NUVOCID®
(oritavancin diphosphate)

Targanta Therapeutics Corporation
# Agenda & Presenters

<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction/Microbiology</td>
<td>Tom Parr, Ph.D. Chief Scientific Officer</td>
</tr>
<tr>
<td>Pharmacology/Efficacy</td>
<td>Pierre Etienne, M.D. Chief Development Officer</td>
</tr>
<tr>
<td>Safety/Benefit-Risk</td>
<td>Susan Moriarty, M.D. Senior Director, Medical Affairs</td>
</tr>
</tbody>
</table>
Additional Experts

Targanta Experts

- Clinical Pharmacology  
  Hylar Friedman, M.D.
- Microbiology  
  Greg Moeck, Ph.D.
- Efficacy  
  Charlotte Hartman, Pharm.D.
- Trial Conduct/Study Design  
  Jill McCollam, Pharm.D.
- Regulatory Affairs  
  Bill Current, Ph.D., RAC
- CMC  
  James Copp, Ph.D.

Consultant Experts

- Toxicology  
  Guy Paulus, M.D.
- PK-PD  
  Paul Ambrose, Pharm.D.
  Sujata Bhavnani, Pharm.D., M.S.
  Alan Forrest, Pharm.D.
Oritavancin
A New Option for Gram-Positive Treatment

- NDA submitted for complicated skin and skin structure infections (cSSSI)
  - Two Phase 3 trials met primary endpoints in cSSSI
  - Experience in 1977 oritavancin-treated study participants, including 1617 patients
Oritavancin’s Structure Confers Multiple Benefits

- Enhances potency
- Active against resistant strains
- Dramatically changes pharmacokinetics and pharmacodynamics
- Adds additional mechanisms of action

Oritavancin
Oritavancin’s Multiple Mechanisms Reduce Probability of Resistance

- **Mask Substrate Prevents Cell Wall Extension**
- **Dimerization Provides Additional Utility**
- **Blocks Transglycosylase Enzyme**
- **Disruption of Membrane Potential**

Outside

D-Ala-D-Ala

Dimerization provides additional utility

Inside

D-Ala-D-Ala

Mask Substrate Prevents Cell Wall Extension

Blocks Transglycosylase Enzyme

Disruption of Membrane Potential
Attributes of Oritavancin

- Greater utility
  - Spectrum/potency
  - Short course of dosing

- Strong safety profile

- Fewer side effects and treatment issues

- Significant future potential
  - Single/infrequent dose studies
  - Bacteremia
  - Clostridium difficile colitis
  - Bacillus anthracis
Oritavancin is Rapidly Bactericidal

- 99.9% kill in 30 minutes, for CA-MRSA (USA 300 clone), at predicted free peak in plasma from 200-mg dose

Vancomycin, 16 μg/mL
Linezolid, 8 μg/mL
Daptomycin, 4 μg/mL
Oritavancin, 4 μg/mL

S. aureus USA300 (CA-MRSA); McKay et al. 2008; ECCMID poster P-544
Oritavancin Is Active in Multiple Animal Models

- Multiple pathogens, multiple disease states
- AUC:MIC and peak:MIC levels best predict efficacy in mice:
  - Neutropenic thigh model (*S. aureus, S. pyogenes*)
  - Pneumonia model (*S. pneumoniae*)
- Concurs with concentration-dependent bactericidal activity of oritavancin in vitro
- Sustained activity in vitro mirrored in vivo
Oritavancin Exerts Sustained Activity In vivo

Rat Granuloma Pouch Model of MSSA Infection

- Results predict utility of once-daily dosing

Lehoux et al. 2006; ICAAC poster B-0404
Oritavancin Profile

- Oritavancin for the treatment of cSSSI using once-daily dosing of 200 or 300 mg for 3 to 7 days
- Demonstrated effectiveness with a strong safety profile

- Once-daily dosing
- 3 to 7 days of dosing
- No special laboratory monitoring (efficacy or safety)
- Enhanced potency/spectrum
- VRE, VRSA activity (in vitro/animal models)
- Multiple mechanisms of action
- Rapidly bactericidal
- Sustained activity

Future potential
Clinical Pharmacology
Clinical Efficacy

Pierre Etienne, M.D.
Chief Development Officer
Targanta Therapeutics Corporation
Phase 3 cSSSI Studies
Oritavancin is Effective

Oritavancin demonstrated efficacy in treating serious gram-positive cSSSI once daily for 3 to 7 days with a low rate of relapse in two Phase 3 studies.

- Clinical pharmacology and pharmacokinetics
- Both Phase 3 studies demonstrated efficacy
  - Study ARRD
  - Study ARRI
- Pooled Phase 3 efficacy results
  - Combined study results are consistent
  - Clinical efficacy demonstrated in subgroups
  - Microbiologically effective
Pharmacology of Oritavancin Has Been Well Characterized

- **Clinical pharmacology**
  - 11 Phase 1 studies
  - $C_{\text{max}}$ and AUC are linear
  - Multi-exponential plasma decline

- **Population pharmacokinetic model**
  - 12 Phase 1, 2, and 3 pooled studies
  - For subjects weighing >110 kg, dose is 300 mg
  - No dose adjustments for age, renal, or hepatic disease
Population Model-Predicted Mean Plasma Concentration-Time Profile of Oritavancin

![Graph showing the population model-predicted mean plasma concentration-time profile of Oritavancin.](image)

- **Y-axis**: Oritavancin Concentration (mcg/mL)
- **X-axis**: Time Since Start of First Infusion (hr)

The graph illustrates the predicted concentration-time profile with repeated infusions over time.
Distribution, Metabolism, and Elimination

- Extensive tissue distribution
- 86% to 90% protein bound
- Not metabolized
- Low likelihood of CYP450 drug interactions
- Slowly eliminated in the urine and feces
Study ARRD and Study ARRI
Study Design
Study ARRD and Study ARRI: Hypothesis

• Short course therapy (3 to 7 days) of once-daily IV oritavancin is noninferior to 10 to 14 days of twice-daily IV vancomycin/PO cephalexin in the treatment of patients with cSSSI presumed or proven to be caused by gram-positive bacteria
Study ARRD and Study ARRI: Definition of cSSSI

- Significant surgical intervention
- Deeper soft tissue involvement
- Significant underlying diseases
Study ARRD and Study ARRI Included Seriously Ill Patients

