In Vivo Activity of Oritavancin in Animal Infection Models and Rationale for a New Dosing Regimen in Humans

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Oritavancin is a novel glycopeptide antibiotic with concentration-dependent killing of Gram-positive cocci and pharmacokinetics characterized by extensive tissue distribution and a long terminal half-life. Its development was hindered by a 16- to 32-fold underestimation of activity against staphylococci and enterococci because of oritavancin’s sticking to vials and tubes. Dose-fractionation studies in animal models suggested the peak concentration was the major index for efficacy. Once-daily intravenous administration of oritavancin was effective in methicillin-resistant *Staphylococcus aureus* (MRSA) endocarditis, penicillin-susceptible and cephalosporin-resistant pneumococcal meningitis in rabbits, staphylococcal and enterococcal central venous catheter infections in rats, and 24-hour postprophylaxis of inhaled anthrax in mice. Orally administered oritavancin was more effective than vancomycin in *Clostridium difficile* infection in hamsters. Pharmacodynamics suggested that a single dose of oritavancin at 1200 mg would be efficacious in humans. Simulation of this dose in neutropenic mice was highly effective in methicillin-sensitive *S. aureus* and MRSA thigh and bacteremia infections and pneumococcal lung infections.

In 1994, Eli Lilly designated oritavancin (LY333328) a candidate for clinical development. It was active against most Gram-positive pathogens including resistant strains. The minimum inhibitory concentrations (MICs) for oritavancin against methicillin-sensitive *Staphylococcus aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), and enterococci were thought to be similar or slightly lower than vancomycin; however, the drug maintained activity against vancomycin-resistant enterococci [1]. In fact, some studies demonstrated that oritavancin differed from vancomycin by exhibiting concentration-dependent killing with staphylococci and both vancomycin-susceptible and vancomycin-resistant *Enterococcus faecium* [2, 3]. Oritavancin also had MICs against *Streptococcus pneumoniae* that were 32- to 64-fold lower than those of vancomycin [1, 4].

The pharmacokinetics of oritavancin in animals and humans were likewise different than vancomycin. Oritavancin has a very long terminal half-life of about 16 days because of slow release of the drug from tissue accumulation sites [5]. A long terminal half-life is also observed in animals [6]. At most of the doses initially evaluated in animals and in humans, the terminal half-life began at plasma concentrations of $\geq 4 \mu g/mL$. It was felt that these concentrations were too low to exert much antimicrobial activity when the MICs for staphylococci and enterococci ranged from 0.5 to 4 $\mu g/mL$ and the drug had significant protein binding. However, doses of oritavancin higher than the 200 and 300 mg initially studied in patients could raise these terminal drug concentrations and contribute more to the total antimicrobial effect. Lower MICs for oritavancin against staphylococci and enterococci than initially reported would have the same beneficial effect.
But it was not until the mid-2000s that it was fully appreciated that oritavancin had a propensity to stick to plastic tubes and wells used for microdilution tests [7]. It was shown that inclusion of 0.002% polysorbate 80 interferes with oritavancin sticking to plastic and reduced the MICs against staphylococci and enterococci approximately 16- to 32-fold [7]. The polysorbate 80 did not alter the MICs against pneumococci, which were already 32- to 64-fold lower than vancomycin, as the standard medium requires supplementation with 5% lysed horse blood that also prevents sticking to plastic. Thus, higher doses and lower MICs can provide rationale for new dosing regimens of oritavancin.

The remainder of this review will compare the pharmacokinetics of oritavancin in various animals and in humans. We will also discuss the basic pharmacodynamics of oritavancin and its efficacy in a variety of animal infection models, such as endocarditis, bacteremia, intravenous catheter–related infections, pneumonia, meningitis, anthrax prophylaxis, and Clostridium difficile colitis. Unfortunately, most of the studies were performed before it was appreciated that the MICs of oritavancin for staphylococci and enterococci were underestimated in broth media without polysorbate 80. Last, we will provide the scientific rationale for a new dosing regimen of oritavancin that is currently in clinical trials.

