Dalbavancin for the Treatment of Osteomyelitis in Adult Patients

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**DISCLOSURES**

Alena Jandourek and Milan Kovacevic were employees of Allergan at the time of study conduct and analysis. Vadym Shevchenko and Alena Shevchenko have no conflicts to disclose. Urania Rappo, Pedro L. Gonzalez, Rosa Miceli, and Gertjan De Bock are employees of Allergan plc. Urania Rappo, Pedro L. Gonzalez, and Sailaja Puttagunta hold stock in Allergan plc. Sailaja Puttagunta and Michael W. Dunne are employees of Iterum Therapeutics.

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Osteomyelitis in adults

- Potential for poor outcomes, including amputations
- *Staphylococcus aureus* most commonly isolated pathogen
- Challenging to treat; requires **prolonged (4–6+ weeks) intravenous antimicrobial therapy** and possibly surgical debridement
  - Antistaphylococcal penicillins (nafcillin/oxacillin), clindamycin, first-generation cephalosporins (cefazolin), and vancomycin are the typical antimicrobials of choice
  - **Increasing incidence of MRSA** often requires use of vancomycin or clindamycin
    - Vancomycin requires indwelling catheter, monitoring of serum drug levels and careful dose adjustments to maintain appropriate levels in the blood
    - Presence of inducible resistance to clindamycin limits its use

MRSA = methicillin-resistant *Staphylococcus aureus*
Dalbavancin

- A second-generation, long-acting, semisynthetic lipoglycopeptide antibiotic
  - Terminal **half-life of 14.4 days**
  - Structurally related to teicoplanin
- Mechanism of action: inhibits cell wall synthesis
- Has **potent** activity against Gram-positive pathogens, including MRSA
  - MIC$_{90}$ of dalbavancin for *S. aureus* is 0.06 µg/mL, with 99.9% of organisms inhibited at 0.12 µg/mL
- 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)

MRSA = methicillin-resistant *Staphylococcus aureus*
**BACKGROUND: 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
  - Concentration of dalbavancin in bone after a single 1000 mg infusion at 12 hours post-dose was 6.3 µg/g and 2 weeks later was 4.1 µg/g
- Mean **bone:plasma AUC penetration** ratio was 13%

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

*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.

**ACKNOWLEDGMENT**

PHARMACOKINETIC MODELING FOR DOSE DETERMINATION

- Two phase 1 studies (bone penetration study and extended-duration dosing study) provided data for PK modeling to determine **dalbavancin dose for osteomyelitis**
  - A **two-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 *S. aureus*** for entire treatment duration up to **8 weeks**
    - Two-dose regimen of **1500 mg on day 1 and 1500 mg on day 8** would also achieve similar area under the curve (AUC) as a regimen of 1000 mg followed by 4 weekly doses of 500 mg

![Simulated mean concentration-time profile in bone with 1500 mg IV on days 1 and 8](image)

Purpose of the Study

Primary objective
• To determine the efficacy of dalbavancin for treatment of the first episode of osteomyelitis known or suspected to be caused by Gram-positive pathogens in adults

Secondary objective
• To assess the safety and tolerability of dalbavancin in adult patients with osteomyelitis
• To estimate clinical response rate in the dalbavancin group at Day 21, Day 180 and Day 365

Here, we report the results of an interim analysis of this ongoing study
**METHODS**

Single-center, randomized, open-label, active-controlled, parallel-group study comparing dalbavancin with SOC therapy in osteomyelitis in adults

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

- **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
  - Prior episode of osteomyelitis or multiple sites of osteomyelitis
  - Gram-negative bacteremia

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

IV=intravenous; SOC=standard of care
Primary efficacy assessment

- Clinical response at Day 42 in the 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 no more than 1 dose of non-study antibiotic for indication other than osteomyelitis.
Secondary efficacy assessments

• Clinical improvement at **Day 21**: no worsening of pain and/or point tenderness relative to baseline, and improvement in inflammation
  - CRP improvement measured at **Day 28**

• Clinical response in the **modified intent-to-treat (mITT) population** (excludes patients from whom only Gram-negative pathogen isolated from blood and/or bone culture) at:
  - **Day 42**
  - **Day 180**
  - **Day 365**
RESULTS

68 patients randomized to treatment (as of Oct 28, 2016)

- **IV dalbavancin**: 1500 mg on Day 1, 1500 mg on Day 8 (n=59)
  - 56 patients: completed both doses of therapy
  - 3 patients: only Gram-negative pathogens isolated from baseline bone culture; prematurely discontinued study drug per protocol & continued to follow up for safety visits

- **IV comparator** for 4–6 weeks (n=9)
  - Most common regimens
    - IV vancomycin x 4 weeks (n=3)
    - IV vancomycin x 4-16 days, followed by IV linezolid or IV levofloxacin to complete 4-6 week course of therapy (n=4)
  - 7 patients: completed therapy
  - 2 patients: only Gram-negative pathogens isolated from baseline bone culture; prematurely discontinued study drug per protocol & continued to follow up for safety visits