Patients allowed:
• Underlying disease or condition
  – Diabetes, HIV/AIDS, neutropenia (all levels), peripheral vascular disease
• No limits on anticipated hospitalization
• Renal and hepatic insufficiency
  – Cirrhosis, end stage renal disease
• Bacteremia
• Polymicrobial infection

Applicable to patients in clinical practice
## Study ARRD and ARRI: Study Design
### Study Drug Treatment Regimens

<table>
<thead>
<tr>
<th>Study Day</th>
<th>1</th>
<th>2</th>
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<tbody>
<tr>
<td>MRSA or Enterococcal Infections</td>
<td>ORI</td>
<td>☑️</td>
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<td>VAN</td>
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</tbody>
</table>

- **Active study drug**: [Image of active drug icon]
- **Placebo**: [Image of placebo icon]

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**2041.03**
### Study ARRD and ARRI: Study Design

#### Study Drug Treatment Regimens

<table>
<thead>
<tr>
<th>Study Day</th>
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<tbody>
<tr>
<td><strong>Other Gram-Positive Infections</strong></td>
<td><strong>ORI</strong></td>
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</tbody>
</table>

- **Active study drug**
- **Placebo**

Optional
Study ARRD
Weight-Based Dose Study
Study ARRD: Weight-Based Dose Study

- Randomized 1:1:1
  - Oritavancin 1.5 mg/kg/day
  - Oritavancin 3.0 mg/kg/day
  - Comparator
- Primary comparisons (ORI 1.5 vs VAN and ORI 3.0 vs VAN)
  - Must win on both
- 15% noninferiority margin per FDA guidance

<table>
<thead>
<tr>
<th>Patient Disposition</th>
<th>ORI 1.5 mg/kg N=173 % (n)</th>
<th>ORI 3.0 mg/kg N=169 % (n)</th>
<th>VAN 15 mg/kg N=175 % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed IV Treatment</td>
<td>72.8 (126)</td>
<td>68.6 (116)</td>
<td>72.6 (127)</td>
</tr>
<tr>
<td>Discontinued IV Treatment</td>
<td>27.2 (47)</td>
<td>31.4 (53)</td>
<td>27.4 (127)</td>
</tr>
<tr>
<td>CE</td>
<td>76.8 (136)</td>
<td>72.3 (128)</td>
<td>73.4 (130)</td>
</tr>
</tbody>
</table>
### Study ARRD: Baseline Disease Categories and Duration of Disease (ITT)

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>ORI 1.5 mg/kg N=173 % (n)</th>
<th>ORI 3.0 mg/kg N=169 % (n)</th>
<th>VAN 15 mg/kg N=175 % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound Infection</td>
<td>20.2 (35)</td>
<td>20.1 (34)</td>
<td>21.7 (38)</td>
</tr>
<tr>
<td>Major Abscess</td>
<td>38.2 (66)</td>
<td>36.1 (61)</td>
<td>36.6 (64)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>41.6 (72)</td>
<td>43.8 (74)</td>
<td>41.7 (73)</td>
</tr>
<tr>
<td>Duration of Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) – Days</td>
<td>6.4 (9.22)</td>
<td>4.8 (3.17)</td>
<td>4.9 (4.27)</td>
</tr>
</tbody>
</table>
## Study ARRD: Depth of Tissue Involvement (ITT)

<table>
<thead>
<tr>
<th>Deepest Tissue Involved</th>
<th>ORI 1.5 mg/kg N=173 % (n)</th>
<th>ORI 3.0 mg/kg N=169 % (n)</th>
<th>VAN 15 mg/kg N=175 % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>8.1 (14)</td>
<td>6.5 (11)</td>
<td>6.9 (12)</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>61.8 (107)</td>
<td>65.7 (111)</td>
<td>62.9 (110)</td>
</tr>
<tr>
<td>Fascial Plane</td>
<td>22.0 (38)</td>
<td>19.5 (33)</td>
<td>17.7 (31)</td>
</tr>
<tr>
<td>Muscle</td>
<td>5.2 (9)</td>
<td>6.5 (11)</td>
<td>10.9 (19)</td>
</tr>
<tr>
<td>Bone</td>
<td>1.2 (2)</td>
<td>0.6 (1)</td>
<td>0.6 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>1.7 (3)</td>
<td>1.2 (2)</td>
<td>1.1 (2)</td>
</tr>
</tbody>
</table>
Study ARRD: Oritavancin was Effective in the Treatment of cSSSI (IDCO)

95% CI
ORI-1.5 mg/kg (-14.4, 5.9)
ORI-3.0 mg/kg (-14.9, 5.7)
Study ARRD: Oritavancin was Effective in the Treatment of cSSSI (IDCO*)

<table>
<thead>
<tr>
<th></th>
<th>ORI 1.5 mg/kg</th>
<th>ORI 3.0 mg/kg</th>
<th>VAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>101 (133)</td>
<td>97 (131)</td>
<td>106 (132)</td>
</tr>
<tr>
<td>CE</td>
<td>100 (132)</td>
<td>95 (126)</td>
<td>100 (125)</td>
</tr>
<tr>
<td>MITT</td>
<td>55 (77)</td>
<td>58 (78)</td>
<td>64 (83)</td>
</tr>
<tr>
<td>ME</td>
<td>55 (77)</td>
<td>58 (76)</td>
<td>61 (80)</td>
</tr>
</tbody>
</table>

95% CI
- ORI-1.5 mg/kg: (-14.4, 5.9)
- ORI-3.0 mg/kg: (-14.9, 5.7)

*Excluding missing and indeterminate
## Study ARRD: Oritavancin was Effective in the Treatment of cSSSI

<table>
<thead>
<tr>
<th>Efficacy Endpoint (Patient Population)</th>
<th>ORI 1.5 mg/kg % (n/N)</th>
<th>ORI 3.0 mg/kg % (n/N)</th>
<th>VAN % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDCO (CE)</td>
<td>75.8 (100/132)</td>
<td>75.4 (95/126)</td>
<td>80.0 (100/125)</td>
</tr>
<tr>
<td>SDCO (CE)</td>
<td>72.1 (98/136)</td>
<td>73.4 (94/128)</td>
<td>75.4 (98/130)</td>
</tr>
<tr>
<td>Patient Level Microbiological Outcome (ME)</td>
<td>65.8 (52/79)</td>
<td>72.7 (56/77)</td>
<td>74.7 (62/83)</td>
</tr>
</tbody>
</table>
Study ARRD: Oritavancin was Effective for all cSSSI Disease Categories (CE)
Multiplicity?