**PHARMACOKINETICS**

The plasma profile of oritavancin is most commonly characterized by a 3-compartment model with a very prolonged terminal half-life [5]. The plasma concentrations over time following intravenous dosing of oritavancin in mice and rabbits at 20 mg/kg and a model predicted dose in humans adjusted to reflect a 3-hour infusion of 1200 mg are shown in Figure 1 [5, 6, 8]. After a rapid initial distribution phase, oritavancin has a second slightly slower and longer elimination phase of 12–24 hours, followed by a very long terminal half-life. The terminal half-life is about 40 hours in mice and rabbits and 393 hours in humans. One can see from the figure that the terminal elimination half-life starts at concentrations of approximately ≤1 µg/mL in animals. However, with the large intravenous dose of oritavancin at 1200 mg, the terminal half-life is predicted to start at concentrations of 15–20 µg/mL.

Significant protein binding can reduce active free drug concentrations, and early studies of protein binding of oritavancin were complicated by the drug binding to filters and dialysis membranes. This problem was solved by comparing arithmetic MICs using small changes in drug concentration in plasma and plasma ultrafiltrate [9]. The MIC for a strain of Staphylococcus aureus varied from 7.8-fold higher in dog serum to 5.5-fold higher in human serum than in serum ultrafiltrate from the same species. This suggests that the protein binding of oritavancin is 85% with little variation among various animal species.

The drug has extensive tissue distribution and accumulates in lysosomes of many eukaryotic cells [10]. The drug is apparently not metabolized and is eliminated from tissue sites exceedingly slowly, with <5% recovered in the urine and <1% in the feces over 7 days after dosing [11]. The penetration of oritavancin into blister fluid in humans provides very stable concentrations that provide an area under the curve (AUC) that is about 18% of the AUC in serum [12]. However, from 12 to 24 hours after a single 800-mg dose of oritavancin, the blister fluid concentration was approximately one-third of the simultaneous plasma concentration. At 7 days after this same single dose, the plasma concentration was still approximately 3 µg/mL, so one would expect the blister concentrations to be about 1 µg/mL. Although such interstitial fluids have lower albumin concentrations than in plasma, the degree of oritavancin protein binding in these fluids is unknown but probably less than in plasma. Even if one assumes that binding is the same as in
plasma, the free drug concentration would be about 0.15 µg/mL. With the higher dose of 1200 mg, the predicted free drug concentrations at 7 days would be approximately 0.25 µg/mL, which is 2-fold higher than the MIC₉₀ (MIC for 90% of strains tested) for oritavancin against \textit{S. aureus} [7]. Thus, one would expect excellent activity of this dose against various pathogens in skin and soft tissue infections. In the neutropenic mouse-thigh infection model, simulation of the human equivalent of a single 1200-mg dose in mice resulted in 2–4 logs of kill for multiple strains of MSSA and MRSA at 72 hours after dosing [13].

**PHARMACOKINETIC/PHARMACODYNAMIC INDEX DETERMINING IN VIVO EFFICACY**

The usual methodology used to determine which pharmacokinetic/pharmacodynamic index best predicts in vivo efficacy is to apply dose fractionation at different dosing intervals over several total doses and correlate the resulting efficacy for each regimen with its C\textsubscript{max} (maximum serum concentration)/MIC, AUC/MIC, and duration of time–plasma concentration exceeding the MIC. Because protein binding reduces antimicrobial activity, the plasma concentrations used for these calculations are those for free unbound drug. Boylan et al [6] did such a study for oritavancin against a strain of \textit{S. aureus} in the neutropenic mouse-thigh model using total doses of 0.5, 1, 2, 4, and 16 mg/kg administered over 24 hours as a single dose, 2 divided doses every 12 hours, 3 divided doses every 8 hours, or 4 divided doses every 6 hours. Plasma radioequivalent concentrations over time were determined using \textsuperscript{14}C oritavancin at doses of 0.5, 1, 5, and 20 mg/kg. The relationships between efficacy and C\textsubscript{max}, AUC, and time above the MIC are shown in Figure 2 using a logarithmic scale that was not used in the initial article [6]. The pharmacokinetic index best predicting the activity of oritavancin was C\textsubscript{max} (r\textsuperscript{2} = 96%). This was followed by time above MIC and AUC (r\textsuperscript{2} = 83% and 77%, respectively). However, the MIC for this strain of \textit{S. aureus} was performed in broth without polysorbate 80, so one would expect much lower MICs resulting in times above MIC with most regimens of 100%.