IV=intravenous
# RESULTS: DEMOGRAPHICS AND MEDICAL HISTORY (SAFETY POPULATION)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dalbavancin (n=59)</th>
<th>Standard of Care (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean ± SD, y (range)</strong></td>
<td>51.4 ± 13.8 (27–80)</td>
<td>54.8 ± 15.9 (31–80)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>48 (94%)</td>
<td>5 (56%)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>59 (100%)</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>Black</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Ethnicity, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Hispanic/Latino</td>
<td>59 (100%)</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Medical history, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (17%)</td>
<td>5 (56%)</td>
</tr>
<tr>
<td><strong>Surgical intervention, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Debridement</td>
<td>59 (100%)</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>Vacuum-assisted closure of wound</td>
<td>8 (14%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Skin graft</td>
<td>1 (2%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td><strong>Aztreonam use, n (%)</strong></td>
<td>7 (12%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Site of osteomyelitis, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tibia:</td>
<td>24 (41%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>Foot:</td>
<td>15 (25%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>Femur:</td>
<td>9 (15%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Humerus:</td>
<td>4 (7%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Hand:</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>Fibula:</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Pelvic bone:</td>
<td>1 (2%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Other:</td>
<td>3 (5%)*</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline diabetic foot infection, n (%)</strong></td>
<td>4 (7%)</td>
<td>1 (11%)</td>
</tr>
</tbody>
</table>

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

SD: Standard Deviation
# Patient Baseline Characteristics (Safety Population)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dalbavancin (n=59)</th>
<th>SOC (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline CRP, mg/L</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>41.8</td>
<td>20</td>
</tr>
<tr>
<td>Median</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td><strong>Baseline ESR, mm/h</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>33.7</td>
<td>26.8</td>
</tr>
<tr>
<td>Median</td>
<td>32</td>
<td>21</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 (11%)</td>
</tr>
<tr>
<td><strong>Baseline pathogen in bone, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSSA</td>
<td>30 (51%)</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>MRSA</td>
<td>4 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Coagulase-negative Staphylococci</td>
<td>12 (20%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>8 (14%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>6 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Streptococci</td>
<td>3 (5%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Other Gram-positive pathogens</td>
<td>4 (7%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Gram-negative pathogens ‡</td>
<td>13 (22%)</td>
<td>3 (33%)</td>
</tr>
</tbody>
</table>

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

*C*CRP normal range=0–6 mg/L.

†ESR normal range = 1–10 mm/h.

‡3 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.
CRP IN DALBAVANCIN GROUP (MITT POPULATION)

Baseline
Mean 39.6
Median 12

Day 8
Mean 21.0
Median 6

Day 28
Mean 12.6
Median 6

Day 42
Mean 9.2
Median 6

Normal CRP ≤6 mg/L
CRP IN STANDARD OF CARE GROUP (MITT POPULATION)

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>22.3</td>
<td>24</td>
</tr>
<tr>
<td>Day 8</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Day 28</td>
<td>14.6</td>
<td>12</td>
</tr>
<tr>
<td>Day 42</td>
<td>19.7</td>
<td>6</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Clinical Improvement</th>
<th>CRP Decrease</th>
<th>Clinical Cure</th>
<th>CRP Decrease</th>
<th>Clinical Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 21</strong></td>
<td><strong>Day 28</strong></td>
<td><strong>Day 42†</strong></td>
<td><strong>Day 180</strong></td>
<td><strong>Day 365‡</strong></td>
</tr>
<tr>
<td>Dalbavancin</td>
<td>SOC</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Percentage**

Dalbavancin

- Clinical Improvement: 54/54
- CRP Decrease: 52/54
- Clinical Cure: 54/54
- Clinical Cure: 50*/54
- Clinical Cure: 5/5

SOC

- Clinical Improvement: 7/7
- CRP Decrease: 5/6
- Clinical Cure: 6/7
- Clinical Cure: 4/5

(Most common: IV vancomycin; IV vancomycin with switch to IV linezolid or to IV levofloxacin)

CE=clinically evaluable; CRP=C-reactive protein; IV=intravenous; mITT=modified intent-to-treat; SOC=standard of care

*Indeterminates: 2/54 (4%); Failure: 2/54 (4%); †Day 42 outcomes apply to both mITT and CE populations; ‡To date; §No patients have reached this time point.
DALBAVANCIN PATIENT WITH RIGHT TIBIA OSTEOMYELITIS

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.

Pathogen: MSSA in Bone Culture & Blood Culture

Baseline: CRP 192 mg/L

Day 42: CRP 6 mg/L
### Adverse Events

**Characteristic** | **Dalbavancin n/N (%)** | **SOC n/N (%)**
--- | --- | ---
Patients experiencing ≥ 1 of the following:

<p>| | | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>TEAE</td>
<td>10/59 (16.9%)&lt;sup&gt;+&lt;/sup&gt;</td>
<td>0/9</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>1/59 (1.7%)</td>
<td>0/9</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>2/59 (3.4%)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>0/9</td>
</tr>
</tbody>
</table>

**TEAE**-treatment-emergent adverse event.

*Includes 3 patients with onset of TEAEs after Day 42 (primary endpoint), not related to study drug; †Both serious TEAEs were not related to study drug and occurred after Day 42 (primary endpoint).
CONCLUSIONS

• Long half-life of dalbavancin 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

• Dalbavancin was well tolerated in this adult population

• Interim results of our phase 2 study suggest that treatment of adult osteomyelitis with a 2-dose, weekly regimen of dalbavancin shows a favorable clinical benefit

IV=intravenous; MIC$_{90}$=90% minimum inhibitory concentration
THANK YOU!

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