Oritavancin Program Results

July 2nd 2013

Presenters
Greg Moeck PhD | Background and rationale
Dimitri Goundis DPhil | Clinical program results
Clive Meanwell MD PhD | Discussion
Oritavancin

Overview of the development program

- Background and Rationale
  - Greg Moeck

- Phase III Clinical Studies
  - Objectives
  - Patients and Methods
  - Results
  - Conclusions
  - Dimitri Goundis

- Discussion
  - Clive Meanwell
Oritavancin Program Results

Background and Rationale

Greg Moeck PhD
Background

*Staphylococcus aureus* including MRSA infections

478,000 hospitalizations in U.S. hospitals 2007
- 278,000 related to MRSA
- 64% of *S. aureus* infections in U.S. ICUs were MRSA by 2004

94,000 persons first invasive MRSA - 19,000 died 2005

14 million outpatient healthcare visits for suspected *S. aureus* skin and soft tissue infections in US 2005

Kleven RS et al. *Clinical Infectious Diseases* 2006;42:389-91
Hersh AL et al. *Arch Intern Med*. 2008;168:1585-91
Background

Oritavancin

Bacteriocidal lipoglycopeptide antibiotic for IV use

Three mechanisms of action:

• Inhibits two key steps of cell wall synthesis:
  - Transglycosylation
  - Transpeptidation

• Disrupts bacterial membrane integrity

Differentiated from vancomycin

• Increased potency and expanded Gram-positive spectrum
• Concentration-dependence
Background
Oritavancin

High level potency against important G+ organisms

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Oritavancin (µg/mL)</th>
<th>Vancomycin</th>
<th>Daptomycin</th>
<th>Linezolid</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>0.06</td>
<td>1</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>MSSA</td>
<td>0.06</td>
<td>1</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>MRSA</td>
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<td>1</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>β streptococci</td>
<td>0.12</td>
<td>0.5</td>
<td>0.25</td>
<td>1</td>
</tr>
<tr>
<td>E. faecalis</td>
<td>0.06</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>E. faecium</td>
<td>0.06</td>
<td>&gt;16</td>
<td>2</td>
<td>2</td>
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</table>

US and European isolates collected between 2010-2012
Concentration-dependent killing

*In vitro* time-kill study with *S. aureus*

Effect on NRS384 CA-MRSA (USA300)

**Oritavancin**

**Vancomycin**
Clinical proof of concept
SIMPLIFI Phase II Study in ABSSSI

Clinical cure in clinically evaluable patients

Dunbar et al. AAC 2011; 55: 3476-84
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Phase III Clinical Studies

Dimitri Goundis DPhil
Oritavancin Phase III Clinical Studies

SOLO program overview

Two identical double-blind randomized controlled studies

ABSSSI due to gram positive organisms including MRSA

Active comparator – vancomycin

Recruitment in United States, Europe and Asia

Protocols based on current regulatory guidance

Non-inferiority design
Oritavancin Phase III Clinical Studies

Primary objectives of both studies for FDA | EMA

**FDA:** To determine non-inferiority for the primary efficacy outcome (as defined by the cessation of spread or reduction in size of the baseline lesion, absence of fever and no rescue antibiotic medication) at Early Clinical Evaluation (ECE) at 48 to 72 hours with single dose IV oritavancin compared with IV vancomycin for 7 to 10 days in the modified intent-to-treat (mITT) population.

**EMA:** To determine non-inferiority for the investigator-assessed clinical cure of treatment with single-dose IV oritavancin compared with IV vancomycin for 7 to 10 days at the post-therapy evaluation (PTE) visit in the mITT population.
Oritavancin Phase III Clinical Studies

Patient eligibility criteria

- At least 18 years of age
- Suspected or proven gram-positive pathogen
- Requiring at least 7 days of IV therapy
- ABSSSI
  - Wound infections (either traumatic or surgical in origin)
  - Cellulitis/erysipelas
  - Major cutaneous abscess
- Each lesion at least 75 cm²
- Signs and symptoms of systemic inflammation.
Oritavancin Phase III Clinical Studies

Treatment randomization

1:1 ratio

**Oritavancin:** Single 1200 mg IV dose of oritavancin followed by IV placebo for 7 to 10 days

**Vancomycin:** 1 g or 15 mg/kg, every 12 hours for 7 to 10 days

Aztreonam and metronidazole were permitted for gram-negative and anaerobic coverage, respectively.
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Pre-specified endpoints (mITT)

Early – at 48-72 hours (ECE)

- **FDA primary composite outcome**
  - Cessation of spread or reduction in size of baseline lesion
  - Absence of fever
  - No rescue antibiotic medication

- **FDA exploratory outcome**
  - At least 20% reduction in lesion area

Post-treatment 7-14 days (PTE)

- **EMA primary composite outcome**
  - Investigator-assessed clinical cure
Oritavancin Phase III Clinical Studies

SOLO-I: primary efficacy (N = 954)

Non-inferiority margin of -10% was met
Oritavancin Phase III Clinical Studies

SOLO-II: primary efficacy (N = 1,005)

Non-inferiority margin of -10% was met
Oritavancin Phase III Clinical Studies
Combined: primary efficacy (N = 1,959)

Non-inferiority margin of -10% was met
Oritavancin Phase III Clinical Studies
Combined MRSA: primary efficacy (N = 405)

Non-inferiority margin of -10% was met
Oritavancin Phase III Clinical Studies
Adverse events including 60-day follow-up period

Favorable comparative results

<table>
<thead>
<tr>
<th></th>
<th>SOLO-I N = 954</th>
<th>SOLO-II N = 1,005</th>
<th>COMBINED N = 1,959</th>
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<tbody>
<tr>
<td>Any AE</td>
<td>ORIT 60% VANC 64%</td>
<td>ORIT 51% VANC 50%</td>
<td>ORIT 55% VANC 57%</td>
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<td>TEAEs</td>
<td>ORIT 23% VANC 31%</td>
<td>ORIT 22% VANC 26%</td>
<td>ORIT 22% VANC 28%</td>
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<tr>
<td>Discontinued due to AEs</td>
<td>ORIT 4% VANC 6%</td>
<td>ORIT 4% VANC 3%</td>
<td>ORIT 4% VANC 4%</td>
</tr>
</tbody>
</table>
Summary
Oritavancin met all prespecified objectives

In two double-blind, randomized, active controlled ABSSSI trials, oritavancin given as a single IV dose:

• Demonstrated clinical non-inferiority to vancomycin given intravenously twice daily for 7-10 days

• Was effective in MRSA infections

• Was associated with favorable safety results
Oritavancin Program Results

Discussion

Clive Meanwell MD PhD