- **History**
  - Study ARRD - the smaller study - designed in accordance with existing regulatory guidance
  - FDA agreed with design of Study ARRD (both arms must meet the 15% NI margin with 95% CI)
  - Study ARRI - the larger study - 10% NI margin and 95% CI

- **Intent of Study ARRD protocol**
  - Both arms must meet 95% CI
  - Study was powered for 95% (not 97.5%)
Study ARRI
Fixed-Dose Study
Study ARRI: Fixed-Dose Study Design

- Randomized 2:1
  - Otitavancin 200 mg/day (300 mg/day if >110 kg)
  - Comparator

- 10% noninferiority margin per ICH guidance

<table>
<thead>
<tr>
<th>Patient Disposition</th>
<th>ORI</th>
<th>VAN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=831</td>
<td>N=415</td>
</tr>
<tr>
<td></td>
<td>% (n)</td>
<td>% (n)</td>
</tr>
<tr>
<td>ITT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed IV Treatment</td>
<td>88.6 (736)</td>
<td>87.5 (363)</td>
</tr>
<tr>
<td>Discontinued IV Treatment</td>
<td>11.4 (95)</td>
<td>12.5 (52)</td>
</tr>
<tr>
<td>CE</td>
<td>80.2 (675)</td>
<td>77.2 (328)</td>
</tr>
</tbody>
</table>
## Study ARRI: Baseline Disease Categories and Duration of Disease (ITT)

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>ORI N=831 % (n)</th>
<th>VAN N=415 % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound Infection</td>
<td>31.9 (265)</td>
<td>33.5 (139)</td>
</tr>
<tr>
<td>Major Abscess</td>
<td>44.0 (366)</td>
<td>42.7 (177)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>24.1 (200)</td>
<td>23.9 (99)</td>
</tr>
<tr>
<td>Duration of Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) – Days</td>
<td>5.4 (5.20)</td>
<td>6.0 (8.96)</td>
</tr>
</tbody>
</table>
## Study ARRI: Depth of Tissue Involvement (ITT)

<table>
<thead>
<tr>
<th>Deepest Tissue Involved</th>
<th>ORI N=831</th>
<th>VAN N=415</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n)</td>
<td>% (n)</td>
</tr>
<tr>
<td>Skin</td>
<td>3.1 (26)</td>
<td>4.6 (19)</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>52.0 (432)</td>
<td>51.8 (215)</td>
</tr>
<tr>
<td>Fascial Plane</td>
<td>32.9 (273)</td>
<td>31.6 (131)</td>
</tr>
<tr>
<td>Muscle</td>
<td>11.3 (94)</td>
<td>11.6 (48)</td>
</tr>
<tr>
<td>Bone</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>0.7 (6)</td>
<td>0.5 (2)</td>
</tr>
</tbody>
</table>
Study ARRI: Oritavancin was Effective in the Treatment of cSSSI

95% CI (-3.0, 8.2)
Study ARRI: Oritavancin was Effective in the Treatment of cSSSI (SDCO*)

<table>
<thead>
<tr>
<th></th>
<th>ORI</th>
<th>VAN</th>
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</thead>
<tbody>
<tr>
<td>ITT</td>
<td>79</td>
<td>76</td>
</tr>
<tr>
<td>CE</td>
<td>79</td>
<td>76</td>
</tr>
<tr>
<td>MITT</td>
<td>79</td>
<td>77</td>
</tr>
<tr>
<td>ME</td>
<td>79</td>
<td>77</td>
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% Clinical Cure

95% CI (-3.0, 8.2)

*Excluding missing and indeterminate
Study ARRI: Oritavancin was Effective in the Treatment of cSSSI

<table>
<thead>
<tr>
<th>Efficacy Endpoint (Patient Population)</th>
<th>ORI % (n/N)</th>
<th>VAN % (n/N)</th>
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<tbody>
<tr>
<td>IDC0 (CE)</td>
<td>82.3 (534/649)</td>
<td>82.5 (254/308)</td>
</tr>
<tr>
<td>SDC0 (CE)</td>
<td>78.5 (530/675)</td>
<td>75.9 (249/328)</td>
</tr>
<tr>
<td>Patient Level Microbiological Outcome (ME)</td>
<td>74.1 (340/459)</td>
<td>71.7 (170/237)</td>
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</tbody>
</table>
Study ARRI: Oritavancin was Effective for all cSSSI Disease Categories (CE)
Pooled ARRD and ARRI Studies
Efficacy Results
Pooled ARRD and ARRI Studies: Oritavancin was Effective in the Treatment of cSSSI

<table>
<thead>
<tr>
<th>Efficacy Endpoint</th>
<th>ORI % (n/N)</th>
<th>VAN % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDCO (CE)</td>
<td>80.4 (729/907)</td>
<td>81.8 (354/433)</td>
</tr>
<tr>
<td>SDCO (CE)</td>
<td>76.9 (722/939)</td>
<td>75.8 (347/458)</td>
</tr>
<tr>
<td>Patient Level Microbiological Outcome (ME)</td>
<td>72.8 (448/615)</td>
<td>72.5 (232/320)</td>
</tr>
</tbody>
</table>
### Pooled ARRD and ARRI Studies: Clinical Efficacy Results in Subgroups (CE)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>ORI % (n/N)</th>
<th>VAN % (n/N)</th>
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<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
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<tr>
<td>≥65 years</td>
<td>72.0 (126/175)</td>
<td>69.0 (60/87)</td>
</tr>
<tr>
<td>≥75 years</td>
<td>68.3 (41/60)</td>
<td>61.3 (19/31)</td>
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<tr>
<td><strong>Creatinine Clearance</strong></td>
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<tr>
<td>&gt;80 mL/min</td>
<td>78.1 (557/713)</td>
<td>77.2 (281/364)</td>
</tr>
<tr>
<td>&gt;30 to ≤80 mL/min</td>
<td>75.7 (140/185)</td>
<td>71.1 (54/76)</td>
</tr>
<tr>
<td>&gt;10 to ≤30 mL/min</td>
<td>60.0 (9/15)</td>
<td>0 (0/1)</td>
</tr>
<tr>
<td><strong>Hepatic Insufficiency</strong></td>
<td>77.4 (24/31)</td>
<td>60.0 (9/15)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>62.2 (125/201)</td>
<td>62.9 (61/97)</td>
</tr>
<tr>
<td><strong>HIV/AIDS</strong></td>
<td>73.7 (14/19)</td>
<td>66.7 (4/6)</td>
</tr>
</tbody>
</table>
ARRD and ARRI