There are several other studies showing improved activity when oritavancin is administered as infrequent large doses rather than as multiple small doses. In a peritonitis model in mice infected with \textit{S. pneumoniae}, the 50% effective dose (ED\textsubscript{50}) of oritavancin in preventing mortality was lowest when a single dose was given once over 48 hours and highest when the drug was administered every 2 hours for 48 hours [14]. The ED\textsubscript{50} for dosing regimens between these 2 extremes gave intermediate values. In another study, rats with subcutaneously tunneled catheters inserted into jugular veins and inoculated with 10\textsuperscript{5} colony-forming units (CFUs) of \textit{S. aureus} received 6 days of treatment with intravenous oritavancin at 2.5 mg/kg every 12 hours, 5 mg/kg every 24 hours, 10 mg/kg every 48 hours, or 20 mg/kg every 96 hours [15]. The overall infection rate and number of CFUs in the catheters demonstrated that large doses given less frequently were superior to smaller doses given more frequently.

**ENDOCARDITIS**

One of the first models to document the bactericidal activity of new drugs such as oritavancin was its efficacy in experimental endocarditis. Oritavancin was compared with vancomycin using the rabbit model of left-sided MRSA endocarditis.
Mycin was only effective for the susceptible strain of the susceptible strain and the VanB phenotype. Last, vancomycin was less active than controls for Gram of vegetation that was significantly less than controls for the other organisms present in the vegetation at the start of therapy was the same organisms were studied but now the number of organisms in the vegetation was heterogeneous with a maximal 1.8-fold difference in concentration among various regions of the vegetation. However, there was no decreasing concentration gradient between the untreated controls. The distribution of radiolabeled oritavancin in the vegetation was approximately 4.8 logs. Oritavancin appeared to have an advantage over the other drugs in reducing relapse 3 days after stopping therapy. Bioluminescent assessments were also performed in this study, but bioluminescence was detected and increased over time primarily in the controls, which produced colony counts >10^5, which was the lower limit of detection with this technique.

A major drawback of most endocarditis models is that they do not measure the bacterial density at the beginning of therapy so one can quantify the degree of killing and be sure that some apparent killing does not reflect growth or only a bacteriostatic effect. This problem is addressed in 1 of 2 additional endocarditis studies in rabbits with a susceptible strain of *E. faecalis* and 1 each vancomycin-resistant strain with VanA and VanB phenotypes. In the first study, controls after 5 days were compared with various intramuscular treatments for 5 days with oritavancin and teicoplanin at 20 mg/kg twice daily after a loading dose of 40 mg/kg, and vancomycin at 50 mg/kg twice daily [18]. Only oritavancin had CFUs per Gram of vegetation that was significantly less than controls for all 3 organisms. Teicoplanin was less active than controls for the susceptible strain and the VanB phenotype. Last, vancomycin was only effective for the susceptible strain of *E. faecalis*. The distribution of radiolabeled oritavancin in the vegetation was heterogeneous with a maximal 1.8-fold difference in concentration among various regions of the vegetation. However, there was no decreasing concentration gradient between the periphery and the core of the vegetation. In the second study, the same organisms were studied but now the number of organisms present in the vegetation at the start of therapy was reported, as well as CFUs in the untreated controls and those receiving various therapies over 5 days [19]. The mean number of organisms at the beginning of therapy was 1.4–2.4 logs lower than at the end of therapy. Oritavancin was administered intravenously in this study but only at 20 mg/kg daily for 5 days with each organism. Gentamicin alone and in combination with oritavancin was also administered intramuscularly at 3 mg/kg twice daily for 5 days against all 3 strains. The daily regimen of oritavancin, which was about half the dose previously studied, was less effective against all 3 organisms than it was in the earlier study. However, the greatest efficacy against all 3 organisms were observed when daily oritavancin was combined with twice-daily gentamicin. Yet the overall mean reduction in organisms from the starting inoculum was modest at 1.5 logs for the susceptible strain, 1.2 logs for the VanB strain, and only 0.3 logs for the VanA strain. There are no data yet on oritavancin in experimental *E. faecium* endocarditis, whereas in vitro studies demonstrate a much better bactericidal activity with oritavancin than with vancomycin [20].

