Non-Inferiority Margin Justification

Alan Forrest, Pharm.D.
Senior Scientist, Pharmacometrics
Institute for Clinical Pharmacodynamics, Ordway Research Institute
Research Professor
Schools of Pharmacy and Medicine, University at Buffalo
Special Government Employee
Office of Clinical Pharmacology and Biopharmaceutics, CDER, FDA
ORITAVANCIN
Two Well-Controlled Clinical cSSSI Studies

• Study ARRD
  – Initiated in February 1999 - completed in June 2001
    ▪ 15% NI margin was built on principles from the 1992 FDA Points-to-Consider (PTC)
  – Phase 3, expected cure 80%, 60% evaluability
  – 531 patients randomized; 74% were evaluable
  – Primary endpoint: oritavancin clinical efficacy (1.5 mg/kg, 3.0 mg/kg) NI to that of vancomycin/cephalexin
  – NI was achieved within the pre-specified 15% NI margin

• Study ARRI
  – Initiated in June 2001 - completed in November 2002
    ▪ In 2001, the FDA reconsidered 1992 PTC and proposed the use of clinical & statistical rationale (in alignment ICH Guidance Documents E9 & E10)
  – Primary endpoint: oritavancin clinical efficacy NI to that of vancomycin/cephalexin
  – 1267 patients randomized; 79% were evaluable
  – NI was achieved within the pre-specified 10% margin
## ORITAVANCIN AND VANCOMYCIN

### Success/Cure Rates at Test-of-Cure Visit

<table>
<thead>
<tr>
<th>Study ARR</th>
<th>Patient Population</th>
<th>ORI 1.5 mg/kg N=173</th>
<th>ORI 3.0 mg/kg N=169</th>
<th>VAN N=175</th>
<th>Difference Between ORI and VAN (Mean, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARRD</td>
<td>CE</td>
<td>75.8</td>
<td>75.4</td>
<td>80.0</td>
<td>-4.2 (-14.4, 5.9)</td>
</tr>
<tr>
<td></td>
<td>ITT</td>
<td>75.9</td>
<td>74.0</td>
<td>80.3</td>
<td>-4.4 (-14.3, 5.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study ARR</th>
<th>Patient Population</th>
<th>ORI 200 mg/300 mg N=831</th>
<th>VAN N=415</th>
<th>Difference Between ORI and VAN (Mean, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARRI</td>
<td>CE</td>
<td>78.5</td>
<td>75.9</td>
<td>2.6 (-3.0, 8.2)</td>
</tr>
<tr>
<td></td>
<td>ITT</td>
<td>78.8</td>
<td>76.3</td>
<td>2.4 (-2.8, 7.6)</td>
</tr>
</tbody>
</table>
SELECTING NON-INFERIORITY MARGINS
Four Considerations

- **ICH Guidance Document (E10)**
  - **Study design characteristics**
    - The details of the study design should adhere closely to that of the relevant historical studies
  - **Study oversight**
    - The study conduct should adhere closely to the relevant historical studies and be of high quality
  - **Historical evidence of sensitivity-to-drug effect**
    - The antimicrobial therapy standard provides an effect superior to that of placebo (of at least a minimum size)
  - **Defining an acceptable non-inferiority margin**
    - The considerations should be based upon acceptable clinical AND statistical criteria
Vancomycin with step-down to cephalexin was selected as a comparator

- **Vancomycin is a relevant comparator** and remains the standard-of-care for the treatment of cSSSI and MRSA infections worldwide

Pivotal studies were well-designed

- Detailed inclusion/exclusion criteria were **in accordance to global regulatory guidelines** and expert organizations (IDSA, ESCMID)
- The protocols provided clear, **concise definitions** of the common types of infections observed in cSSSI category, including **wound** (28% of patients), **major abscess** (42% of patients) & **cellulitis** (29% of patients)
- Patients for whom IV therapy was considered an appropriate standard of care were enrolled with **substantial comorbidities**, including diabetes, HIV, bacteremia, neutropenia, burns, radiation therapy, organ transplant, renal dysfunction and alcoholism, etc.
During World War One, with surgical debridement, mortality rates ranged from 50-75%; conversely the anticipated survival rate/placebo cure rate was approximately 25-50%.