Patients with Bacteremia at Baseline

- Based on reported cultures and adverse events
  - 90% (26/29) ORI with no evidence of ongoing bacteremia
  - 89% (8/9) VAN with no evidence of ongoing bacteremia
### Pooled ARRD and ARRI Studies: Microbiological Outcome by Baseline Pathogen (ME)

<table>
<thead>
<tr>
<th>Baseline Pathogen</th>
<th>ORI % (n/N)</th>
<th>VAN % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSSA</td>
<td>70.7 (319/451)</td>
<td>72.8 (163/224)</td>
</tr>
<tr>
<td>MRSA</td>
<td>74.1 (226/305)</td>
<td>74.5 (123/165)</td>
</tr>
<tr>
<td></td>
<td>63.2 (72/114)</td>
<td>67.3 (33/49)</td>
</tr>
<tr>
<td><strong>Streptococcus pyogenes</strong></td>
<td>77.9 (81/104)</td>
<td>66.7 (46/66)</td>
</tr>
<tr>
<td><strong>Streptococcus agalactiae</strong></td>
<td>66.7 (24/36)</td>
<td>85.7 (12/14)</td>
</tr>
<tr>
<td><strong>Streptococcus anginosus</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>79.6 (43/54)</td>
<td>81.5 (22/27)</td>
</tr>
<tr>
<td><strong>Streptococcus dysgalactiae</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>50.0 (6/12)</td>
<td>33.3 (1/3)</td>
</tr>
<tr>
<td><strong>Enterococcus faecalis</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td>75.6 (31/41)</td>
<td>68.0 (17/25)</td>
</tr>
</tbody>
</table>

<sup>a</sup> *Streptococcus anginosus* group includes *S. anginosus*, *S. intermedius* and *S. constellatus*.

<sup>b</sup> *Streptococcus dysgalactiae* includes *S. dysgalactiae* and *S. dysgalactiae* subsp. *equisimilis*.

<sup>c</sup> Vancomycin-susceptible strains only.
Oritavancin Non-Susceptibility Not Observed in Clinical Trials

• Surveillance MICs remain similar to clinical trial susceptibility

• Emergence of non-susceptibility has not been observed to date during oritavancin therapy of cSSSI
Pooled ARRD and ARRI Studies: Relapse Rates at Late Follow-Up Visit

<table>
<thead>
<tr>
<th></th>
<th>ORI</th>
<th>VAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>2.3% (17/724)</td>
<td>2.0% (7/351)</td>
</tr>
<tr>
<td>CE</td>
<td>2.4% (16/663)</td>
<td>1.9% (7/315)</td>
</tr>
</tbody>
</table>
Oritavancin demonstrated efficacy in treating serious gram-positive cSSSI once daily for 3 to 7 days with a low rate of relapse in two Phase 3 studies.

- Noninferiority demonstrated in two Phase 3 studies
- Consistent efficacy in patient populations
- Consistent efficacy across disease categories
- Efficacy in patients with underlying diseases
- Microbiological efficacy established
Clinical Safety
Benefit/Risk

Susan R. Moriarty, M.D.
Senior Director, Medical Affairs
Targanta Therapeutics Corporation
Overall Safety Summary

- Oritavancin is well-tolerated with a favorable benefit-risk profile in patients with cSSSI
- No dose adjustments are required in special populations
- No special laboratory monitoring is indicated for safety
Oritavancin Exposure Summary
Phase 3 cSSSI Safety Population

ITT population = cSSSI patients who received any amount of study drug

- **1173 oritavancin Phase 3 ITT patients**
  - 96% (n=1124) received IV therapy for 3 to 7 days
  - 85% (n=993) received the recommended cumulative dose of $\geq 600$ to $\leq 2100$ mg
  - Mean (SD) duration of active oritavancin therapy
    - 5.1 (1.6) days

- **Duration of patient follow-up**
  - 39 to 90 days from first dose
Adverse Event Overview
Phase 3 cSSSI Safety Population

% Patients with ≥1 TEAE

<table>
<thead>
<tr>
<th></th>
<th>ORI (N=1173)</th>
<th>VAN (N=590)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall During Study</td>
<td>54.0%</td>
<td>62.0%</td>
</tr>
<tr>
<td>Overall During IV Therapy</td>
<td>42.0%</td>
<td>50.0%</td>
</tr>
<tr>
<td>Possibly Related to Study Drug</td>
<td>18.0%</td>
<td>25.0%</td>
</tr>
</tbody>
</table>

ORI IV vs VAN IV

*p<.001
Most Common Adverse Events
Phase 3 cSSSI Safety Population

- Nausea
- Headache
- Insomnia
- Diarrhoea
- Vomiting
- Constipation
- Dizziness
- Hypertension
- Pyrexia
- Pruritis
- Hypokalemia
- Rash
- Abdominal Pain

% of Patients

ORI (N=1173)
VAN (N=590)
ORI significantly lower
ORI significantly higher
Adverse Events of Interest
Phase 3 cSSSI Safety Population

Those events most likely to be treatment related

Defined as adverse events either:

- Potentially drug-class related, or

- Occurred in $\geq 1\%$ of oritavancin patients
  
  - During IV therapy
  
  - Significantly different percentage between oritavancin and vancomycin
Adverse Events of Interest
Phase 3 cSSSI Safety Population

- Infusion site pain
- Infusion site phlebitis
- Pruritis
- Rash
- Phlebitis
- Erythema
- Pruritis generalized
- Flushing
- Red man syndrome
- Urticaria
- Infusion site pruritis
- Infusion site erythema

% of Patients

- ORI (N=1173)
- VAN (N=590)

- ORI significantly lower
Notable Adverse Events
Phase 3 cSSSI Safety Population

<table>
<thead>
<tr>
<th></th>
<th>ORI (N=1173)</th>
<th>VAN (N=590)</th>
<th>*p=.006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious Adverse Events</td>
<td>9.1%</td>
<td>11.4%</td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>1.6%</td>
<td>2.0%</td>
<td></td>
</tr>
<tr>
<td>Discontinued Study Drug due to Adverse Event</td>
<td>3.0%</td>
<td>5.8%</td>
<td></td>
</tr>
</tbody>
</table>

