Role of Extended Dosing Interval Antimicrobials in OPAT

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**DISCLOSURE**

_Urania Rappo_ is an employee of Allergan plc and holds stock in Allergan plc
OVERVIEW

- Increasing use of **long-acting antimicrobials and less frequent dosing** in infections requiring prolonged courses of IV antibiotic therapy
  - Osteomyelitis, endocarditis, bacteremia, other infections
- **Dalbavancin**: data from randomized clinical trial using 2-dose regimen for 6 week course; other available data
- **Oritavancin**: available data using extended dosing intervals
- **Teicoplanin**: 3x/week dosing
- **Amikacin**: 3x/week dosing
Dalbavancin
Osteomyelitis in Adults

• Major clinical challenge with potential for poor outcomes, including amputations

• **Diagnosis** by bone biopsy with culture in conjunction with clinical symptoms, elevated inflammatory markers such as CRP, and radiologic findings

• **Debridement** of infected tissue and surgical resection of necrotic bone often needed

• **Staphylococcus aureus** most commonly isolated pathogen in adults

• Requires **prolonged (4–6+ weeks) parenteral and oral antibiotics**
  - Antistaphylococcal penicillins (nafcillin/oxacillin), clindamycin, first-generation cephalosporins (cefazolin), and vancomycin are the typical antimicrobials of choice
  - **Increasing incidence of MRSA** and **methicillin-resistant coagulase-negative staphylococci** often require use of vancomycin
    • Vancomycin requires indwelling catheter, monitoring of serum drug levels and careful dose adjustments to maintain appropriate levels in the blood
  - **Better treatment options are needed** which would not require long-term daily IV or oral antibiotics

MRSA=methicillin-resistant Staphylococcus aureus; CRP=C-reactive protein

DALBAVANCIN

• A long-acting lipoglycopeptide antibiotic
  – Terminal **half-life of 14.4 days**¹
  – Structurally related to teicoplanin²

• Mechanism of action: inhibits cell wall synthesis

• No known drug-drug interactions

• **Potent** activity against Gram-positive pathogens, including MRSA
  – **MIC**₉₀ of dalbavancin for *S. aureus* (MRSA and MSSA) is 0.06 µg/mL, with 99.9% of organisms inhibited at 0.12 µg/mL³,⁴
  – 16-fold more potent compared to vancomycin; 8-fold more potent compared to daptomycin³

• Extensive clinical trial data
  – 17 Phase 1, 2 Phase 2, and 6 Phase 3 studies

• Approved for the treatment of acute bacterial skin and skin structure infection (ABSSSI) in adults in the United States and European Union as a 30 minute infusion administered as a single dose regimen (1500 mg IV) or as a 2-dose regimen (1000 mg IV followed 1 week later by 500 mg) in 300 mL ¹,⁵

BACKGROUND
Phase 1 Studies on Distribution of Dalbavancin in Bone and Articular Tissue and Extended-Duration Dosing
## Dalbavancin Bone Concentrations

- **Phase 1** **bone penetration study** evaluated the PK of dalbavancin in **bone & articular tissue** in 30 healthy volunteers who received dalbavancin up to 14 days before elective orthopedic surgery
  - Mean dalbavancin levels in bone were **6.3 µg/g at 12 hours** and were sustained **2 weeks later at 4.1 µg/g**, after a 1000 mg IV infusion
- **Mean bone:plasma AUC penetration** ratio was 13%

### Dalbavancin Concentration (Mean ± SD) at Post-dose Sample Collection Timepoint

<table>
<thead>
<tr>
<th></th>
<th>12 h (0.5 days)</th>
<th>24 h (1 day)</th>
<th>72 h (3 days)</th>
<th>168 h (7 days)</th>
<th>240 h (10 days)</th>
<th>336 h (14 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma, µg/mL</strong></td>
<td>85.3 ± 18.9 n=31</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>15.3 ± 4.1 n=31</td>
</tr>
<tr>
<td><strong>Synovium, µg/g</strong></td>
<td>25.0 ± 0 n=3</td>
<td>17.9 ± 7.8 n=3</td>
<td>19.5 ± 4.9 n=3</td>
<td>19.2 ± 8.9 n=4</td>
<td>25.0 ± 0 n=2</td>
<td>15.9 ± 7.9 n=3</td>
</tr>
<tr>
<td><strong>Synovial fluid, µg/mL</strong></td>
<td>22.9 n=1</td>
<td>27.4 ± 10.8 n=4</td>
<td>19.2 ± 4.9 n=3</td>
<td>11.6 ± 3.3 n=2</td>
<td>13.9 ± 1.0 n=3</td>
<td>6.2 ± 1.7 n=2</td>
</tr>
<tr>
<td><strong>Bone, µg/g</strong></td>
<td>6.3 ± 3.1 n=5</td>
<td>5.0 ± 3.5 n=5</td>
<td>4.6 ± 3.8 n=5</td>
<td>3.8 ± 2.7 n=5</td>
<td>3.7 ± 2.2 n=5</td>
<td>4.1 ± 1.6 n=5</td>
</tr>
<tr>
<td><strong>Skin, µg/g</strong></td>
<td>19.4 ± 7.9 n=2</td>
<td>12.5 ± 6.5 n=3</td>
<td>13.8 ± 1.4 n=3</td>
<td>15.7 ± 1.0 n=2</td>
<td>21.6 n=1</td>
<td>13.8 ± 2.1 n=2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>†Bone samples and concomitant samples of skin and synovium (and synovial fluid if available) were collected post-dose</td>
</tr>
<tr>
<td>*Mean ± SD plasma concentrations in 31 patients at 772 and 1080 h were 6.2 ± 2.4 and 3.4 ± 1.7, respectively. †Concentrations above the upper limit of quantification are reported as 25 µg/unit</td>
</tr>
<tr>
<td>AUC=area under the curve; MIC&lt;sub&gt;90&lt;/sub&gt;=90% minimum inhibitory concentration; ND=not done</td>
</tr>
</tbody>
</table>

Pharmacokinetic Modeling for Dose Determination

- Phase 1 study was done to evaluate the PK and safety of dalbavancin dosed as 1000 mg IV once, then 500 mg weekly for 7 weeks.
- Population PK modeling from these 2 studies (bone penetration study and extended-duration dosing study) led to proposed dalbavancin dosing regimen for osteomyelitis.
- A 2-dose, 1500 mg once-weekly regimen was proposed for osteomyelitis:
  - Regimen would provide tissue exposure at or above dalbavancin MIC\textsubscript{99.9} of 0.12 µg/mL for \textit{S. aureus} for up to 8 weeks.
  - While drug concentrations above MIC are reassuring, PK/PD parameter most likely to predict efficacy of dalbavancin is AUC/MIC.
  - 2-dose regimen of 1500 mg on day 1 and day 8 would achieve similar area under the curve (AUC) as 1000 mg followed by 4 weekly doses of 500 mg.
  - 2-dose regimen more likely to show clinical benefit based on animal studies showing better outcomes when same total dose delivered in larger amounts earlier and less frequently.