## BACTEREMIA AND CENTRAL VENOUS CATHETER INFECTIONS

A bacteremia model was established in normal mice by intraperitoneal injection of 10^7 CFUs of *S. aureus* in 5% gastric hog mucin [21]. One hour after infection, mice were treated intravenously with oritavancin simulating human doses of 100, 400, and 800 mg daily for 3 days and a single dose of 1200 mg. The initial level of *S. aureus* in the blood was approximately 4.8 logs. The level of bacteremia rapidly increased in untreated mice, resulting in death by 24 hours. The 100-mg daily human equivalent dose reduced the bacteremia by 1.7 logs by 72 hours, whereas the other doses reduced the number to the limit of detection or by about 2.8 logs. The number of organisms in the spleen was also determined at 3 days and showed reductions of CFUs by 1.3, 1.8, 2.4, and 1.8 logs for human equivalent doses of 100, 400, and 800 mg daily and a single human equivalent dose of 1200 mg.

Intracellular staphylococci can be a cause of persistent bacteremia despite appropriate therapy. Strains of *S. aureus* in a patient who had failed therapy with daptomycin and vancomycin showed excellent intracellular bactericidal activity with oritavancin resulting in over 2.5 logs of killing in 24 hours [22]. Oritavancin also had greater and faster intracellular killing of a small-colony variant of *S. aureus* from a cystic fibrosis patient that was superior to the killing observed with other antimicrobials [23].

As stated previously, large infrequent doses of oritavancin were more effective than multiple small doses of the drug against *S. aureus* in a central venous catheter infection in rats [15]. In a similar model infected with a strain of *E. faecium* with the VanA phenotype, a single intravenous dose of oritavancin at 20 mg/kg was compared with no therapy [24]. On day 8, 87% of untreated...
controls still had infected catheters and 100% had metastatic infections in other tissues, whereas only 12% of those receiving the single intravenous dose of oritavancin had infected catheters and there were no metastatic infections.

**PNEUMONIA**

In the neutropenic mouse model, efficacy of oritavancin against *S. pneumoniae* was very similar in the lungs and thighs of simultaneously infected mice (see Figure 3) [25]. In this model, lung infection resulted from inhalation or aspiration of the inoculum from the nasopharynx. Single intravenous doses of oritavancin of 1–3 mg/kg were associated with stasis over 3 days, whereas doses of ≥10 mg/kg resulted in ≥3 logs of killing at 72 hours [25, 26]. Oritavancin does bind to surfactant but at a much lower extent than daptomycin. As shown in Table 1, the oritavancin MIC against *S. pneumoniae* ATCC 6303 in the presence of 0.002% polysorbate 80 increased 8-fold when exposed to 5% surfactant [26]. Still, the resulting MIC was 0.008 μg/mL, which should be treatable with most of the doses used in humans. In contrast, the oritavancin MIC against *S. aureus* ATCC 29213 in polysorbate 80 increased from 0.06 to 1 μg/mL (16-fold) and would be much harder to treat even with a single intravenous dose of 1200 mg. The MIC of daptomycin for the same strain of *S. aureus* increased from 0.5 to 128 μg/mL (256-fold) when exposed to surfactant, which makes daptomycin ineffective for inhaled or aspirated infections with staphylococci.