Number of Patients:

- ORI: 107 / 1173
- VAN: 67 / 590
- ORI: 19 / 1173
- VAN: 12 / 590
- ORI: 35 / 1173
- VAN: 34 / 590
Rate of Onset: Treatment-Emergent Events
Phase 3 cSSSI Safety Population

Cumulative Rate of Onset of TEAE per Patient

Study Day

Ori
Van

28-90 Cumulative
Clinical Laboratory and Vital Signs
Phase 3 cSSSI Safety Population

- No clinically relevant differences observed between oritavancin and vancomycin groups in:
  - Chemistry, hematology, or liver function laboratory findings
  - Vital signs findings

- No safety signals identified in the oritavancin group in clinical laboratory or vital signs measurements
No clinically relevant safety findings in:

- Demographics subgroups (age, gender, race, weight)
- Patients with:
  - Hepatic insufficiency
  - Renal insufficiency
  - Diabetes
  - Underlying immunocompromise
    - HIV/AIDS
    - Immunosuppressive concomitant medications
    - Neutropenia at baseline
Potential Glycopeptide-Related Effects
Phase 3 cSSSI Safety Population

- Overall, compared with vancomycin, oritavancin showed:
  - No evidence of drug-associated nephrotoxicity, ototoxicity, vestibular toxicity, or clinically relevant neutropenia, thrombocytopenia, or pancytopenia
  - Comparable incidence and severity of injection site phlebitis events
  - Significantly lower percentage of patients with possible histamine-like infusion reactions
Cardiac Safety
No Clinically Relevant Effect on QT/QTc

• Nonclinical
  – Human Ether-a-go-go Related Gene (hERG) studies
  – In vivo ECG studies in dogs

• Clinical
  – Thorough QT/QTc Study QT002
    ▪ Moxifloxacin with significant increase in QTcF
    ▪ Oritavancin with no QT/QTc effect with clinical (200 mg) or supratherapeutic (800 mg) dose
  – Phase 1, 2, 3 studies (139 healthy subjects and 323 patients), including earlier QT/QTc Study OCSI-008
    ▪ No clinically relevant cardiac safety concerns
Targeted Analyses of Hepatotoxicity Phase 3 cSSSI Safety Population

• Liver laboratory test review:
  – No signal of clinically relevant liver toxicity

• Laboratory criteria used to screen for potential drug-induced liver injury cases were:
  – ALT or AST values $> 3 \times$ ULN
  – Total bilirubin value $\geq 34.2 \text{ µmol/L}$ (or $\geq 2.0 \text{ mg/dL}$)
  – Regardless of alkaline phosphatase results
Potential Drug-Induced Liver Injury Phase 3 cSSSI Safety Population

- 0.2% (3/1763) Phase 3 ITT patients met criteria
  - 0.2% (2/1173) oritavancin patients
    - Both with liver disease at study entry
    - Neither had clinically relevant worsening of liver function tests after exposure to oritavancin
      - One met criteria at baseline
  - 0.2% (1/590) vancomycin patients
    - Had a lung resection 20 days prior to study entry & multiple postoperative complications

No oritavancin-treated patients met “Hy’s Law” criteria
Oritavancin Safety Summary

• Compared with vancomycin, oritavancin patients had:
  – Significantly lower percentages of:
    ▪ ≥1 adverse event
    ▪ ≥1 possibly related adverse event
    ▪ Discontinuations of study drug due to adverse events
  – Comparable or lower percentages of potential glycopeptide-related effects

• Oritavancin does not need to be dose adjusted in special populations

• Oritavancin does not require special laboratory monitoring to ensure safety
Benefit/Risk
Ongoing Medical Need

• Limitations of available therapies:
  – Antibacterial spectrum/development of resistance
  – Intolerance
  – Efficacy and/or safety in certain patient populations

• Continued need for alternative therapies for medically complex patients with cSSSI
Oritavancin
Benefits

- Demonstrated efficacy in treatment of cSSSI in medically complex patients
- Favorable safety profile versus a standard comparator
  - Fewer patients with:
    - Adverse events
    - Possible drug-related adverse events
    - Adverse events that led to discontinuation of study drug
    - Possible histamine-like infusion reactions
Oritavancin Benefits

- Potent, bactericidal activity with multiple MOAs
  - Reduced potential for oritavancin resistance

- Demonstrated clinical efficacy and safety
  - Simple, once-daily, IV dosing regimen
    - 200 mg (or 300 mg for weight >110kg)
    - No dose adjustments indicated for patients with hepatic or renal insufficiency
    - No indication for monitoring of therapeutic concentrations for efficacy or safety
    - No indication for special monitoring of laboratory parameters for safety
Oritavancin
Risks

• Risk of adverse events not observed in clinical studies
  – Monitoring of safety post-approval and in clinical trials

• Risk of development of resistance
  – Monitoring of resistance
    ▪ Planned surveillance studies
    ▪ Future clinical studies
### Oritavancin: Benefit/Risk Profile

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demonstrated efficacy</td>
<td>Injection site phlebitis</td>
</tr>
<tr>
<td>Favorable safety profile</td>
<td>Histamine-like infusion reactions</td>
</tr>
<tr>
<td>No special laboratory monitoring</td>
<td>Rare adverse events</td>
</tr>
<tr>
<td>Once-daily 3 to 7 day course</td>
<td>Development of resistance</td>
</tr>
<tr>
<td>Single dose adjustment</td>
<td></td>
</tr>
<tr>
<td>Multiple mechanisms of action</td>
<td></td>
</tr>
<tr>
<td>Potent in vitro activity</td>
<td></td>
</tr>
</tbody>
</table>
Back-up Slides
Presented
### Study ARRI: Clinical Cures in Patients with *Staphylococcus aureus* at Baseline (MITT)

Table 6.5 FDA Briefing Document

<table>
<thead>
<tr>
<th>Baseline Pathogen</th>
<th>ORI   % (n/N)</th>
<th>VAN   % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>70.6 (303/429)</td>
<td>71.2 (158/222)</td>
</tr>
<tr>
<td>MSSA</td>
<td>76.6 (219/286)</td>
<td>74.4 (116/156)</td>
</tr>
<tr>
<td>MRSA</td>
<td>55.9 (66/118)</td>
<td>67.9 (36/53)</td>
</tr>
</tbody>
</table>
MRSA and MSSA Susceptibility to Oritavancin are Near Identical

