NDA 22-269

ICLAPRIM: Concentrate for Solution for Infusion

Indication: Complicated Skin and Skin Structure Infections (cSSSI)

Anti-Infective Drugs Advisory Committee Meeting

November 20, 2008

Presentation Agenda

Introduction
Khalid Islam, PhD

Microbiology
Mark E. Jones, PhD

Clinical Efficacy and Safety
Wayne M. Dankner, MD, Senior Medical Director,
Therapeutic Area Lead – ID, PAREXEL International

LJ Wei, PhD, Professor of Biostatistics
Harvard University

Medical Need for a New Antibiotic: The Case for Iclaprim
Vance G. Fowler, Jr. MD, MHS
Associate Professor of Medicine, Duke University

Concluding Remarks
Khalid Islam, PhD

Additional Experts

Cardiology

Peter Kowey, MD
Chief of the Division of Cardiovascular Diseases
Lankenau Hospital

Hepatology

James H. Lewis, MD, Professor of Medicine,
Director of Hepatology
Georgetown University Hospital

Statistics

Charles Davis, PhD, Statistical Consultant

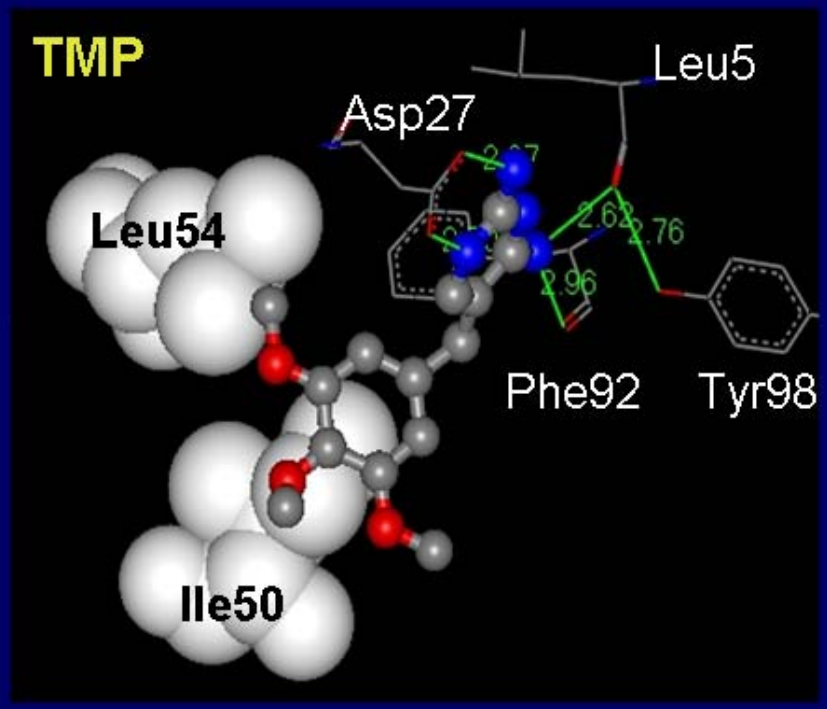
Current Treatments in cSSSI: Emerging Challenges

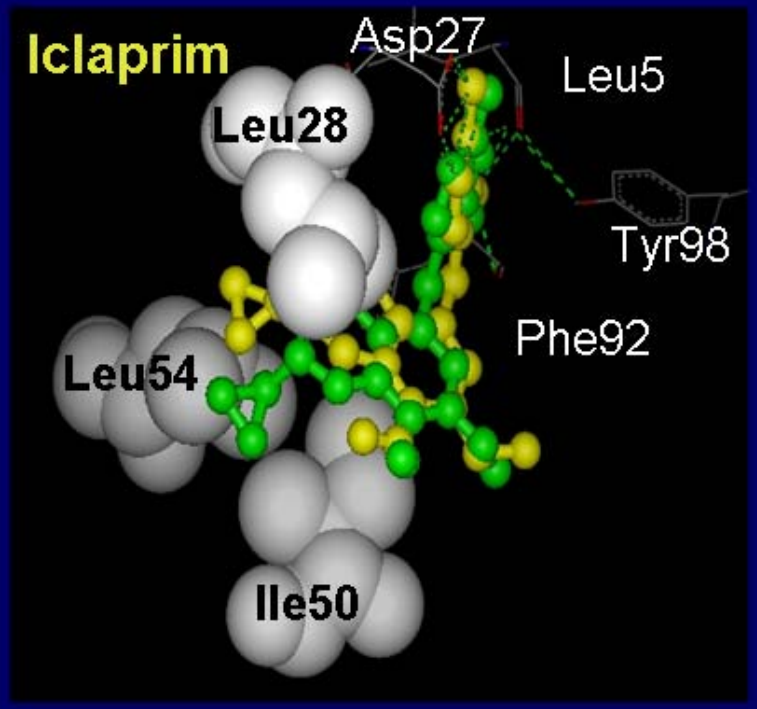
- **Cell wall / membrane inhibitors**
  - **β -lactams:** ***High resistance rates (MRSA)***
  - **Glycopeptides / lipoglycopeptide:** ***VISA / VRSA / MIC creep***
- **Protein synthesis inhibitors**
  - **Oxazolidinones (linezolid) –** ***emerging resistance***
  - **Tetracyclines (tigecycline)**