A hematogenous pneumonia infection model with a strain of MRSA was established in rats in which binding to surfactant would have less of an effect on activity [27]. Rats were treated for 6 days with daily intravenous doses of oritavancin at 50 mg/kg, daily subcutaneous doses of vancomycin at 100 mg/kg, or daptomycin at 50 mg/kg, and twice-daily subcutaneous doses of nafcillin at 150 mg/kg. On day 7 oritavancin was the most effective agent, resulting in 3.5 logs of killing. Daptomycin was next, resulting in 2.4 logs of killing. Vancomycin resulted in only 1.3 logs of killing, and nafcillin was no different than untreated controls as one would expect for MRSA. The daily dosing regimen for vancomycin was not optimal because of the relatively rapid clearance of this drug in rats. No data were provided on 2 or 3 times per day dosing of vancomycin.

**MENINGITIS**

Because of the very low MICs for oritavancin against *S. pneumoniae*, oritavancin has been evaluated in the standard meningitis model in rabbits [28]. The pneumococcal strain used was a serotype 3 with a MIC and minimum bactericidal concentration (MBC) for oritavancin of 0.015 and 0.03 μg/mL, respectively. Rabbits received single doses of oritavancin at 1, 2.5, 10, and 40 mg/kg infused intravenously over 30 minutes. Ceftriaxone was used as a positive control and was administered as a bolus of 20 mg followed by a continuous infusion of 10 mg/kg/hour. Based on a comparison of AUC in cerebrospinal fluid (CSF) to serum, the penetration of oritavancin into CSF was about 2%–5%. Mean maximum CSF concentrations for doses of 2.5, 10, and 40 mg/kg were 0.54, 0.76, and 1.36 μg/mL, respectively. Concentrations did not change much over the 12 hours of study and were ≥10 times the MBC for oritavancin against this strain, although binding to CSF albumin could have reduced this ratio. Overall, a dose of 1 mg/kg of oritavancin was only bacteriostatic, whereas doses of 2.5 mg/kg and 10 mg/kg of oritavancin were similar in efficacy to ceftriaxone. However, 40 mg/kg of oritavancin (studied in only 2 rabbits) resulted in faster killing over 12 hours than ceftriaxone.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Drug</th>
<th>MIC (μg/mL) Without 5% Surfactant</th>
<th>MIC (μg/mL) With 5% Surfactant</th>
<th>Fold Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. pneumoniae</em></td>
<td>Oritavancin</td>
<td>0.001</td>
<td>0.008</td>
<td>8</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>Oritavancin</td>
<td>0.03</td>
<td>1.0</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Daptomycin</td>
<td>0.5</td>
<td>128</td>
<td>256</td>
</tr>
</tbody>
</table>

All MICs were performed with 0.002% polysorbate 80.

Abbreviation: MIC, minimum inhibitory concentration.
In another study using the rabbit meningitis model, oritavancin was compared with ceftriaxone against a cephalosporin-resistant strain of *S. pneumoniae* [29]. The strain was a serotype 23F with a ceftriaxone MIC of 2 μg/mL and an oritavancin MIC of 0.008 μg/mL. Rabbits received doses of 10 mg/kg of oritavancin and 100 mg/kg of ceftriaxone, which resulted in similar efficacy. The use of both drugs in combination did not result in any in vivo synergy.

There have been no studies examining the efficacy of oritavancin against *S. aureus* or coagulase-negative staphylococci in animal meningitis models. The latter organisms are common causes of CSF shunt infections. Now that it is known that the true oritavancin MICs against coagulase-negative staphylococci are usually 0.03–0.06 μg/mL, oritavancin might be an effective alternative for treatment of these infections.