Simulated mean concentration-time profile in bone:
- 1500 mg IV on days 1 and 8.

\begin{itemize}
  \item 1500 mg Day 1
  \item 1500 mg Day 8
\end{itemize}
Phase 2 Randomized Clinical Trial in Adults with Osteomyelitis
OBJECTIVE

To describe the efficacy and safety of dalbavancin for the first episode of osteomyelitis in adults

• Known or suspected to be caused by gram-positive pathogens
METHODS

Single-center, randomized, open-label, active-controlled, parallel-group study comparing dalbavancin with standard of care (SOC) therapy in osteomyelitis in adults (NCT02685033)

- Conducted between **March 2016 and December 2017**
- Cherkasy Regional Hospital, 860-bed tertiary teaching hospital in Cherkasy, Ukraine
  - Site had participated in 3 pivotal dalbavancin ABSSSI trials
  - Large orthopedic referral center for 20 regions, would allow enrollment in reasonable timeframe
  - **Bone biopsy with culture** obtained as standard of care in all patients

IV=intravenous; SOC=standard of care
**Key Inclusion Criteria**

- Diagnosis of **first episode of osteomyelitis** defined as:
  - **Pain or point tenderness** on palpation, or probing to bone  
    AND  
  - **Elevated CRP levels**  
    AND  
  - **X-ray or MRI** consistent with osteomyelitis OR Gram-positive cocci documented on baseline Gram-stain from bone specimen

CRP=C-reactive protein; IV=intravenous; MRSA=methicillin-resistant *Staphylococcus aureus*; SOC=standard of care
KEY EXCLUSION CRITERIA

• >24 hours of IV antibacterial therapy for osteomyelitis within 96 hours of randomization, unless pathogen isolated was documented to be MRSA that was resistant to administered antibiotic

• Prosthetic material at site of infection at time of study initiation

• Prior episode of osteomyelitis or failed course of therapy for osteomyelitis

• Osteomyelitis associated with burn wound, with sacral decubitus ulcer, or with multiple sites of osteomyelitis

• Septic arthritis that is non-contiguous to osteomyelitis diagnosed by isolation of pathogen from synovial fluid culture

• Concomitant endocarditis or necrotizing fasciitis

• Gram-negative bloodstream infection
Randomization and treatment

- Two treatment groups randomized in a 7:1 ratio
  - **Dalbavancin 1500 mg** IV on **day 1** and **day 8**
    - 70 patients
  - **SOC antibiotic** for osteomyelitis based on investigator judgment for 4–6 weeks (IV or oral antibiotic allowed)
    - 10 patients
  - Adjunctive **aztreonam** was permitted at randomization for presumed coinfection with a **Gram-negative pathogen** and a switch to an oral antibiotic for Gram-negative coverage was allowed after clinical improvement
  - Patients with Gram-negative pathogens only in bone cultures at baseline were discontinued from study drug per protocol and received Gram-negative coverage, while continuing safety followup in the study

* Dalbavancin dose was adjusted to 1000 mg IV for patients not on dialysis with a creatinine clearance < 30 mL/min
STUDY DESIGN

Randomization

Dalbavancin
2 doses 1500 mg IV

Comparator
(standard of care, IV/oral)

Day 1  8  15  22  29  42

Clinical Response
6 months
1 year

Clinical Improvement

Day 42 EOT
Primary Endpoint

EOT: End of treatment; IV: Intravenous
**PRIMARY ENDPOINT**

- Clinical response at **Day 42** in the clinically evaluable (CE) population*
  - **Cure**: Recovery without need for further antibiotic therapy
  - **Failure**: Additional antibiotics required, >6 weeks of antibiotic therapy in comparator arm, new purulence, amputation due to infection progression, or death
  - **Indeterminate**: Lost to follow-up or amputation due to vascular insufficiency

CE=clinically evaluable; mITT=modified intent-to-treat

*CE population: subset of mITT population who received ≥1 dose of dalbavancin (or ≥ 2 weeks of comparator), AND ≤ 1 dose of non-study antibiotic for indication other than osteomyelitis
SECONDARY ENDPOINTS

• Clinical improvement at **Day 21 in the modified intent-to-treat (mITT) population** (excludes patients from whom only Gram-negative pathogen was isolated from blood and/or bone culture):
  - No worsening of pain and/or point tenderness relative to baseline, and improvement in inflammation (also assessed at Day 28)
  - CRP improvement measured at **Day 28**

• Clinical response in the **mITT population**:
  - **Day 42** (6 weeks)
  - **6 months** (Day 180)
  - **1 year** (Day 365)

CRP=C-reactive protein
Safety data collected at each visit

- Baseline, Day 1, Day 8, Day 21, Day 28, Day 42, 6 months, 1 year
  - Included adverse events, physical exam
- Chemistry and hematology: Baseline, Day 8, Day 28
- Inflammatory markers
  - CRP and ESR: Baseline, Day 8, Day 28, Day 42, 6 months
81 patients assessed for eligibility

• One screen failure: did not meet inclusion criteria

80 patients randomized to treatment

• IV dalbavancin: 1500 mg on Day 1, 1500 mg on Day 8 (n=70)
  • 67 patients completed both doses of therapy
    • One patient received renal dose reduction per protocol at 1000 mg on Day 1, 1000 mg on Day 8
  • 3 patients discontinued study drug per protocol when baseline bone culture results showed only Gram-negative pathogens; given appropriate Gram-negative antibiotic & continued to follow up for safety visits

• IV comparator every 12 hours for 4–6 weeks (n=10)
  • 8 patients completed therapy
    • IV vancomycin alone x 4 weeks (n=3)
    • IV vancomycin x 5-16 days, then IV linezolid or IV levofloxacin to complete 29 days of therapy (n=4)
    • IV vancomycin x 7 days, then IV linezolid plus IV cefotaxime x 43 days (n=1)
  • 2 patients discontinued study drug per protocol when baseline bone culture results showed only Gram-negative pathogens; given appropriate Gram-negative antibiotic & continued to follow up for safety visits

