.

Abstract

Background: Oritavancin (ORI) is a lipoglycopeptide antibiotic characterized by rapid, concentration dependent bactericidal activity against gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA). The efficacy and safety of ORI have been assessed in over 3000 patients and healthy volunteers (HVs). This thorough QT (TQT) study was conducted to evaluate the cardiac effects of ORI.

Methods: This was a double-blind, randomized, placebo-controlled, parallel design study with an open-label positive control, testing a supratherapeutic dose of ORI in HVs. A total of 150 subjects were randomized to one of the following: ORI 1600 mg 3 hour IV infusion, matching placebo (PLB) IV infusion, or moxifloxacin (MOX) 400 mg tablet. Twelve-lead ECGs were extracted from continuous recordings at serial time points 24 hours prior to and post dosing on Days 0 and 1. PLB-corrected mean change from baseline (ΔΔ) in QTcF (ΔΔQTcF), ΔΔHR, ΔΔPR, and ΔΔQRS were analyzed.

Results: 48, 52 and 49 subjects received ORI, MOX and PLB, respectively. ΔΔQTcF was small and mostly negative (no prolongation) up to 6 hours after ORI dosing and the largest mean value (2.6 msec; upper bound of 90% CI: 6.9 msec) was observed 12 hours after the end of infusion. Assay sensitivity was demonstrated by lower bound of the 90% CI of MOX ΔΔQTcF above 5 msec at several time points. ORI did not have a clinically relevant effect on heart rate (HR) with mean ΔΔHR ranging from -2.0 to 2.4 bpm. ΔΔPR increased at every time points after ORI treatment from 3 to 7 hours post dose with mean values between 4.6 and 7.7 msec. A linear PK-PD modeling predicts a non-clinically relevant 3.2 msec change in the PR interval for the maximum plasma concentration observed in Phase III studies after 1200 mg of ORI (mean C_{max} from SOLO I and II was 138 µg/mL). ORI did not prolong the QRS interval with mean ΔΔQRS ranging from -0.3 to 2.6 msec.

Conclusion: Based upon the results of this TQT study, a therapeutic 1200 mg dose of ORI is not anticipated to cause any clinically significant effect on ECG parameters studied.

Introduction

Oritavancin is a new lipoglycopeptide with potent antibacterial activity against gram-positive bacteria, including methicillin- and vancomycin-resistant staphylococci and penicillin-resistant streptococci. The current proposed therapeutic use of oritavancin is the treatment of ABSSSIs caused by susceptible gram-positive bacteria (1).

The cardiac safety of oritavancin was previously evaluated in a Phase I, double-blind, randomized, placebo- and positive-controlled, single-dose, parallel-design thorough QT (tQT) study in 240 healthy adult subjects (2). In this study, a single IV infusion of 200- to 800 mg oritavancin was administered and compared with a single oral tablet of 400 mg moxifloxacin and placebo. Results of this study demonstrated no clinically significant repolarization effect of single 200 mg or 800 mg IV doses of oritavancin.

The current study was designed to generate cardiac safety data using 1600 mg oritavancin, which represents the supratherapeutic dose to the new single 1200 mg IV oritavancin dose, in order to support global registration.

Methods

This was a double-blind, randomized, placebo-controlled, parallel-design cardiac safety study with an open-label positive control (moxifloxacin) using a supratherapeutic dose of oritavancin in healthy volunteers. Moxifloxacin is known to prolong the QT/QTc interval and was therefore used as the positive control for this study as per ICH E14 guidance (3).

A total of 150 healthy subjects were randomized to one of the following treatment groups and stratified by gender with a ratio of male and females of approximately 1:1 in each treatment group:

- Oritavancin 1600 mg IV infusion over 3 hours
- Matching placebo infusion
- Oral moxifloxacin 400 mg tablet

This study plan included the following:

- Screening (up to 21 days)
- Check-in and Baseline (Day 0 and Day -1)
- Treatment (Day 1)
- Discharge (day 2 after 24 hour post-dose monitoring)
- Follow up (day 7 ± 3 days)
- Final Follow up (day 14 ± 3 days)

Oritavancin dose of 1600 mg in 1500 mL of D5W administered with a constant rate (8.9 mg/min) IV infusion over 3 hours. The dose was equally divided (750 mL per infusion bag) and administered via 2 dedicated, peripheral venous lines (1 line in each arm). In the placebo, oritavancin and moxifloxacin groups there were 48, 47 and 51 completers, respectively.