**ANTHRAX PROPHYLAXIS**

Oritavancin has been studied as an alternative agent to ciprofloxacin for prophylaxis against inhaled *Bacillus anthracis* [30]. The efficacy of oritavancin administered intraperitoneally for 14 days or as a single intravenous dose in a mouse model of inhaled anthrax is shown in Figure 4. For 24 hours postchallenge 100% protection is observed with oritavancin at doses as low as 3 mg/kg intraperitoneally for 14 days and at 50 mg/kg as a single intravenous dose. Decreasing doses are associated with increasing mortality. At 42 hours postchallenge a single dose of oritavancin at 50 mg/kg dose results in only 55% survival. Similarly, 48 hours postchallenge the efficacy of 10 mg/kg intraperitoneally every 48 hours for 14 days falls to only 50% protection. In addition, pretreatment of mice with a single 50-mg dose of oritavancin for up to 14 days prior to challenge resulted in 100% protection from death. On the other hand, pretreatment of mice with ciprofloxacin for 24 hours before challenge resulted in 100% death by 5 days. Further study of oritavancin for prophylaxis against inhaled anthrax needs to be conducted in nonhuman primate models.

**C. DIFFICILE COLITIS**

Oritavancin has also been evaluated as oral therapy for *C. difficile* colitis with some interesting results. The drug is active against the organism even in its spore form [30]. In the hamster model of *C. difficile* infection with mortality over time as the outcome, oritavancin at 50 mg/kg and 100 mg/kg has been more effective than vancomycin at 50 mg/kg [31]. Although therapy with the vehicle alone (85% polyethylene glycol 400) resulted in 100% mortality, 50 mg/kg of vancomycin for 5 days resulted in 40% survival at day 28. Oritavancin at 50 mg/kg and 100 mg/kg in the same formulation and duration of therapy resulted in 80% and 100% survival, respectively. The drug has <0.1% bioavailability following oral therapy in hamsters [32]. In an in vitro model to simulate human *C. difficile* infection, therapy with vancomycin and oritavancin both reduced vegetative *C. difficile* numbers and the production of cytotoxin, but only oritavancin reduced the number of spores [31]. After stopping therapy there was a recrudescence in *C. difficile* numbers and cytotoxin production with vancomycin, but not with oritavancin.

**RATIONALE FOR THE ORITAVANCIN DOSING REGIME**

Two observations, one pharmacodynamic and the other pharmacokinetic, form the basis for oritavancin’s unique 1200-mg single-dose regimen for the treatment of acute bacterial skin and skin structure infections. First, oritavancin displays a concentration-dependent pattern of in vitro bactericidal activity [20]. That is, as drug concentration increases, so too do the rate and extent of bacterial killing. Second, from a pharmacokinetic perspective, oritavancin’s profile is distinguished from most other antimicrobial agents by a long terminal elimination half-life (360 hours), which results in marked accumulation over time [5]. One consequence of this observation is that with a fixed-dose strategy, such as 200 mg once daily, it would take oritavancin many days to reach steady-state exposures in patients. This is exactly what we do not want clinically; the goal clinically is to have the greatest drug exposure early in drug therapy to maximize the probability of positive clinical outcomes.
Thus, oritavancin’s unique pharmacokinetic and pharmaco-
dynamic profile led to a hypothesis that administering front-
loaded exposures would result in improved efficacy relative to
that of standard fixed dosing strategies. To test this hypothesis,
the neutropenic murine-thigh infection model was used. This
model is appropriate, as results from this model have been used
to forecast efficacy in patients with acute bacterial skin and
skin structure infections [34].

The study design used in these models was different than
most animal studies in that oritavancin was dosed in a manner
that resulted in concentration–time profiles that more closely
mimicked that expected in humans [35]. Of the oritavancin
regimens evaluated, one mimicked a 400-mg once-daily
regimen for 3 days in humans and the other mimicked a single
1200-mg dose. In both instances, the challenge isolates (n = 5,
including MSSA, MRSA, and vancomycin-resistant S. aureus)
were the same with oritavancin MIC values ranging from
0.06 mg/L to 0.25 mg/L.