IV=intravenous
## Demographics and Medical History (Safety Population)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dalbavancin n=70</th>
<th>Standard of Care n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, years (range)</td>
<td>49.2 ± 13.3 (26-79)</td>
<td>54.4 ± 15.3 (29-79)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>59 (84.3%)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>70 (100%)</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Hispanic/Latino</td>
<td>70 (100%)</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>26.1 ± 5.1</td>
<td>30.7 ± 7.4</td>
</tr>
<tr>
<td>Median (Min, Max)</td>
<td>24.7 (18.6, 40.1)</td>
<td>33.8 (21.6, 40.3)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>10 (14.3%)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>Prior fracture and surgical repair at site</td>
<td>33 (47.1%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Debridement with bone culture, n (%)</td>
<td>70 (100%)</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Vacuum-assisted closure of wound, n (%)</td>
<td>8 (11.4%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Skin graft, n (%)</td>
<td>1 (1.4%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Aztreonam use, n (%)</td>
<td>8 (11.4%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Baseline diabetic foot infection, n (%)</td>
<td>4 (5.7%)</td>
<td>1 (10%)</td>
</tr>
</tbody>
</table>

SD: Standard Deviation
Key baseline characteristics

- All patients in both study arms had baseline debridement with bone culture and histology
- *Staphylococcus aureus*: pathogen most commonly isolated from bone
  - 60% of dalbavancin patients
  - 60% of SOC patients
**SITE OF OSTEOMYELITIS**

**Dalbavancin Group (N=70)**
- Tibia, 39%
- Femur, 16%
- Foot, 24%
- Humerus, 6%
- Hand, 6%
- Ulna, 1%
- Fibula, 3%
- Pelvic bone, 1%
- Other, 4%

**SOC Group (N=10)**
- Tibia, 20%
- Foot, 20%
- Femur, 40%
- Pelvic bone, 10%
- Fibula, 10%

"Other" sites include patella (n=1), clavicle (n=1), finger (n=1)

Most common sites in both groups:
- Tibia
- Foot
- Femur
### Patient Baseline Characteristics (Safety Population)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dalbavancin n=70</th>
<th>SOC n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline CRP, mg/L</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>43.9 ± 54.8</td>
<td>20.4 ± 11.4</td>
</tr>
<tr>
<td>Median (Min, Max)</td>
<td>24 (12, 192)</td>
<td>18 (12, 48)</td>
</tr>
<tr>
<td><strong>Baseline ESR, mm/h</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>33.2 ± 17.6</td>
<td>30.6 ± 18.2</td>
</tr>
<tr>
<td>Median (Min, Max)</td>
<td>34 (2, 70)</td>
<td>24 (12, 65)</td>
</tr>
<tr>
<td><strong>Baseline bacteremia, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSSA</td>
<td>2 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Coagulase-negative Staphylococci</td>
<td>2 (3%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td><strong>Baseline bone histology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute inflammatory cells</td>
<td>56 (80%)</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>Necrotic bone</td>
<td>43 (61.4%)</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Edema</td>
<td>11 (15.7%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Granulations</td>
<td>8 (11.4%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Vascular congestion</td>
<td>4 (5.7%)</td>
<td>0</td>
</tr>
</tbody>
</table>

CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; MSSA=methicillin-susceptible *S aureus*; SOC=standard of care.

*CRP normal range=0–6 mg/L. †ESR normal range = 1–10 mm/h.
# Baseline Pathogens (Safety Population)

<table>
<thead>
<tr>
<th>Pathogens in Bone, n (%)*</th>
<th>Dalbavancin n=70</th>
<th>SOC n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA</td>
<td>38 (54.3%)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>MRSA</td>
<td>4 (5.7%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Coagulase-negative Staphylococci</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>6 (8.6%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td><em>Staphylococcus haemolyticus</em></td>
<td>4 (5.7%)</td>
<td>0</td>
</tr>
<tr>
<td><em>Staphylococcus hominis</em></td>
<td>2 (2.9%)</td>
<td>0</td>
</tr>
<tr>
<td><em>Staphylococcus pasteuri</em></td>
<td>1 (1.4%)</td>
<td>0</td>
</tr>
<tr>
<td><em>Staphylococcus simulans</em></td>
<td>1 (1.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Enterococci</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>7 (10%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td><em>Enterococcus faecium</em></td>
<td>1 (1.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>9 (12.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Streptococci</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
<td>1 (1.4%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td><em>Streptococcus dysgalactiae</em></td>
<td>1 (1.4%)</td>
<td>0</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>1 (1.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Other Gram-positive pathogens</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Corynebacterium striatum</em></td>
<td>2 (2.9%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td><em>Aerococcus viridans</em></td>
<td>1 (1.4%)</td>
<td>0</td>
</tr>
<tr>
<td><em>Globicatella species</em></td>
<td>1 (1.4%)</td>
<td>0</td>
</tr>
<tr>
<td><em>Micrococcus luteus</em></td>
<td>1 (1.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Mixed (Gram-positives and aerobic Gram-negatives)</td>
<td>11 (15.7%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Gram-negative pathogens only†</td>
<td>3 (4.3%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>No growth†</td>
<td>5 (7.1%)</td>
<td>0</td>
</tr>
</tbody>
</table>

MRSA=methicillin-resistant *Staphylococcus aureus*; MSSA=methicillin-susceptible *S. aureus*; SOC=standard of care.

*Categories are not mutually exclusive. 13 patients in dalbavancin arm and 2 patients in SOC arm were premature discontinuations from study drug due to only Gram-negative pathogens isolated from bone culture. † 5 patients in dalbavancin arm had no growth on bone biopsy; histology results showed necrotic bone in 3/5 (60%) and acute inflammatory cells in 2/5 (40%).
CRP (MITT POPULATION)

A

Dalbavancin Group

- Baseline: Mean=42.1, Median=24
- Day 8: Mean=19.1, Median=6
- Day 28: Mean=11.4, Median=6
- Day 42: Mean=8.7, Median=6
- 6 months: Mean=7.2, Median=6

Normal CRP ≤6 mg/L

B

SOC Group

- Baseline: Mean=22.5, Median=24
- Day 8: Mean=19.7, Median=12
- Day 28: Mean=18.8, Median=18
- Day 42: Mean=20.3, Median=6
- 6 months: Mean=11.1, Median=6

Normal CRP ≤6 mg/L
**Clinical Outcomes (mITT Population*)**

<table>
<thead>
<tr>
<th></th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dalbavancin</td>
</tr>
<tr>
<td>Clinical Improvement</td>
<td>97%</td>
</tr>
<tr>
<td>CRP Decrease</td>
<td>94%</td>
</tr>
<tr>
<td>Clinical Cure</td>
<td>94%</td>
</tr>
<tr>
<td>6 months</td>
<td>94%</td>
</tr>
<tr>
<td>1 year</td>
<td>100%</td>
</tr>
</tbody>
</table>

mITT=modified intent-to-treat; SOC=standard of care

*3 patients on dalbavancin and 2 on SOC had only Gram-negative pathogens isolated from bone cultures and were excluded from mITT population and efficacy analyses, per protocol.