Electrocardiograms: ECGs were obtained digitally using a Mortara X-12+ ECG continuous 12-lead digital recorder, and were obtained at baseline and following the start of the treatments. ECGs were extracted from the continuous ECG data stream in triplicates approximately 1 minute apart at hours 3.5, 4, 5, 6, 7, 9, 11, 15, and 24 (23.5 on day 0) hours on day 0 and day 1.

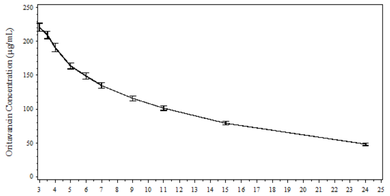
The core laboratory staff remained blinded to treatment, time and study day identifiers. Lead II was the lead of choice for the over-reads. The lead's median beat was used for measurements. The baseline and on-treatment ECGs were based upon the same lead. In addition, each individual subject's ECGs were read by a single reader.

Pharmacokinetics: Blood samples from subjects treated with oritavancin/placebo were collected at the following ECG time-matched timepoints: –0.5, 3, 3.5, 4, 5, 6, 7, 9, 11, 15, and 24 hours for PK analysis. One blood sample for PK analysis was collected from moxifloxacin group at 3 hours after dose. Plasma oritavancin concentration data were analyzed by noncompartmental analysis using WinNonlin Professional (Pharsight, Mountain View, California, USA). Actual sampling times were used for the evaluation.

Results

Drug Exposure

Mean (±SD) plasma oritavancin concentration-time profile



Summary of Plasma Oritavancin Pharmacokinetic Parameters (Pharmacokinetic Population)

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

The C_{max} exposures to oritavancin were consistent with expectations and met the objective of achieving a supratherapeutic C_{max} of 232 µg/ml, greater than that observed in pivotal Phase 3 studies SOLO I and II, in which, 1200 mg dose given with same infusion duration of 3 hours , C_{max} was 138 µg/ml (4).

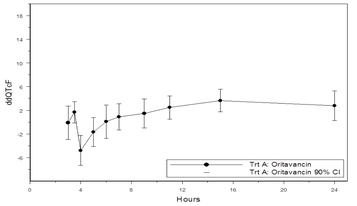
Plasma moxifloxacin concentrations were quantifiable in all subjects at the 3 hr timepoint. Moxifloxacin concentrations in the single samples ranged from 1312.5 ng/mL to 3692.7 ng/mL, with a mean (SD) value of 2274.19 (587.023) ng/mL.

Safety

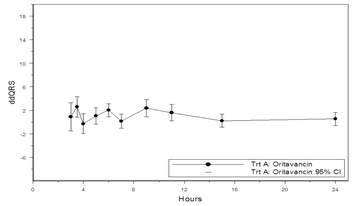
Oritavancin administered as a single infusion at a supratherapeutic dose of 1600 mg was well tolerated. A higher percentage of subjects reported Treatment-emergent AEs (TEAE) in the oritavancin group (41.7%) compared with the placebo (28.6%) and moxifloxacin (23.1%) groups. TEAEs reported by more than 2 subjects in the oritavancin group were oral paresthesia (10.4%), nausea (8.3%), and headache, vomiting, and infusion site pain (6.3% each); in the placebo group were headache (8.2%) and dizziness (6.1%), and in the moxifloxacin group was nausea (7.7%). Most TEAEs were mild in severity. No deaths, SAEs, or severe TEAEs were reported. No clinically notable trends were observed in clinical laboratory results, vital sign measurements, safety 12-lead ECG results, or physical examination findings.

ECG Intervals:

ΔΔQTcF (msec): Oritavancin



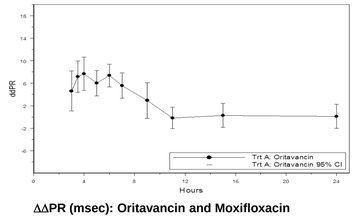
ΔΔQRS (msec): Oritavancin



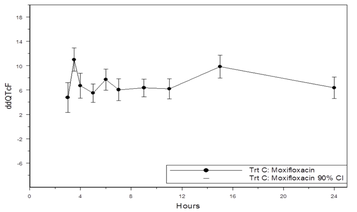
ΔΔQTcF (msec): Mixed-Effects Model

Parameter (unit)	Oritavancin Mean	Oritavancin 90% CI	Moxifloxacin Mean	Moxifloxacin 90% CI
3	-0.8	-5.1, 3.5	7.5	3.3, 11.7
3.5	1.2	-3.1, 5.5	15.7	11.5, 19.9
4	-5.8	-10.1, -1.5	10.9	6.7, 15.1
5	-3.0	-7.3, 1.3	9.4	5.2, 13.6
6	-0.3	-4.6, 4.0	11.3	7.1, 15.5
7	0.5	-3.8, 4.8	10.3	6.1, 14.5
9	1.7	-2.6, 6.0	11.4	7.2, 15.6
11	1.3	-3.0, 5.6	9.7	5.5, 13.9
15	2.6	-1.7, 6.9	12.1	7.9, 16.3
24	1.9	-2.4, 6.2	9.9	5.7, 14.1