Figure 5A shows the results for a representative isolate
(MSSA ATCC 13709) of the 400-mg once-daily study, whereas
Figure 5B shows results for the 1200-mg single-dose study. In
each panel, oritavancin drug concentration and the bacterial
burden (CFUs) over time are shown. When comparing the
differences in CFUs between experiments, there are 2 note-
worthy observations. First, there is less CFU variability over
time for the 1200-mg single-dose regimen relative to that of the
400-mg once-daily regimen. Second, the 1200-mg regimen re-
sulted in a reduction in the CFUs over the time course of the
experiment, whereas the 400-mg once-daily regimen did not.
Because of the more rapid drug elimination of oritavancin in
mice than in humans, additional smaller drug doses were ad-
ministered at various times to mice to simulate human AUCs
for both the daily 400-mg doses and the single 1200-mg dose.
It is especially important to note that in both the 400-mg
once-daily and 1200-mg studies, the same oritavancin expo-
sure, as measured by the AUC, was administered to the mice
and had markedly different effects. The peak concentrations
at 24 and 48 hours in the mice resulting from simulation of
the single human 1200-mg dose were still lower than those
observed in the simulation of daily human 400-mg doses ad-
ministered at the same time. The key result from these studies
was that the shape of the oritavancin AUC mattered, which
supported the hypothesis that front-loading oritavancin expo-
sure would lead to greater efficacy.

Based on the animal model observations, a phase 2 study
in patients with acute bacterial skin and skin structure in-
fecions was undertaken to further test the hypothesis [36].
In brief, a total of 302 patients were randomized into 1 of
3 treatment groups of equal size. The first group received

Table 2. Clinical Response at the Test-of-Cure Visit for Patients
Treated With 3 Different Oritavancin Dosing Regimens for Acute
Bacterial Skin and Skin Structure Infections

<table>
<thead>
<tr>
<th>Population</th>
<th>200 mg Daily for 3–7 d</th>
<th>800 mg on Day 1 ± 400 mg on Day 5</th>
<th>1200 mg Single Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT (n = 300)</td>
<td>72.4</td>
<td>78.2</td>
<td>81.8</td>
</tr>
<tr>
<td>Clinically evaluable (n = 228)</td>
<td>72.4</td>
<td>77.5</td>
<td>81.5</td>
</tr>
<tr>
<td>Microbiologically evaluable (n = 161)</td>
<td>69.1</td>
<td>81.3</td>
<td>79.3</td>
</tr>
</tbody>
</table>

Abbreviation: ITT, intend to treat.
oritavancin 200 mg once daily for 3–7 days, the second group received 800 mg on day 1 of therapy plus a 400-mg dose on day 5 at the discretion of the treating physician, whereas the third group received a single 1200-mg dose. Table 2 shows the top-line results from the study. Note that regardless of the patient population evaluated, as early exposure intensity increases, so too does the clinical response rate. These clinical data further supported the hypothesis that administering front-loaded oritavancin exposures would result in improved efficacy relative to that of standard fixed dosing strategies.

Currently, 2 large randomized phase 3 studies are under way in which the safety and efficacy of a single 1200-mg oritavancin dose is being compared with that of vancomycin for the treatment of acute bacterial skin and skin structure infections (ClinicalTrials.gov: NCT01252719 and NCT01252732). From a pharmacokinetics/pharmacodynamics perspective, such a regimen offers a number of advantages. First, as demonstrated in the murine-thigh infection models, front-loading oritavancin exposure results in more rapid and complete bacterial killing. Second, having the highest oritavancin exposure at the time of greatest bacterial density results in the greatest kill possible, which is predicted to optimize the likelihood of positive clinical outcome, reduce the likelihood of spontaneous mutation and offer the best chance to eradicate a preexisting resistant subpopulation of bacteria.

Notes

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