Placebo vs. impetigo (uSSSI)
- 14 impetigo studies (1974-2008): response rates ranged from 0 to 52%; pooled average 25%

Placebo vs. active drug (cSSSI)
- Flores (1943) response rates: placebo 50%; active 98%
- Cruikshank (1947) response rates: placebo 15, 31%; active 77, 85%

Since 2000, seven published Phase 3 clinical trials in cSSSI used vancomycin as the standard comparator
- In ITT or mITT populations, vancomycin response rates ranged from 74 to 81%, with a pooled average of 81%
Model developed using data from 134 levofloxacin-treated patients with either urinary, pulmonary, or cSSSI or uSSSI.

Final logistic regression model for clinical response included drug exposure and infection site.

The model-predicted probability of clinical response was ~48% as drug exposure approached zero and ~100% at high exposures, for patients with skin and soft tissue infections.

SELECTING NON-INFERIORITY MARGINS
Exposure-Response Evidence of Drug Effect

- Model developed using data from 76 tigecycline-treated patients with cSSSI
- Patients stratified based upon pathogen(s)
- In patients with *S. aureus* and/or *S. pyogenes* infection, the model-predicted probability of response was ~20% as drug exposure approached zero and approached 100% response at AUC:MIC > 40

SELECTING NON-INFERIORITY MARGINS

Defining an Acceptable NI Margin

- The basis of a NI margin should be acceptable clinical and statistical criteria
- Comparison to recent registration studies confirm study clinical cure rates, historical reliability and reproducibility
- cSSSI comprises a diverse group of patients with varying response rates dependent upon disease severity, site of infection and underlying comorbidities;
  - The literature suggests a placebo response rate of no more than 20-50% in severe cSSSI infections including cellulitis, wound and abscess
  - A typical vancomycin response rate of ~80% is a very conservative estimate; in pharmacodynamic studies in evaluable patients, the upper asymptote is 90-100%
First, some useful definitions:

- **M1** = the smallest treatment effect of active or standard therapy over that of placebo

- **M2** = a fraction of M1, chosen because the test drug should retain some substantial fraction of the effect of the standard drug

The table on the next slide assumes:

- An **80% cure rate for the standard therapy** group (conservatively-low) with differing rates of clinical cure in a placebo group

- Per the most commonly-used value, a **fraction of 50% of M1** was used for **M2**; 66% of M1 was also computed for comparison
SELECTING NON-INFERIORITY MARGINS
Defining an Acceptable NI Margin

<table>
<thead>
<tr>
<th>Placebo Response Rate</th>
<th>Effect of Vancomycin (M1)</th>
<th>NI Margin at 50% M1 (M2)</th>
<th>NI Margin at 66% M1 (M2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td>60%</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td>25%</td>
<td>55%</td>
<td>27.5%</td>
<td>18.3%</td>
</tr>
<tr>
<td>30%</td>
<td>50%</td>
<td>25%</td>
<td>16.7%</td>
</tr>
<tr>
<td>35%</td>
<td>45%</td>
<td>22.5%</td>
<td>15%</td>
</tr>
<tr>
<td>40%</td>
<td>40%</td>
<td>20%</td>
<td>13.5%</td>
</tr>
<tr>
<td>45%</td>
<td>35%</td>
<td>17.5%</td>
<td>11.7%</td>
</tr>
<tr>
<td>50%</td>
<td>30%</td>
<td>15%</td>
<td>10%</td>
</tr>
</tbody>
</table>

- The placebo rates represent a **conservative range** of **20 to 50%** from the historical literature and contemporary exposure-response data.

- For example, ensuring **≥ 50% treatment effect**, with a **35% historical placebo response** and an active-control effect (M1) of **45%**, a **non-inferiority margin of 22.5%** would be acceptable and at a placebo response of **50%**, the **non-inferiority margin would still be 15%**.

- Thus, **non-inferiority margins** of **15%** (for Study ARRD) and **10%** (for Study ARRI) would have **exceeded** necessary power to discriminate from placebo.
Both studies adhered to the major NI margin considerations, as well as the contemporary regulatory guidance principles and good clinical practice standards.

The NI margins selected for Studies ARRD (15%) and ARRI (10%) are clinically relevant and statistically sound.

Similar to the literature, the oritavancin cSSSI population was inclusive of patients with severe infections that were complicated by substantial underlying comorbidities.

If the NI margin is to safely discriminate drug effect from that of placebo in seriously ill patients with significant comorbidities, a NI margin of 15% is very conservative.
Acknowledgements

Evelyn J. Ellis-Grosse, Ph.D.
   e2g Biopharmaceutical Consulting
   Atlanta, GA

Paul Ambrose, Pharm.D., FIDSA and
Sujata Bhavnani, Pharm.D., MS
   Institute for Clinical Pharmacodynamics,
   Ordway Research Institute
   Albany, NY