†2 patients on dalbavancin were lost to followup before Day 21 visit; both had clinical improvement (decreased pain and point tenderness) at Day 8 visit. ‡1 patient on SOC was lost to followup before 6 month visit; he was a clinical cure at Day 42 visit.

![Graph](image-url)
**Hospital Stay and Antibiotic Treatment (mITT Population)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dalbavancin n=67</th>
<th>SOC n=8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Length of hospital stay, days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>15.8 ± 7.1</td>
<td>33.3 ± 14.2</td>
</tr>
<tr>
<td>Median (Min, Max)</td>
<td>15.0 (8, 38)</td>
<td>30.5 (11, 56)</td>
</tr>
<tr>
<td><strong>Days of IV antibiotic treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>2.0 ± 0</td>
<td>31.6 ± 7.0</td>
</tr>
<tr>
<td>Median (Min, Max)</td>
<td>2 (2, 2)</td>
<td>29 (29, 49)</td>
</tr>
<tr>
<td><strong>Total IV infusion duration, hours</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.0 ± 0.02*</td>
<td>101.3 ± 20.8</td>
</tr>
<tr>
<td>Median (Min, Max)</td>
<td>1.0 (1.0, 1.1)*</td>
<td>112.6 (66.9, 113.3)</td>
</tr>
</tbody>
</table>

IV=intravenous; mITT=modified intent-to-treat; SD=standard deviation

* All patients in mITT population received both doses of dalbavancin at Day 1 and Day 8 visits (over approximately 30 minutes [range 29-32 minutes]).
DALBAVANCIN PATIENT WITH RIGHT TIBIA OSTEOMYELITIS

Pathogen: MSSA in Bone Culture & Blood Culture

Baseline: CRP 192 mg/L  
Day 42: CRP 6 mg/L

Baseline X-ray: Periosteal reaction in area of right tibia external condyle, with sites of sequestration and bone defect. Signs of deforming arthrosis of the right knee joint.

Day 42 X-ray: No signs of periosteal reaction or sequestration.
## Adverse Events

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dalbavancin n=70</th>
<th>SOC n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients experiencing ≥ 1 of the following:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEAE</td>
<td>10 (14.3%)</td>
<td>0</td>
</tr>
<tr>
<td>TEAE leading to premature discontinuation of study drug</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Drug-related TEAE</td>
<td>1 (1.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>2 (2.9%)†</td>
<td>0</td>
</tr>
</tbody>
</table>

TEAE=treatment-emergent adverse event

†Both serious TEAEs were not related to study drug and occurred after Day 42 (primary endpoint)
DISCUSSION

- Most patients had a **Gram-positive organism** isolated from bone (89% in dalbavancin group, 80% in SOC group) consistent with previous literature.
- **High clinical cure rates** in dalbavancin group at day 42 (97% in CE, mITT and micro-mITT populations), sustained through 1 year.
- Patients in **dalbavancin** group had **total IV duration of 1 hour** vs SOC group with average **duration of 101.3 hours** per patient.
Dalbavancin Osteomyelitis Study Summary

• Long half-life of dalbavancin and its high bone penetration after a short treatment regimen allows once-weekly dosing and maintains serum concentrations above the MIC$_{90}$ for most Gram-positive pathogens, including S aureus over at least 6 weeks

• Good bone penetration of dalbavancin after a short dosing regimen is relevant for osteomyelitis

• The 2-dose, once-weekly regimen may offer advantages to patients and physicians
  – Eliminates need for prolonged IV access
  – Optimizes adherence for infection requiring treatment duration of 4–6 weeks
  – Brief 2-dose regimen may be suitable for outpatient setting, eg emergency rooms, infusion centers and hospital outpatient departments

• Dalbavancin was well tolerated in this adult population

• Outcomes at 6 weeks, 6 months, and 1 year suggest that treatment of adult osteomyelitis with a 2-dose, weekly regimen of dalbavancin shows a favourable and durable clinical benefit

IV=intravenous; MIC$_{90}$=90% minimum inhibitory concentration
ADDITIONAL DATA ON DALBAVANCIN IN OSTEOMYELITIS

• Findings from randomized clinical trial consistent with efficacy of dalbavancin in other reports
  – Animal model with MRSA sternal osteomyelitis
  
• Observations of high response rates in treatment of osteomyelitis with dalbavancin
  – Case report of multiple weekly dosing of dalbavancin for native vertebral osteomyelitis with MRSA bacteremia (1000 mg IV weekly x 2 wks, followed by 500 mg weekly x 6 wks, plus daily oral rifampin)
  – Case report of weekly dalbavancin in deep sternal wound infection with MRSA after coronary artery bypass surgery (1500 mg IV with repeat dose of 1500 mg IV after 2 wks)
  – Multicenter retrospective review of 31 patients with gram-positive osteomyelitis treated with weekly dalbavancin from 3 U.S. hospitals
    • 90% success; no adverse events related to dalbavancin
    • 5 patient admissions were prevented; these patients received entire course in outpatient setting
    • Remaining 26 patients received 1st dose of dalbavancin at discharge and then completed any weekly doses as outpatients
      – Dalbavancin doses ranged from 500 to 1500 mg/dose, and number of doses varied from single dose to 14 doses based on rate of improvement, duration of therapy remaining and other factors; median duration of prior antibiotics: 20 days (range 2-55 days)
      – Mean reduction in LOS: 28 ± 10 days per patient
      – Estimated total cost-savings of $649,954

DALBAVANCIN IN OTHER INFECTIONS

- Retrospective study of adults treated with dalbavancin for various infections in 29 institutions in Spain¹
  - 69 patients received dalbavancin as weekly regimen
  - Most common infections: prosthetic joint infection, acute bacterial skin and skin structure infection, osteomyelitis, catheter-related bacteremia and endocarditis
    - Dalbavancin dose: most common 1000 mg IV followed by 500 mg weekly to cover 14-42 days (n=40), or 1500 mg alone (n=17)
    - 97.1% received dalbavancin as 2nd line therapy, after median 18 days of antibiotics
    - Dalbavancin given for median 21 days (range 7-168); 36% on concomitant antibiotic
  - Overall 84% success; 10 of the 11 clinical failures due to inadequate source control
  - Reduced hospital stay by 1160 days
  - 50 of 69 patients were treated in outpatient setting
  - Overall cost reduction at €211 481, or €3064 per patient

