Interference of Oritavancin on Coagulation Tests as Assessed In Vitro and in a Phase 1 Study of Normal Healthy Volunteers

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Presented at ONS 2015, October 29-30, 2015, New Orleans, LA

1807

Abstract

Background: Oritavancin (ORI) is a lipoglycopeptide 5-6 antibiotic that is approved for the treatment of complicated skin and skin structure infections (CSSSI) and Nelson pneumonia. Oritavancin exhibits a concentration-dependent effect on multiple phospholipid-dependent coagulation tests in vitro, including activated partial thromboplastin time (aPTT), activated clotting time (ACT), silica clot time (SCT) and DRVVT.

Methods: Coagulation testing was performed using a standard INR and aPTT assay in plasma from subjects in the phase 1 study (n=12). Plasma was collected at selected time points following a single 1200 mg dose of oritavancin. Oritavancin concentration was determined using a validated liquid chromatography method (LC/MS/MS). Coagulation tests were performed using drug and maximum values, defined as the interval from the start of drug exposure to the time point at which 90% of subjects reached resolution (P90). Statistical analysis was performed by non-parametric methods. P<0.05 was considered significant.

Results

Table 1. Interference of oritavancin in phospholipid-dependent coagulation tests in vitro occurs in a concentration-dependent manner.

<table>
<thead>
<tr>
<th>Coagulation test</th>
<th>Assay</th>
<th>Test Units</th>
<th>Mean ± SD</th>
<th>Percent Change Relative to Control (%)</th>
<th>Assayed ORI Concentration (µg/mL)</th>
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<tbody>
<tr>
<td>PT/INR</td>
<td>APTT</td>
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<td>1.2 ± 0.2</td>
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Figure 1. The oritavancin concentration-time profiles determined in subjects (n=30) in the phase 1 study and from patients in the SOLO phase 3 studies are comparable.

Coagulation Tests in Vitro

Oritavancin powder (The Medicines Company, Parsippany, NJ, USA) was hydrated with Actin (Dade Diagnostics, San Diego, CA), and maximum values, defined as the interval from the start of drug exposure to the time point at which 90% of subjects reached resolution (P90). Statistical analysis was performed by non-parametric methods. P<0.05 was considered significant.

Phase 1 Clinical Study

The phase 1 open-label, single center, single-oral dose study was conducted to evaluate 12 doses of oritavancin in 108 subjects. Subjects were required to have a study entry value that was ≤1.25 times the upper limit of normal (ULN) for the coagulation test being examined. Baseline coagulation test results were within the normal range for all subjects except for aPTT (mean 30.6 s; range 23.6-41.0 s) and DRVVT (mean 38.6 s; range 25.0-61.6 s).

Conclusion: With respect to the safety and pharmacological conditions of oritavancin, the results of this study demonstrate that the phospholipid-dependent coagulation tests were not affected by a single intravenous dose of oritavancin in fasting healthy volunteers and the time to resolution for all these tests was within the range of time for the baseline coagulation test.

Disclosures

Support and funding for this study was provided by The Medicines Company.

References


Conclusions

• A single dose of oritavancin was assessed in fasting healthy volunteers and the results of some phospholipid-dependent coagulation tests were concentration-dependent, as evident by the effects of oritavancin on phospholipid-activated samples (Table 1).

• Oritavancin had no effect on the coagulation tests performed following a single 1200 mg dose in fasting in vitro studies (Table 1). Thus, the estimates of time to resolution of phospholipid-dependent coagulation test is subject to expect those in in vivo studies.

• A relationship between oritavancin concentration and interference of coagulation tests in vitro occurs in a concentration-dependent manner.

Table 2. Oritavancin causes variable prolongation of the phospholipid-dependent assays PT/INR or aPTT determined in plasma from subjects in the phase 1 study and patients in the SOLO phase 3 studies.

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Figure 2. Increases in PT or aPTT in the phase 1 study are dependent on the oritavancin plasma concentrations determined in subjects.

Figure 3. The maximum time-to-resolution of test interference varies among coagulation tests determined in subjects administered a single 200 mg dose of oritavancin in the phase 1 study.

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The maximum time-to-resolution of test interference was determined using drug and maximum values, defined as the interval from the start of drug exposure to the time point at which 90% of subjects reached resolution (P90).