ΔΔPR (msec): Oritavancin



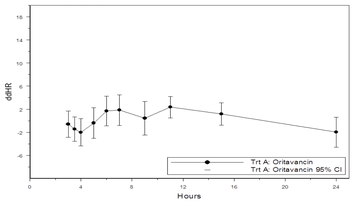
Sensitivity Analysis, QTcF in Moxifloxacin
Assay sensitivity was demonstrated by lower bound of the 90% CI of MOX ΔΔQTcF above 5 msec at several time points.



ΔΔPR (msec): Oritavancin and Moxifloxacin

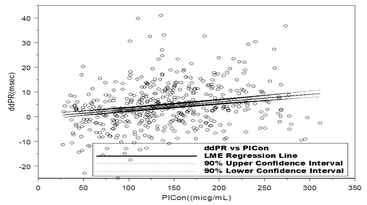
Parameter (unit)	Oritavancin Mean	Oritavancin 90% CI	Moxifloxacin Mean	Moxifloxacin 90% CI
3	4.6	-0.48, 9.70	-7.8	-12.28, -3.38
3.5	7.2	3.43, 10.89	-0.2	-3.73, 3.39
4	7.7	3.76, 11.60	2.1	-1.20, 5.48
5	6.0	2.53, 9.47	3.8	0.28, 7.26
6	7.4	4.78, 9.96	3.3	0.77, 5.83
7	5.6	2.63, 8.53	1.0	-2.22, 4.30
9	2.9	-0.85, 6.73	-0.7	-3.38, 2.02
11	-0.2	-3.02, 2.66	-1.8	-4.76, 1.14
15	0.3	-2.73, 3.27	-1.8	-5.02, 1.48
24	0.1	-4.24, 4.26	0.1	-4.07, 4.59

ΔΔHR (bpm): Oritavancin



Linear PK-PD modeling was performed (5) to further evaluate the change in PR in the oritavancin group. The relationship is statistically significantly (p=0.0005) positive with a slope of 0.02347, which predicts a non-clinically relevant 3.2 msec change in the PR interval for the maximum plasma concentration observed in Phase III studies after 1200 mg of ORI (mean C_{max} from SOLO I and II was 138 µg/mL).

Oritavancin Plasma Concentration – PR Interval Relationship



Conclusions

- This thorough QT study demonstrated no QT-prolongation liability for oritavancin.
- Oritavancin did not increase QTc at a supratherapeutic dose given IV over 3 hours. There was no clinically significant change in HR or QRS ; however, a modest and non-clinically relevant oritavancin-associated prolongation in PR interval was demonstrated.
- There were no abnormal diagnostic statements related to the appearance or worsening of ST-, T-, or U-wave morphology.
- Based upon the results of this TQT study, a therapeutic 1200 mg dose of ORI is not anticipated to cause any clinically significant effect on ECG parameters studied.

Disclosures/Acknowledgments

S. E. Bellibas, K. Fusaro and S. Good are employees of The Medicines Company

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C. Sanabria and J. Mason are employees/contractors for Spaulding Clinical.

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References

1. Orbactiv®, US Package Insert, 8/2014, The Medicines Company, Parsippany, NJ, USA.
2. Darpo B, Lee SK, Moon TE, Sills N, Mason JW. Oritavancin, a new lipoglycopeptide antibiotic – results from a thorough QT study. J Clin Pharmacol 50:895-903, 2010.
3. Food and Drug Administration, HHS. International Conference on Harmonization; guidance on E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs; availability. notice. Fed Regist. 2005;70(202):61134-5.
4. C. M. Rubino, S. M. Bhavnani, G. Moeck, S. E. Bellibas, P. G. Ambrose. Population Pharmacokinetic (PPK) Analysis for Oritavancin (ORI) Based on Data from Patients with Acute Bacterial Skin and Skin Structure Infections (ABSSSI). ICAAC 2014, Abstract No: A-1308, September 5-9, Washington, DC.
5. Patterson, Scott D, Jones Byron and Zariffa Nevine (2005) Modeling and Interrelating QTc Prolongation in Clinical Pharmacology Studies, Drug Information Journal 39, 437-445.

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