DALBAVANCIN IN ENDOCARDITIS AND BACTEREMIA

- Retrospective study of adults treated with dalbavancin for **gram-positive infective endocarditis (IE)** in University Hospital of **Vienna** as weekly or q 2 week regimen\(^1\)
  - **27 patients**: 16 native valve IE, 6 prosthetic valve IE, 5 cardiac-device IE
    - Dalbavancin dose
      - 1000 mg followed by 500 mg weekly (n=9), or
      - 1500 mg followed by 1000 mg every 2 wks (n=18)
    - Median duration of dalbavancin: 6 weeks (range 1-30 weeks)
  - 93% microbiological and clinical success
  - 23 of the 27 patients were treated in OPAT setting

- Case reports of successful treatment of **bacteremia** with dalbavancin
  - **MSSA bacteremia** due to septic phlebitis treated with dalbavancin 1000 mg on discharge and 500 mg as outpatient 1 week later; had received prior therapy with 6 days of cefazolin\(^2\)
  - PICC-line associated bacteremia with **vancomycin-susceptible Enterococcus faecalis** treated with 1500 mg single dose of dalbavancin in outpatient infusion center in intravenous drug user\(^3\)

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Oritavancin
Oritavancin Background

- Semisynthetic lipoglycopeptide approved for acute bacterial skin and skin structure infection (ABSSSI) in US and EU; launched in US
  - 1200 mg dose as a 3-hour infusion (in 1000 mL)
  - Active against gram-positive bacteria including S. aureus (MSSA, MRSA) and Enterococcus spp.
  - Terminal half-life of 10.2 days

- Drug-drug interactions
  - Nonspecific weak inhibitor (CYP2C9 and CYP2C19)
  - Weak inducer (CYP3A4 and CYP2D6)
  - Avoid oritavancin with drugs with narrow therapeutic window that are predominantly metabolized by one of the affected CYP450 enzymes

- Interference with coagulation tests: artificially prolongs aPTT (up to 120h), PT/INR (up to 12h) and ACT (up to 24h)
  - Use of IV heparin contraindicated for 120h (5 days) after oritavancin
  - Patients on warfarin should be monitored for bleeding

1Orbactiv® (oritavancin) full prescribing information, 2018.
**ORITAVANCIN DATA IN OTHER INFECTIONS**

- **Case report** of successful treatment of **MSSA osteomyelitis** with multiple doses of weekly oritavancin (1200 mg 2 days before surgery to remove infected tibial nail, then 1200 mg weekly x 6 wks)
  - Supported by rabbit study showing bone concentrations above MIC$_{90}$ for *S. aureus* (0.06 μg/mL) for 7 days

- **Retrospective review** of oritavancin at **US medical center** for multiple doses
  - 17 patients treated for osteomyelitis, surgical site infection, intravascular infections and pneumonia (empiric therapy n=5, definitive/targeted therapy n=12)
    - Oritavancin dose per institutional protocol: initiated at 1200 mg, then 800 mg weekly or 1200 mg every 9-12 days (range 2-18 doses)
  - All had clinical success or improvement
  - 4 patients had adverse event requiring discontinuation of oritavancin

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Oritavancin Data in Other Infections

• Retrospective review in US center of patients treated with oritavancin for indication other than ABSSSI¹
  – 10 patients treated primarily for bacteremia with MSSA, group B Streptococcus with endocarditis, CoNS, vancomycin-susceptible Enterococcus
    • Oritavancin dose: 1200 mg x 1 (n=9); 1200 mg x 3 every 14-19 days (n=1)
  – 70% success; all patients had prior antibiotics before oritavancin and combination therapy with other antibiotics

• Case report of oritavancin in vancomycin-resistant Enterococcus faecium prosthetic valve endocarditis²
  – Oritavancin dose: 1200 mg every other day x 3 doses, then 1200 mg weekly x 6 wks; 8 days later, reinitiated after recurrence of VRE bacteremia at 1200 mg twice weekly, underwent valve replacement and continued 1200 mg twice weekly x 10 wks post-op

Teicoplanin
• Glycopeptide antibiotic approved and available in EU, indicated for
  - **Parenteral** treatment
    • Complicated skin and soft tissue infections
    • Bone and joint infections
    • Hospital acquired pneumonia, community-acquired pneumonia
    • Complicated urinary tract infections
    • Infective endocarditis
    • Peritonitis associated with continuous ambulatory peritoneal dialysis
    • Bacteraemia with any of the above
  - **Oral** treatment for *Clostridium difficile* infection-associated diarrhoea and colitis
• Active against **Gram-positive** bacteria, including *S. aureus*, coagulase-negative staphylococci, *Enterococcus* spp., *Streptococcus* spp., Gram-positive anaerobes
• Elimination **half-life** varies from **4-7 days**
Teicoplanin dosage guidelines in OPAT

- Teicoplanin useful for OPAT due to long half-life\(^1\)
  - Since 2000: 2x/week (twice-weekly) or 3x/week (thrice-weekly) dosing used by Glasgow OPAT service, usually combined with a 2\(^{nd}\) active oral agent
  - Study analyzed routinely generated teicoplanin concentration data from OPAT clinic in Glasgow, using a population pharmacokinetic approach
    - Data from 94 patients for model development and 36 patients for validation
  - Dosage guidelines developed for **thrice-weekly** dosing
    - Success rates of **91% in deep-seated infections** (primarily bone & joint, endocarditis) and **95% in other infections** (primarily cellulitis and wound infections)

NHS TAYSIDE GUIDELINES FOR BONE AND JOINT INFECTIONS:THRICE-WEEKLY TEICOPHPLANIN DOSING

1. Loading dose – Doses should be given 24 hourly for the first 3 days

<table>
<thead>
<tr>
<th>Target Trough Concentration</th>
<th>Ideal Body Weight (kg)* see IBW guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-30mg/L</td>
<td>40-59 60-79 &gt;80</td>
</tr>
<tr>
<td>CLCR&lt;60ml/min</td>
<td>1000mg 1200mg 1400mg</td>
</tr>
<tr>
<td>CLCR&gt;60ml/min</td>
<td>1200mg 1400mg 1600mg</td>
</tr>
</tbody>
</table>

*Use Actual Body weight if lower than Ideal Body Weight

2. Maintenance doses – doses should be given three times weekly on Mon, Wed and Fri.

<table>
<thead>
<tr>
<th>CrCLml/min (Use ABW to calculate CrCL) **</th>
<th>Target Trough Concentration 20-30mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>400mg</td>
</tr>
<tr>
<td>25-40</td>
<td>600mg</td>
</tr>
<tr>
<td>41-54</td>
<td>800mg</td>
</tr>
<tr>
<td>55-74</td>
<td>1000mg</td>
</tr>
<tr>
<td>75-89</td>
<td>1200mg</td>
</tr>
<tr>
<td>90-104</td>
<td>1400mg</td>
</tr>
<tr>
<td>105-120</td>
<td>1600mg</td>
</tr>
<tr>
<td>&gt;120</td>
<td>1800mg</td>
</tr>
</tbody>
</table>