Sahm et al. ICAAC/IDSA 2008 Poster C1-144
Methicillin Resistance Does Not Mediate Exposure Necessary for Success in the Thigh Infection Model

Oritavancin Exposure Necessary for Success in Thigh Infection Model

- MSSA (13709)
- MRSA (USA400)
- MRSA (USA300)
- VRSA (VRS1)
- VRSA (VRS5)
- MRSA all
- VRSA all

AUC target

- Stasis
- 1 log kill
- 2-Log kill
- 3-Log kill

2605.02
## Study ARRI: Analysis of Failures in Patients with Baseline MRSA (MITT)

<table>
<thead>
<tr>
<th>Reasons for assignment to clinical failure</th>
<th>ORI % (n)</th>
<th>VAN % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Clinical Failures</td>
<td>52/118</td>
<td>17/53</td>
</tr>
<tr>
<td>Concomitant Antibiotic Procedure/Intervention (&gt;48 hrs after study drug start)</td>
<td>42.3 (22)</td>
<td>52.9 (9)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>21.2 (11)</td>
<td>23.5 (4)</td>
</tr>
<tr>
<td>Missing</td>
<td>13.5 (7)</td>
<td>11.8 (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- This chance imbalance in timing of surgical intervention in the ARRI MRSA subgroup led to a disproportionate decrease in failures in the vancomycin group.
## Study ARRI: Analysis of Failures (ITT)

<table>
<thead>
<tr>
<th>Reasons for assignment to clinical failure</th>
<th>ORI % (n)</th>
<th>VAN % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Clinical Failures</td>
<td>237/831</td>
<td>131/415</td>
</tr>
<tr>
<td>Concomitant Antibiotic</td>
<td>40.1 (95)</td>
<td>45.0 (59)</td>
</tr>
<tr>
<td>Procedure/Intervention (&gt;48 hrs hours after start of study drug)</td>
<td>46.8 (111)</td>
<td>48.9 (64)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>10.1 (24)</td>
<td>9.2 (12)</td>
</tr>
<tr>
<td>Missing</td>
<td>22.4 (53)</td>
<td>23.7 (31)</td>
</tr>
</tbody>
</table>
## Study ARRI: Failure Analysis in Patients with Surgery >48 Hours after Start of Study Drug (ITT)

<table>
<thead>
<tr>
<th></th>
<th>ORI % (n)</th>
<th>VAN % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery &gt;48 hrs after start of study drug</td>
<td>n=111</td>
<td>n=64</td>
</tr>
<tr>
<td>Baseline indication for earlier surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mod-Severe Devitalized Tissue</td>
<td>57 (63)</td>
<td>55 (35)</td>
</tr>
<tr>
<td>Mod-Severe Purulent Drainage</td>
<td>21 (23)</td>
<td>25 (16)</td>
</tr>
<tr>
<td>Both</td>
<td>17 (19)</td>
<td>23 (15)</td>
</tr>
</tbody>
</table>
## Study ARRI: Failure Analysis in Patients with Surgery >48 Hours after Start of Study Drug and Baseline MSSA (MITT)

<table>
<thead>
<tr>
<th></th>
<th>ORI</th>
<th>VAN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgery &gt;48 hrs after start of study drug</strong></td>
<td>n=29</td>
<td>n=19</td>
</tr>
<tr>
<td><strong>Baseline indication for earlier surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mod-Severe Devitalized Tissue</td>
<td>55 (16)</td>
<td>58 (11)</td>
</tr>
<tr>
<td>Mod-Severe Purulent Drainage</td>
<td>52 (15)</td>
<td>58 (11)</td>
</tr>
<tr>
<td>Both</td>
<td>21 (6)</td>
<td>16 (3)</td>
</tr>
</tbody>
</table>
## Study ARRI: Failure Analysis in Patients with Surgery >48 Hours after Start of Study Drug and Baseline MRSA (MITT)

<table>
<thead>
<tr>
<th></th>
<th>ORI % (n)</th>
<th>VAN % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery &gt;48 hrs after start of study drug</td>
<td>n=26</td>
<td>n=5</td>
</tr>
<tr>
<td>Baseline indication for earlier surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mod-Severe Devitalized Tissue</td>
<td>65 (17)</td>
<td>40 (2)</td>
</tr>
<tr>
<td>Mod-Severe Purulent Drainage</td>
<td>19 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Both</td>
<td>19 (5)</td>
<td>0</td>
</tr>
</tbody>
</table>
ARRD and ARRI – Study Design
Disease Category Definition

• Wound infection
  – Surgical or trauma sites within 30 days of incision/trauma, or
  – Infected ulcers >30 days, and
  – Purulent drainage from wound or ulcer not from organ space, and
  – Fever (38°C), or localized pain, or erythema, or localized swelling

• Cellulitis ≥3% (510 cm²) defined as:
  – Acute onset within 7 days before enrollment, pain or tenderness, cutaneous erythema, advancing edema or induration, measured or subjective fever within 3 days prior to enrollment, (ARRI - or elevated WBC count)

• Major abscess defined as:
  – Acute onset within 7 days before enrollment; purulent drainage or purulent aspirate; erythema; induration or tenderness; evidence of loculated fluid requiring intervention within 48 hrs of enrollment
ARRD and ARRI Study Design: First Follow-up Visit Definition IDCO = Cure

Investigator-Defined Clinical Outcome = Cure

**ARRD**
- Resolution of:
  - Purulent drainage (or aspirate)
  - Pain
  - Edema
  - Fever
  - Erythema
  - Tenderness, and
  - Induration
- Allowed for the presence of serous drainage and/or granulation tissue

**ARRI**
- Resolution of:
  - Purulent drainage (or aspirate)
  - Pain
  - Edema
  - Fever
  - Erythema
  - Tenderness
Study ARRI: Clinical Cures (IDCO)

% Clinical Cure

<table>
<thead>
<tr>
<th></th>
<th>ORI</th>
<th>VAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>83</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>608</td>
<td>736</td>
</tr>
<tr>
<td>CE</td>
<td>82</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>534</td>
<td>649</td>
</tr>
<tr>
<td>MITT</td>
<td>81</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>407</td>
<td>503</td>
</tr>
<tr>
<td>ME</td>
<td>81</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>363</td>
<td>448</td>
</tr>
</tbody>
</table>

Note: ORI = Original Intent, VAN = Various Analysis
Study ARRI: Clinical Cures by Baseline Pathogen S. Aureus (IDCO)

