

Outline / Agenda

- **Justification of NI margin in cSSSI**
- **A proposal for future NI trials in cSSSI**

Khalid Islam, PhD

Charles S. Davis, PhD, Statistical Consultant

L.J. Wei, PhD, Professor of Biostatistics, Harvard

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Justification of NI Margin in cSSSI

- ICH guidelines for selection of NI margins
- Application to cSSSI
- NI margin with linezolid as the comparator

ICH Guidelines E9: Non-Inferiority Trials

- Protocol should clearly specify that testing for non-inferiority is the explicit intention
- NI margin should be specified in the protocol
 - Choice should be **justified clinically**
- Statistical analysis is generally based on the use of confidence intervals
 - For non-inferiority trials a **one-sided confidence interval** should be used

ICH Guidelines E10: NI Margin

- “The **degree of inferiority of the test treatment to the control that the trial will attempt to exclude statistically**”
- The NI margin generally is identified based on **past experience in placebo-controlled trials** of adequate design under conditions similar to those planned for the new trial

Prospective Rationale for Selecting NI Margin

- **Arpida followed ICH E9 and E10 guidelines**
- **No placebo-controlled studies in cSSSI**
- **NI margins of 10-15% have been used in registration trials**
- **Linezolid was thought to be the superior comparator**

Justification of NI Margin for cSSSI Trials Based on Phase 2 Dalbavancin cSSSI Trial

- Estimate of antibiotic efficacy is based on comparison between two doses and one dose; therefore likely to be conservative when compared with placebo
 - Two-dose arm is 30% more efficacious than one-dose arm (91% vs 60%)
 - Preservation of 50% of the treatment effect suggests that a 15% NI margin would be reasonable for a cSSSI study
- Subsequent Phase 3 study using two doses demonstrated clinical cure rates similar to those from the Phase 2 study (89% vs 91%)

Justification of NI Margin for cSSSI Trials Based on Estimated Cure Rates for Placebo and Active Comparator

- **Although difficult to quantify, the placebo cure rate in cSSSI is likely less than 50%**
- **The cure rate for the active control (linezolid) is at least 75%**

Linezolid Cure Rates

Study

ITT

Wilcox et al. (2004)

113 / 117 (97%)

Jauregui et al. (2005)

234 / 283 (83%)

Weigelt et al. (2005)

439 / 583 (75%)

Stevens et al. (2000)

278 / 400 (70%)

Pooled estimate

77%

95% CI

(75%, 79%)

Linezolid Cure Rates

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Wilcox et al. (2004)	113 / 117 (97%)
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Stevens et al. (2000)	278 / 400 (70%)
Pooled estimate	77%
95% CI	(75%, 79%)
ASSIST-1	220 / 248 (90%)
ASSIST-2	199 / 243 (82%)
Pooled estimate	79%
95% CI	(77%, 81%)

Linezolid Cure Rates from Meta-Analysis¹

- Based on data from eight studies in skin and soft-tissue infections
- The pooled cure rate for linezolid was 90.3%
- The 95% CI is (88.8%, 91.8%)

NI Margins Based on Linezolid Cure Rates and Assumed Placebo Rates

Placebo Cure Rate	Linezolid 75%	Linezolid 77%	Linezolid 89%
35%	20.0%	21.0%	27.0%
50%	12.5%	13.5%	19.5%

Is There Evidence to Support a Different NI Margin if Linezolid is the Comparator?

- **Vancomycin is an appropriate choice for MRSA infections. However, for the treatment of infections due to MSSA, semi-synthetic penicillins are superior compared to vancomycin ¹**
- **Linezolid is approved for infections caused by MRSA, MSSA, and streptococci ²**

1. Medical reviewer comment Cubicin NDA 21-572.

2. Linezolid approved label.

Linezolid Cure Rates

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Randomized, Parallel-Group Trials of Linezolid in cSSSI

Study	Linezolid	Comparator
1. Wilcox et al. (2004)	113 / 117 (97%)	103 / 111 (93%)
2. Jauregui et al. (2005)	234 / 283 (83%)	437 / 571 (76%)
3. Weigelt et al. (2005)	439 / 583 (75%)	402 / 575 (70%)
4. Stevens et al. (2000)	278 / 400 (70%)	274 / 419 (65%)

Linezolid was shown more efficacious than:

- 1. Teicoplanin by 4%**
- 2. Dalbavancin by 6%**
- 3. Vancomycin by 5%**
- 4. Semi-synthetic penicillins by 4%**

Pooled Analysis of Randomized, Parallel-Group Trials of Linezolid in cSSSI

■ Difference (linezolid – comparator):

- Point estimate: **5.0%**
- 95% CI: **(2.1%, 7.8%)**

Pooled Analysis Based on Falagas et al. (2008)

■ Difference (linezolid – comparator):

- Point estimate: **4.5%**
- 95% CI: **(2.2%, 6.8%)**

Conclusions

- **An NI margin of at least 12.5% is reasonable, especially in populations with significant MRSA**
- **A larger NI margin is reasonable when choosing linezolid, rather than vancomycin, as the active control**

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Choosing the Ideal NI Margin

- How much efficacy to give up from the active control chosen?
- How to quantify the loss of active control efficacy due to resistance over time?
- How to account for different types of infection that are included in clinical trials?

Use the contrast between placebo and active control to set the NI margin

Weighted Average NI Margin

Degree of Severity	Patient Proportion (planned)	Placebo Rate (liberal)	Active Control Rate (conservative)	NI Margin
Severe	0.33	0.40	0.80	0.20
Serious	0.33	0.55	0.85	0.15
Not serious	0.33	0.80	0.90	0.05

Weighted Average NI Margin = 0.13

Planning the Sample Size

Use the weighted average NI margin to plan the sample size via one-sided confidence interval estimate

Monitoring the Study

- **Closely match the planned proportions of subjects in each severity category**
- **If the proportions cannot be attained, determine the possible change in weighted NI margin and potentially adjust the sample size**
- **Use the ‘prediction’ idea to assess the feasibility / futility of demonstrating noninferiority at the end of the trial**

Final Analysis

- Use the observed proportions of patients before unblinding to adjust the NI margin for the final analysis

NI Margin Example Based on Weighted Average

Infection Type (IDSA Margin)	Linezolid ¹	Daptomycin ²	Tigecycline ³	Iclaprim ⁴
Wounds & Ulcers (21)	2.4 (11.5)	13.3 (63.4)	1.9 (9)	8.2 (39)
Cellulitis (14)	6.3 (44.8)	*	8.3 (59)	4.6 (32.9)
Abscesses and others (7)	3.1 (43.7)	2.6 (36.6)	2.2 (32)	2.0 (28.1)
Weighted NI margin	12%	16%	12%	15%

1. Study 55.
2. Cubicin label.
3. Combined Tygacil-Adis report.
4. ASSIST combined.

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Focus of Future Efforts

- **Retention of efficacy in different scenarios**
- **Accounting for the mix of pathogens**
- **Proper comparator choices**
- **Better surveillance data**

Now this is not the end.

It is not even the beginning of the end.

**But it is, perhaps, the end of the
beginning!**

Winston Churchill, November 10, 1942