
Non-Inferiority Margin Justification

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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

Study ARRD Patient Population	ORI 1.5 mg/kg N=173	ORI 3.0 mg/kg N=169	VAN N=175	Difference Between ORI and VAN (Mean, 95% CI)	
				ORI 1.5 mg/kg	ORI 3.0 mg/kg
CE	75.8	75.4	80.0	-4.2 (-14.4, 5.9)	-4.6 (-14.9, 5.7)
ITT	75.9	74.0	80.3	-4.4 (-14.3, 5.6)	-6.3 (-16.4, 3.9)

Study ARRI Patient Population	ORI 200 mg/ 300 mg N=831	VAN N=415	Difference Between ORI and VAN (Mean, 95% CI)
CE	78.5	75.9	2.6 (-3.0, 8.2)
ITT	78.8	76.3	2.4 (-2.8, 7.6)

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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

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Study Design Characteristics

- 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.

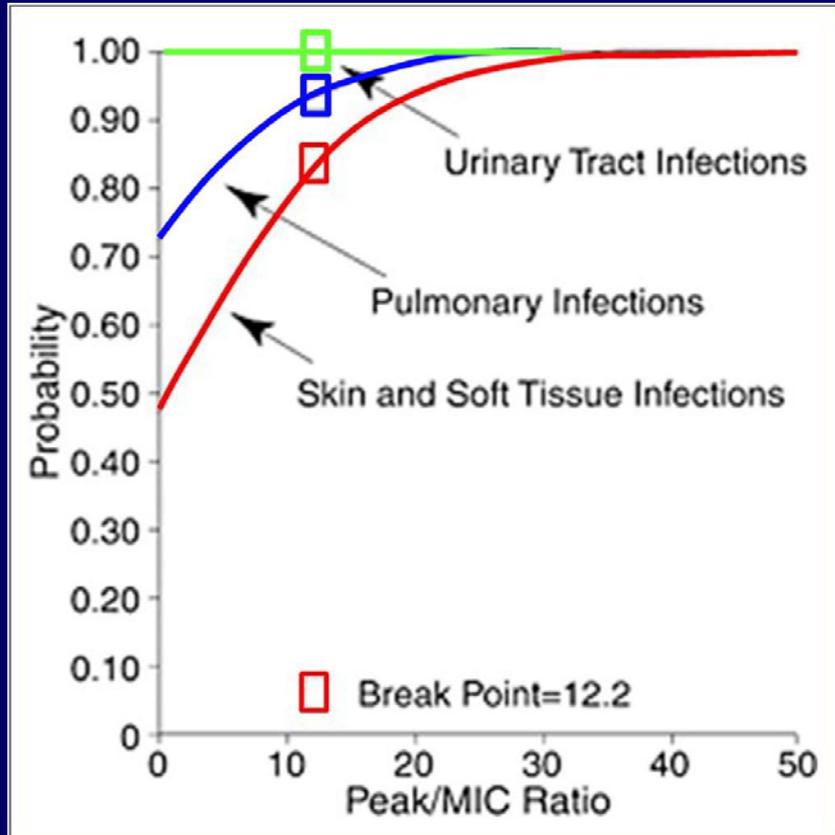
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Historical Evidence of Sensitivity-to-Drug Effect

- 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%**

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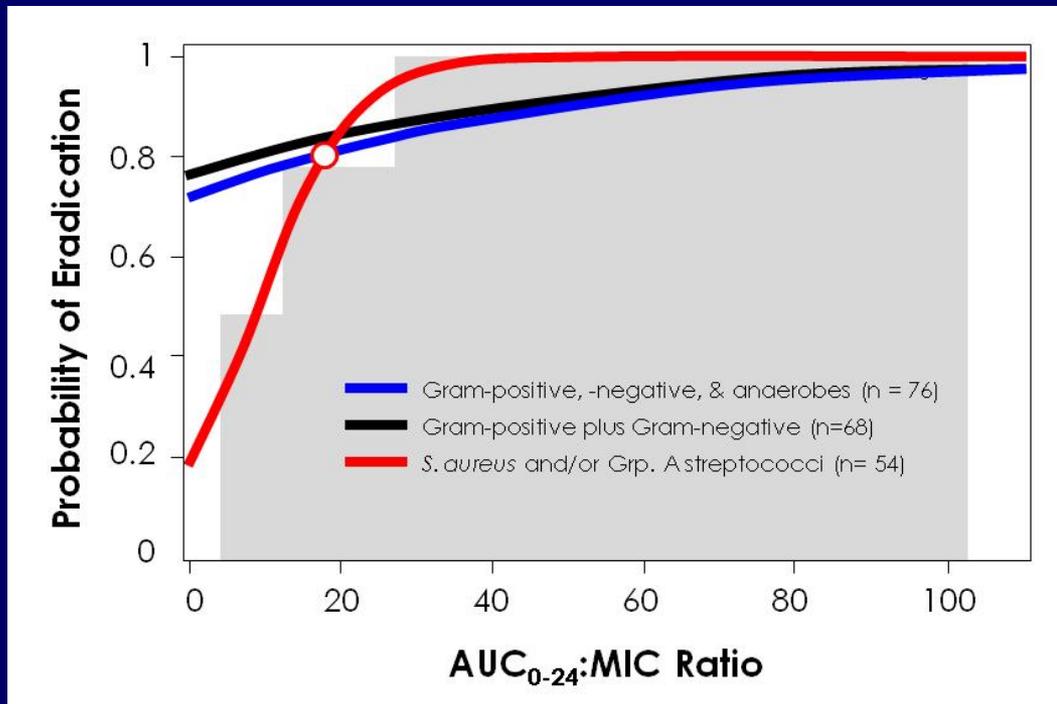
Exposure-Response Evidence of Drug Effect



- 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**

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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**

Meagher A, Passarell J, Cirincione B, Van Wart S, Liolios K, Babinchak T, Ellis-Grosse EJ, Ambrose PG. Exposure-response analysis of the efficacy of tigecycline in patients with complicated skin and skin structure infections. *Antimicrob Agents Chemother.* 2007;51:1939-1945.

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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%

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Defining an Acceptable NI Margin

- 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

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Defining an Acceptable NI Margin

Placebo Response Rate	Effect of Vancomycin (MI)	NI Margin at 50% M1 (M2)	NI Margin at 66% M1 (M2)
20%	60%	30%	20%
25%	55%	27.5%	18.3%
30%	50%	25%	16.7%
35%	45%	22.5%	15%
40%	40%	20%	13.5%
45%	35%	17.5%	11.7%
50%	30%	15%	10%

- The placebo rates represent a **conservative range** of **20 to 50%** from the historical literature and contemporary exposure-response data
- For example, ensuring \geq **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

NON-INFERIORITY MARGIN JUSTIFICATION

Conclusions

- 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, theoritavancin 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**

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