% Clinical Cure

<table>
<thead>
<tr>
<th></th>
<th>ORI</th>
<th>VAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>MITT</td>
<td>81</td>
<td>88</td>
</tr>
<tr>
<td>311/384</td>
<td>163/186</td>
<td></td>
</tr>
<tr>
<td>ME</td>
<td>81</td>
<td>88</td>
</tr>
<tr>
<td>276/340</td>
<td>145/164</td>
<td></td>
</tr>
</tbody>
</table>
Study ARRI: Clinical Cures by Baseline Pathogen MRSA (IDCO)

% Clinical Cure

<table>
<thead>
<tr>
<th></th>
<th>ORI</th>
<th>VAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>MITT</td>
<td>71</td>
<td>86</td>
</tr>
<tr>
<td>ME</td>
<td>69</td>
<td>85</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MITT</th>
<th>68/96</th>
<th>36/42</th>
</tr>
</thead>
<tbody>
<tr>
<td>ME</td>
<td>57/83</td>
<td>28/33</td>
</tr>
</tbody>
</table>
SDCO and Pathogen-Level Outcome, S. aureus (MRSA) by Baseline MIC, MITT Population
Clinical and Microbiological Responses by Vancomycin MIC, *S. aureus*, MITT Population

<table>
<thead>
<tr>
<th>VAN MIC at baseline (µg/mL)</th>
<th>ORI Treatment</th>
<th>VAN Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cure n/N (%)</td>
<td>Eradication n/N (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.25</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0.5</td>
<td>126/164 (77%)</td>
<td>116/164 (71%)</td>
</tr>
<tr>
<td>1</td>
<td>213/277 (77%)</td>
<td>199/277 (72%)</td>
</tr>
<tr>
<td>2</td>
<td>3/3 (100%)</td>
<td>3/3 (100%)</td>
</tr>
<tr>
<td>ALL</td>
<td>342/444 (77%)</td>
<td>318/444 (72%)</td>
</tr>
</tbody>
</table>

**Clinical and microbiological responses against *S. aureus*, ORI arm, were not impacted by VAN MIC**
Phase 3 Common Adverse Events
Treatment-Emergent Dizziness Oritavancin

• 3% (35 of 1173) ORI Phase 3 ITT patients had at least 1 treatment-emergent event of dizziness
  – Verbatim Terms:
    ▪ Dizziness/dizzy (n=28)
    ▪ Lightheaded (n=4)
    ▪ Giddiness (n=3)
  – Serious: none
  – Discontinuations: none
  – Intensity: 80% mild; 20% moderate; 0% severe
  – Duration
    ▪ 91% (32 of 35) ≤ 7 days
    ▪ 3% (1 of 35) intermittent mild episodes x 25 days, unrelated
    ▪ 6% (2 of 35) ongoing, both mild, both unrelated
Significance of eosinophilic granules

- Translate ultrastructurally into large secondary lysosomes containing lamellar membrane inclusions and punctiform electron dense material
- EM picture is indicative of phospholipidosis (PL)
- In vitro secondary lysosomes are associated with high concentrations of oritavancin
- Presence of PL is not evidence of toxicity but is the result of an adaptive cellular process as a reaction against the intracellular concentrations of drug
- Functional or toxic effects are the result of either excessive accumulation of phospholipids or the intrinsic toxic properties of the drug at high intracellular concentrations
Oritavancin Repeated Dose Studies
Persistent Histiocytosis (3)

- Cumulative doses in dogs with persistent histiocytosis show a large multiple over cumulative dose in man during a standard course of treatment

<table>
<thead>
<tr>
<th>Cumulative Dose In Man</th>
<th>Cumulative Dose In Dog</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg/day 3-7 days ≈ 20 mg/kg</td>
<td>45 mg/kg/day 90 days ≈ 4000 mg/kg</td>
</tr>
</tbody>
</table>

- In the dog 2 week study with 4 week reversibility at the 15 mg/kg dose (cumulative dose: 225 mg/kg)
  - Persistence of histiocytes with eosinophilic granular cytoplasm is minimal in liver, spleen, bone marrow
  - Perivascular inflammation is no longer present at the injection site at the end of the reversibility period
## Phase 3 Liver Function Laboratory Results

### Normal Shifts to Substantially Abnormal (1)

<table>
<thead>
<tr>
<th>Analyte</th>
<th>ORI (N=1173)</th>
<th>VAN (N=590)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;3-5 % (n)</td>
<td>&gt;3-5 % (n)</td>
</tr>
<tr>
<td></td>
<td>&gt;5 % (n)</td>
<td>&gt;5 % (n)</td>
</tr>
<tr>
<td></td>
<td>&gt;10 % (n)</td>
<td>&gt;10 % (n)</td>
</tr>
</tbody>
</table>

### Normal Baseline Shifts to Substantially Abnormal Maximum High Value

<table>
<thead>
<tr>
<th>x ULN</th>
<th>ORI (N=1173)</th>
<th>VAN (N=590)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>975 0.8 (8)</td>
<td>478 1.5 (7)</td>
</tr>
<tr>
<td>AST</td>
<td>944 0.4 (4)</td>
<td>465 1.1 (5)</td>
</tr>
</tbody>
</table>

---

**ALT**

- ORI: 975 cases, >3-5: 0.8%, >5: 0.1%, >10: 0%
- VAN: 478 cases, >3-5: 1.5%, >5: 0%, >10: 0.2%

**AST**

- ORI: 944 cases, >3-5: 0.4%, >5: 0.2%, >10: 0%
- VAN: 465 cases, >3-5: 1.1%, >5: 0%, >10: 0.2%
# Phase 3 Liver Function Laboratory Results

Normal Shifts to Substantially Abnormal (2)

<table>
<thead>
<tr>
<th>Analytes</th>
<th>ORI (N=1173)</th>
<th>VAN (N=590)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥3 x ULN</td>
<td>≥3 x ULN</td>
</tr>
<tr>
<td>Alk Phos</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>% (n)</td>
<td>% (n)</td>
</tr>
<tr>
<td>972</td>
<td>0.1 (1)</td>
<td>492</td>
</tr>
<tr>
<td>T.Bilirubin</td>
<td>≥ 2.0 mg/dL</td>
<td>≥ 2.0 mg/dL</td>
</tr>
<tr>
<td></td>
<td>% (n)</td>
<td>% (n)</td>
</tr>
<tr>
<td>982</td>
<td>0.1 (1)</td>
<td>478</td>
</tr>
<tr>
<td></td>
<td>0.4 (2)</td>
<td></td>
</tr>
</tbody>
</table>
### TEAEs by SOC Disorders in ≥1% of Phase 3 cSSSI ITT Patients - Late Post Study Drug Period