** CrCl = (140 - age x weight (kg) x (1.23 male
Serum creatinine or 1.04 female)

[NB: Serum creatinine in µmol/L]

https://www.nhstaysideadtc.scot.nhs.uk/Antibiotic%20site/pdf%20docs/Teicoplanin%20three%20times%20weekly.pdf

Dosing regime above aims to achieve a trough of 20-30mg/L
BEFORE 6th dose (e.g. 15-30 mins before) check trough Teicoplanin level

Adjust maintenance dose based on Teicoplanin level or renal function
NB: Teicoplanin levels may take 7 to 10 days to be reported

<table>
<thead>
<tr>
<th>Teicoplanin Level (mg/L)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>Recheck CrCL as per above table</td>
</tr>
<tr>
<td>10-20</td>
<td>Consider increasing dose to achieve trough 20-30mg/L</td>
</tr>
<tr>
<td>20-30</td>
<td>No dose adjustment. Recheck levels after 1 week</td>
</tr>
<tr>
<td>&gt;30</td>
<td>Decrease frequency of dosing – give SAME dose twice weekly. Recheck levels after 1 week. Recheck CrCL</td>
</tr>
</tbody>
</table>

NB: Add RIFAMPICIN 450mg bd to regime if Prosthetic joint/implant/graft in situ. Check for Rifampicin sensitivity – if resistant seeks ID/Micro advice. Rifampicin should be prescribed after consideration of co-morbidities, potential hypersensitivity and drug interactions.

https://www.nhstaysideadtc.scot.nhs.uk/Antibiotic%20site/pdf%20docs/Teicoplanin%20three%20times%20weekly.pdf

TEICOPLANIN COST-MINIMIZATION ANALYSIS

• Retrospective audit of 55 treatment episodes of bone and joint infections

• Mean cost of care with teicoplanin
  - Ambulatory setting £1749.15
  - In-patient setting £11400
  - Hypothetical treatment with oral linezolid in home setting £2546

• Parenteral teicoplanin delivered by specialist outpatient service associated with lower financial costs vs in-patient care or hypothetical oral linezolid

Amikacin
AMIKACIN CHARACTERISTICS

• Semi-synthetic, **aminoglycoside** antibiotic\(^1\)
  
  − Bactericidal
  
  − Indicated in short-term treatment of **serious infections** due to susceptible **Gram-negative** bacteria; may at times be indicated for known or suspected **staphylococcal disease**
  
  − Broad spectrum of Gram-negative organisms, including *Pseudomonas aeruginosa*, *E. coli*, and some Gram-positive organisms, including *Staphylococcus aureus*, and some MRSA
  
  − Intramuscular or intravenous administration
  
  − Elimination **half-life**: 2-3 hours
  
  − Special warnings: potential **ototoxicity** and **nephrotoxicity**

• **Active** against **Mycobacteria**\(^2,3\)
  
  − Thrice-weekly dosing as add-on therapy for
    
    • **Fibrocavitary or severe** lung disease, in combination with a 3-drug regimen (eg azithromycin plus rifampicin plus ethambutol)
    
    • **Mycobacterium avium complex** lung infections with cavitary disease or macrolide resistance (if amikacin MIC ≤ 64 mcg/mL) for first 8-16 weeks of therapy

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\(^1\)Amikacin SPC 2015.  
\(^2\)Haworth CS et al. Thorax 2017  
\(^3\)Kasperbauer S et al. Uptodate.com 2018
Study compared incidence of nephrotoxicity and ototoxicity with daily vs thrice-weekly amikacin in MDR-tuberculosis or complicated non-tuberculous mycobacterial infection

- Patients randomized to IV amikacin, streptomycin or kanamycin
  - 15 mg/kg daily (Mon-Fri) or
  - 25 mg/kg 3 times/week
- In the group randomized to IV amikacin 3x/week (n=11), median duration of therapy was 23 weeks (range 2-43 weeks)
- Size of dosage and frequency not associated with ototoxicity, vestibular toxicity or nephrotoxicity
  - Amikacin, streptomycin and kanamycin can be administered either daily or 3x/week without affecting likelihood of toxicity

Peloquin CA et al. Clin Infect Dis 2004
THrice Weekly IV Amikacin in M. abscessus

- Limited options for *Mycobacterium abscessus* pulmonary disease, especially in outpatient settings
  - Among parenteral antibiotics, IV amikacin considered one of the most active vs *M. abscessus*
- **Retrospective case series** of 13 outpatients with *M. abscessus* pulmonary disease treated with IV amikacin
  - IV amikacin was added 6.1 months (on average) after start of anti-mycobacterial therapy
    - IV amikacin administered for median duration of 4 months (range 3-9 months)
  - Starting dose of IV amikacin 15 mg/kg 3x/week, with dose adjustment based on trough
    - More than half the patients had dose reduction; median dose decreased to 12.5 (8.3-16.2) mg/kg
- Addition of IV amikacin 3x/week led to
  - Sputum conversion in 10 of 13 patients, including 8 who continued to have negative sputum status >1 year after the end of amikacin treatment
  - No severe adverse events, such as ototoxicity, vestibular toxicity and renal toxicity
    - Attributed to lower starting dose of amikacin and dose reduction based on troughs
SUMMARY:
ANTIMICROBIALS WITH LESS FREQUENT DOSING

- **Dalbavancin**
  - **Osteomyelitis**
    - Randomized clinical trial (n=80): dalbavancin weekly x 2 (1500 mg IV on day 1 and day 8) for at least 6 weeks of coverage (n=70), vs SOC antibiotic x 4-6 weeks (n=10)
      - High clinical cure rates in dalbavancin group at day 42 (97%), through 1 year, with LOS reduction
    - Multicenter retrospective review in US (n=31): 90% success with LOS reduction and cost savings
    - Case reports of successful treatment with weekly dalbavancin
  - **Various infections**
    - Multicenter retrospective review in Spain (n=69): 84% success with LOS reduction and cost savings
    - Retrospective review in Vienna (n=27): gram-positive endocarditis; 93% success with mostly OPAT
    - Case reports of successful treatment in bacteremia

- **Oritavancin**
  - **Osteomyelitis**
    - Case report of successful treatment with multiple weekly doses
  - **Various infections**
    - Retrospective review in US (n=17): all had clinical success or improvement; 4 discontinued drug due to AE
    - Retrospective review in US (n=10): 70% success
    - Case report of use in VRE prosthetic valve endocarditis
SUMMARY (CONT’D)

• **Teicoplanin**
  - 3x/week dosing guidelines developed from routine clinical data in *Glasgow OPAT clinic*
    - 91% success in deep-seated infections; 95% success in other infections
  - **Bone & joint** infections--*NHS Tayside* guidelines
    - Loading dose every 24h x 3 days, then maintenance doses 3x/week (M/W/F)
    - Trough before 6th dose; goal trough 20-30 mg/L

• **Amikacin IV**
  - 3x/week dosing vs daily dosing in MDR-tuberculosis or complicated NTM infection
    - Amikacin daily as 15 mg/kg (n=11) or 3x/week as 25 mg/kg (n=11) did not affect likelihood of toxicity
  - **Retrospective review (n=13 outpatients)** in *M. abscessus* pulmonary disease
    - Lower starting dose 3x/week as 15 mg/kg with dose adjustment based on trough: fewer severe AEs
Acknowledgements

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- Dalbavancin Osteomyelitis Study previously presented at ECCMID, Vienna, Austria, 22–25 April 2017 (oral), ASM/ESCMID Conference on Drug Development to Meet the Challenge of Antimicrobial Resistance, Boston, Massachusetts, 6–8 September 2017 (poster), and ECCMID, Madrid, Spain, 21–24 April 2018 (mini-oral ePoster)
Thank You!
Backup Slides
Phase 1 study of dalbavancin in bone and synovial tissue

- Adults undergoing elective orthopedic surgery (22 knee replacements, 8 hips)
  - Assigned to 1 of 6 cohorts (5 patients per cohort)
    - Subjects received a single dose of 1000 mg of dalbavancin at appropriate timepoint before surgery
    - Tissue sampling at 12h, 24h, 3 days, 7 days, 10 days, 14 days POST-DOSE
    - Plasma PK sampling in all subjects: 1h, 4h, 12h, 14 days, 30 days, 45 days POST-DOSE
    - 31 subjects, 30 evaluable bone samples
    - Mean conc of dalbavancin in bone at 12h post-dose: 6.3 mcg/g, and at 14 days: 4.1 mcg/g
      - Remained >10-fold above MIC90 of S. aureus (0.06 mcg/mL) through final sample collection at 14 days

Dunne et al. AAC 59:1849-1855.
Phase 1 Study evaluated 18 subjects in 3 cohorts (6 patients per cohort)

Cohort 1
- 4 weekly dalbavancin doses (1000 mg D1, then 500 mg weekly x 3), cumulative dose of 2500 mg

Cohort 2
- 6 weekly dalbavancin doses (1000 mg D1, then 500 mg weekly x 5), cumulative dose of 3500 mg

Cohort 3
- 8 weekly dalbavancin doses (1000 mg D1, then 500 mg weekly x 7), cumulative dose of 4500 mg

Plasma PK sampling
- Plasma PK sampling on D1 (multiple timepoints post-dose) and pre- & post dosing on D8, D15, time of last dose at D22 (cohort 1), D36 (cohort 2), D50 (cohort 3), and also at 4 weeks after intense PK sampling
Based on 2 Phase 1 studies in healthy adults and population PK modeling

- Proposed dosing regimen for osteomyelitis
  - Two 1500 mg IV infusions 1 week apart (D1, D8)
    - Dalbavancin exposure at or above the S. aureus MIC99.9 for dalbavancin of 0.12 mcg/mL for entire treatment duration (8 weeks)
  - 1500 mg regimen on D1 & D8 (cum dose 3000 mg) expected to achieve AUC similar to 1000 mg D1, followed by 500 mg weekly x 4 (cum dose 3000 mg)
  - 2 dose regimen (1500 mg D1 & D8) over 2 weeks selected over regimen with same cum dose of 3000 mg over 1 month (1000 mg D1, 500 mg weekly x 4 on D8, D15, D22, D29)
    - Better outcomes observed if same total dose delivered in larger amounts earlier and less frequently in animal studies
    - With translation of animal data to humans, anticipate that 2-dose 1500 mg regimen → more likely to achieve success

Dunne et al. AAC 2015; 59:1849-1855
Andes et al. AAC 2007; 51:1633-1642
DALBAVANCIN PLASMA & BONE PK MODELING: SIMILAR EXPOSURES THROUGH 8 WEEKS WITH 3000 MG CUMULATIVE DOSE

PLASMA
2 dose regimen (1500 mg D1/D8)

PLASMA
5 dose regimen (1000 mg D1, 500 mg D8/D15/D22/D29)

BONE LEVELS
2 dose regimen (1500 mg D1/D8)

BONE LEVELS
5 dose regimen (1000 mg D1, 500 mg D8/D15/D22/D29)

Dunne et al. AAC 59:1849-1855.
PATIENT DISPOSITION

80 patients randomized

70 Randomized to receive 1500 mg dalbavancin on Day 1 and 1500 mg on Day 8
* 70 received drug as randomized

3 Discontinued from study drug (received only day 1 dose of dalbavancin)
* Baseline bone culture results showed only gram-negative pathogens (per protocol); given appropriate gram-negative antibiotics and remained in study for followup

70 Included in ITT and Safety populations

67 Included in mITT analysis
* 3 Excluded due to only gram-negative pathogens isolated from bone culture

67 Included in CE-Day 21, CE-Day 42 analyses

66 Included in CE-Day 180, CE-Day 365 analyses
* 1 Excluded due to concomitant antibiotic not for failure

10 Randomized to receive SOC for 4-6 weeks
* 10 received drug as randomized

2 Discontinued from study drug
* Baseline bone culture results showed only gram-negative pathogens (per protocol); given appropriate gram-negative antibiotics and remained in study for followup