<table>
<thead>
<tr>
<th>SOC Disorders in which ≥1% of Patients had a TEAE</th>
<th>≥Day 37 ≤ Day 90</th>
<th>Percentage of Patients with ≥ 1 TEAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>1.6 (16)</td>
<td>1.2 (6)</td>
</tr>
<tr>
<td>General</td>
<td>1.1 (11)</td>
<td>1.0 (5)</td>
</tr>
<tr>
<td>Infections &amp; infestations</td>
<td>2.8 (29)</td>
<td>2.8 (14)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>1.1 (11)</td>
<td>0.8 (4)</td>
</tr>
<tr>
<td>Nervous system</td>
<td>1.0 (10)</td>
<td>0.6 (3)</td>
</tr>
<tr>
<td>Respiratory, thoracic &amp; mediastinal</td>
<td>0.5 (5)</td>
<td>1.4 (7)</td>
</tr>
<tr>
<td>Skin and subcutaneous</td>
<td>1.0 (10)</td>
<td>1.0 (5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>ORI (N=1173) % (n)</th>
<th>VAN (N=590) % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of Patients with ≥ 1 TEAE</td>
<td>7.9 (81)</td>
<td>6.3 (32)</td>
</tr>
</tbody>
</table>

At end of study, 2.9% (34/1173) ORI and 2.7% (16/590) VAN patients had ongoing treatment-related adverse events.
0.3% (4/1173) ORI and 0% (0/590) VAN patients had serious adverse events of septic shock

- 2 ORI patients – septic shock likely gram-positive etiology

- Case specifics
  - ARRD 069-3283
    - Study entry condition diabetes mellitus of moderate intensity
    - ORI 268 mg Day 1-7 for cellulitis of upper leg
    - Day 43: septic shock due to *gangrenous* colon
    - Day 44: death
  - ARRI 005-0007
    - ORI Day 1-6, aztreonam Day 1-7
    - Day 6: *Gram-negative* bacteremia
    - Day 7: Septic shock
    - Day 12: Death
Serious Adverse Events Septic Shock (2)  
Phase 3 cSSSI Safety Population

- Case specifics (continued)
  - **ARRD 705-7200**
    - Study entry condition diabetes mellitus of severe intensity
    - ORI 201 mg Day 1 for cellulitis of lower leg, *E. faecalis* and *S. aureus* bacteremia
    - Day 2: Septic shock post surgical debridement of subcutaneous tissue and muscle. Per Investigator, unrelated to study drug or study disease
    - Day 2: Death
  - **ARRD 069-2864**
    - ORI 127 mg Day 1
    - Day 1: Septic shock led to discontinuation of study drug
    - Large shoulder abscess from skin popping
      - MSSA; blood cultures negative
      - Hypotension after surgical drainage
      - Medication error, IV nitroglycerine instead of IV dopamine
      - Subsequent profound shock, death
Adverse Events – Osteomyelitis Summary
Phase 3 cSSSI Safety Population

- 1.0% (12/1173) ORI and 0.2% (1/590) VAN patients had treatment-emergent osteomyelitis
  - None were considered to be possibly related to study drug by their Investigator
  - None had imaging studies reported at study entry or >1 day prior to “onset” of osteomyelitis adverse event

- 0.3% (5/1173) ORI patients had SAEs of osteomyelitis
  - Onset Day 1-7 for 2, Day 8-14 for 2, and Day 43 for 1

- Of 12 ORI patients with osteomyelitis
  - 6 with likely contiguous osteomyelitis on or before Day 7
    - 1 had MRI Day 2, 1 had X-ray Day 5, 1 had X-ray Day 6
  - 4 with likely contiguous osteomyelitis between Days 8 and 14
    - 1 had X-ray and bone scan Day 13
  - 2 with osteomyelitis reported late in study (Day 41 and Day 43)

- 1 VAN patient with likely contiguous osteomyelitis on Day 6
0.5% (6 of 1173) oritavancin patients had 7 events of pseudomembranous colitis/CDI
  - 2 mild, 4 moderate
  - 1 severe (onset Day 39, unrelated to study drug, ongoing)
  - Onset between Days 5 to 48
  - All received other systemic antibiotics prior to event

0.5% (3 of 590) vancomycin patients had 4 events of pseudomembranous colitis/CDI
  - All moderate
  - Onset between Days 22 to 32
  - All received other systemic antibiotics prior to event
TEAEs Possibly Related to Immunosuppression Phase 3 cSSSI Safety Population

- No imbalance and low percentage of patients with TEAEs in
  - SOC of Infections and Infestations
    - 16.9% (198/1173) ORI patients
    - 18.3% (108/590) VAN patients
  - SOC of Neoplasms, Benign, Malignant, Unspecified
    - 0.2% (2/1173) ORI patients
    - 0.8% (5/590) VAN patients
    - p-value ORI vs VAN = 0.046
  - HLT of fungal infections NEC
    - 0.9% (10 /1173) ORI patients
    - 0.8 % (5/590) VAN patients
  - HLT of candida infections
    - 1.7% (20/1173) ORI patients
    - 2.0% (12/590) VAN patients
  - HLT of myobacterial tuberculosis
    - 0.1% (1/1173) ORI patients
    - 0.0% (0/590) VAN patients
ORITAVANCIN
Weight-Based Dose Adjustment Rationale

- Dose-normalized exposures for 200 mg (adjusted for weight > 110 kg) and 3 mg/kg for the 360 infected patients included in the population PK model
93.8 and 100% of MSSA and *S. pyogenes* are susceptible using CLSI interpretive criteria \(^1\)

For staphylococci, the PK-PD goal of therapy for net bacterial stasis is 25% T>MIC and that for streptococci is 30% T>MIC \(^2\)

Figure shows the regression curve and individual cephalaxin concentrations of 12 volunteers after administration of a 1 gm dose \(^3\)

The MIC\(_{50/90}\) for MSSA and *S. pyogenes* is 4/8 and 1/1 mg/L, respectively \(^1\)

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CEPHALEXIN IN VITRO ACTIVITY
Methicillin-Susceptible S. aureus and S. pyogenes