10 Included in ITT and Safety populations

8 Included in mITT analysis
* 2 Excluded due to only gram-negative pathogens isolated from bone culture

8 Included in CE-Day 21, CE-Day 42 analyses

8 Included in CE-Day 180, CE-Day 365 analyses
## Treatment Regimens for SOC Group

<table>
<thead>
<tr>
<th>Regimen (every 12 hours)</th>
<th>SOC (n=10)</th>
<th>Baseline Pathogen(s) in Bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin IV x 29–30 d (D1–29 or D1–30)</td>
<td>3 (30%)</td>
<td>Corynebacterium striatum (n=1); Staphylococcus epidermidis (n=1); MSSA + Enterococcus faecalis (n=1)(^b)</td>
</tr>
<tr>
<td>Vancomycin IV x 5 d (D1–5); linezolid IV x 25 d (D5–29)</td>
<td>1 (10%)</td>
<td>MSSA + Staphylococcus epidermidis + Streptococcus agalactiae</td>
</tr>
<tr>
<td>Vancomycin IV x 6 d (D1–6); linezolid IV x 24 d (D6–29)(^b)</td>
<td>1 (10%)</td>
<td>MRSA + Klebsiella pneumoniae + Proteus mirabilis</td>
</tr>
<tr>
<td>Vancomycin IV x 8 d (D1–8); levofloxacin IV x 22 d (D8–29)</td>
<td>1 (10%)</td>
<td>MSSA</td>
</tr>
<tr>
<td>Vancomycin IV x 16 d (D1–16); levofloxacin IV x 15 d (D15–29)</td>
<td>1 (10%)</td>
<td>MSSA</td>
</tr>
<tr>
<td>Vancomycin IV x 7 d (D1–7); linezolid IV + cefotaxime IV x 43 d (D7–49)(^c)</td>
<td>1 (10%)</td>
<td>MSSA + Pseudomonas aeruginosa + Raoultella planticola + Serratia marcescens</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Excluded from mITT (only Gram-negatives in bone)</strong></td>
</tr>
<tr>
<td>Vancomycin IV x 16 d (D1–16); amikacin IV x 13 d (D8–20)(^d,e)</td>
<td>1 (10%)</td>
<td>Klebsiella pneumoniae + Proteus mirabilis</td>
</tr>
<tr>
<td>Vancomycin IV x 5 d (D1–5); IV ceftriaxone x 25 d (D4–29)(^d)</td>
<td>1 (10%)</td>
<td>Enterobacter cloacae complex + Escherichia coli + Klebsiella oxytoca</td>
</tr>
</tbody>
</table>

\(IV=\) intravenous; \(d=\) days; \(D=\) Study Day. MRSA=methicillin-resistant *Staphylococcus aureus*; MSSA=methicillin-susceptible *S. aureus*; SOC=standard of care; mITT=modified intent-to-treat
\(^a\)Indeterminate at 6 months and 1 year due to loss to followup. \(^b\)Received adjunctive aztreonam. \(^c\)Clinical failure at day 42 due to receipt of antibiotics > 6 weeks. \(^d\)Discontinued study drug per protocol when baseline bone culture results showed only gram-negative pathogens; given appropriate gram-negative antibiotic. \(^e\)Withdrawn from study on day 20 (withdrew consent)
**Baseline Pathogens in Mixed Infection: Gram-Positive + Gram-Negative Aerobes in Bone (Safety Population)**

<table>
<thead>
<tr>
<th>Baseline Pathogen, by Patient</th>
<th>Site</th>
<th>Clinical Response at Day 42</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dalbavancin Group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. MSSA, <em>Escherichia coli</em> (plus anaerobes <em>Bacteroides fragilis, Peptoniphilus harei</em>)</td>
<td>Hand</td>
<td>Cure</td>
</tr>
<tr>
<td>2. <em>Enterococcus faecalis, Enterobacter cloacae complex</em> (plus anaerobe <em>Prevotella intermedia</em>)</td>
<td>Tibia</td>
<td>Cure</td>
</tr>
<tr>
<td>3. MSSA, <em>E. faecalis, E. coli, K. pneumoniae</em> (plus anaerobes <em>Bacteroides fragilis, Bacteroides vulgatus</em>)</td>
<td>Diabetic foot</td>
<td>Cure</td>
</tr>
<tr>
<td>4. <em>Staphylococcus haemolyticus, Streptococcus dysgalactiae, Escherichia coli, Klebsiella pneumoniae</em></td>
<td>Foot (not diabetic)</td>
<td>Cure</td>
</tr>
<tr>
<td>5. MSSA, <em>M. morganii, P. mirabilis</em> (plus anaerobes <em>B. thetaiotaomicron, Porphyromonas asaccharolytica</em>)</td>
<td>Foot (not diabetic)</td>
<td>Cure</td>
</tr>
<tr>
<td>6. MSSA, <em>Morganella morganii</em> (plus anaerobe <em>Finegoldia magna</em>)</td>
<td>Foot (not diabetic)</td>
<td>Cure</td>
</tr>
<tr>
<td>7. <em>S. epidermidis, E. faecalis, Escherichia hermannii, Pluralibacter gergoviae, Raoultella planticola</em></td>
<td>Diabetic Foot</td>
<td>Cure</td>
</tr>
<tr>
<td>8. MSSA, <em>Staphylococcus haemolyticus, Acinetobacter calcoaceticus</em></td>
<td>Patella</td>
<td>Cure</td>
</tr>
<tr>
<td>9. <em>Staphylococcus simulans, Pseudomonas aeruginosa</em></td>
<td>Tibia</td>
<td>Cure</td>
</tr>
<tr>
<td>10. MSSA, <em>Pseudomonas aeruginosa</em></td>
<td>Femur</td>
<td>Cure</td>
</tr>
<tr>
<td>11. MSSA, <em>Enterobacter cloacae complex</em> (plus anaerobes <em>Peptoniphilus harei, Prevotella disiens</em>)</td>
<td>Foot (not diabetic)</td>
<td>Cure</td>
</tr>
</tbody>
</table>

MRSA=methicillin-resistant *Staphylococcus aureus*; MSSA=methicillin-susceptible *S. aureus*; SOC=standard of care
# Baseline Pathogens in Mixed Infection (Con’d)

<table>
<thead>
<tr>
<th>Baseline Pathogen, by Patient</th>
<th>Site</th>
<th>Clinical Response at Day 42</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOC Group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. MSSA, <em>Pseudomonas aeruginosa</em>, <em>Raoultella planticola</em>, <em>Serratia marcescens</em></td>
<td>Tibia</td>
<td>Failure</td>
</tr>
<tr>
<td>2. MRSA, <em>Klebsiella pneumoniae</em>, <em>Proteus mirabilis</em></td>
<td>Femur</td>
<td>Cure</td>
</tr>
</tbody>
</table>

MRSA=methicillin-resistant *Staphylococcus aureus*; MSSA=methicillin-susceptible *S. aureus*; SOC=standard of care
**Baseline Pathogens (Safety Population): Mutually Exclusive Categories**

<table>
<thead>
<tr>
<th>Pathogens in Bone, n (%)</th>
<th>Dalbavancin (n=70)</th>
<th>SOC (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monomicrobial Gram-positive infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSSA</td>
<td>27 (38.6%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>MRSA</td>
<td>4 (5.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Coagulase-negative Staphylococci</td>
<td>6 (8.6%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Enterococci</td>
<td>2 (2.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Streptococci</td>
<td>1 (1.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Other Gram-positive pathogens</td>
<td>4 (5.7%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td><strong>Polymicrobial infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymicrobial Gram-positive infection</td>
<td>4 (5.7%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Mixed Gram-positive and aerobic Gram-negative infection ± anaerobes</td>
<td>11 (15.7%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Mixed Gram-positive and anaerobic infection</td>
<td>3 (4.3%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Gram-negative infection only</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No growth</td>
<td>5 (7.1%)</td>
<td>0</td>
</tr>
</tbody>
</table>

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