Community-acquired MRSA (CA-MRSA)

- Genotypically different from HA-MRSA
- Toxin production (PVL)
- Spreading from community to hospital

Rationally Designed vs a Clinically Established Target: DHFR Enzyme





>4 decades of clinical experience with TMP: Safe and well tolerated

Iclaprim is designed to target Gram-positive pathogens

Dale GE, et al. *J Mol Biol.* 1997;266:23. Rouch DA, et al. *Mol Microbiol.* 1989;3:161. Burdeska A, et al. *FEBS Lett.* 1990;266:159. Oefner C, et al. *18th ECCMID.* 2008; Abstract O486. Schneider P, et al. *Bioorg Med Chem Lett.* 2003;13:4217-4221.

Advantages of Iclaprim

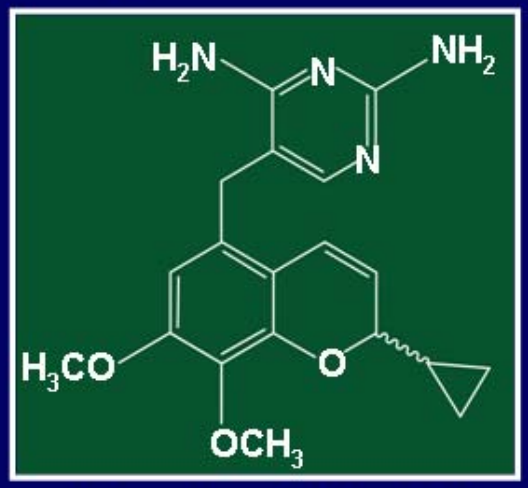
- Differentiated mechanism of action
- Targeted Gram-positive spectrum of activity
- Potent activity against resistant bacteria
- Rapidly bactericidal
- Low propensity for development of resistance
- High distribution in tissues and organs
- Low potential for drug-drug interactions
- Reduced impact on commensal bacterial flora
- Orally bio-available

Microbiology

Mark E. Jones, PhD

Iclaprim: A New Generation DHFR Inhibitor

- Diaminopyrimidine with potentiated binding to DHFR
  - Increased potency against Gram-positive pathogens
  - Rapid bactericidal activity
  - Low propensity for resistance development
- Extensive distribution in tissues
- No antagonism with >30 different antibiotics
- Orally bio-available



Iclaprim, MW=354

Hawser S, et al. *Biochem Pharmacol* 2006;71:941-948. Hawser S et al. *3rd ISRGPI 2006*; Abstract CPLA 34. Hawser et al. *42nd ICAAC* 2002; Abstract F-2028. Jones ME et al. *47th ICAAC* 2007; Abstract E-906.

Surveillance Study Establishes Iclaprim's Potency Against Important cSSSI Pathogens

USA and Europe, 2004-2006

		MIC_{90} (µg/mL)
	N	ICL
S. aureus	4516	0.12
MRSA	3003	0.12
MSSA	1513	0.12
GAS	604	0.03
GBS	204	0.25

Sader HS, et al. Presented at: *47th ICAAC* 2007; Abstract E902.
Jones RN, et al. Presented at: *47th ICAAC* 2007; Abstract E911.

Also Active Against Other Resistant MRSA Phenotypes

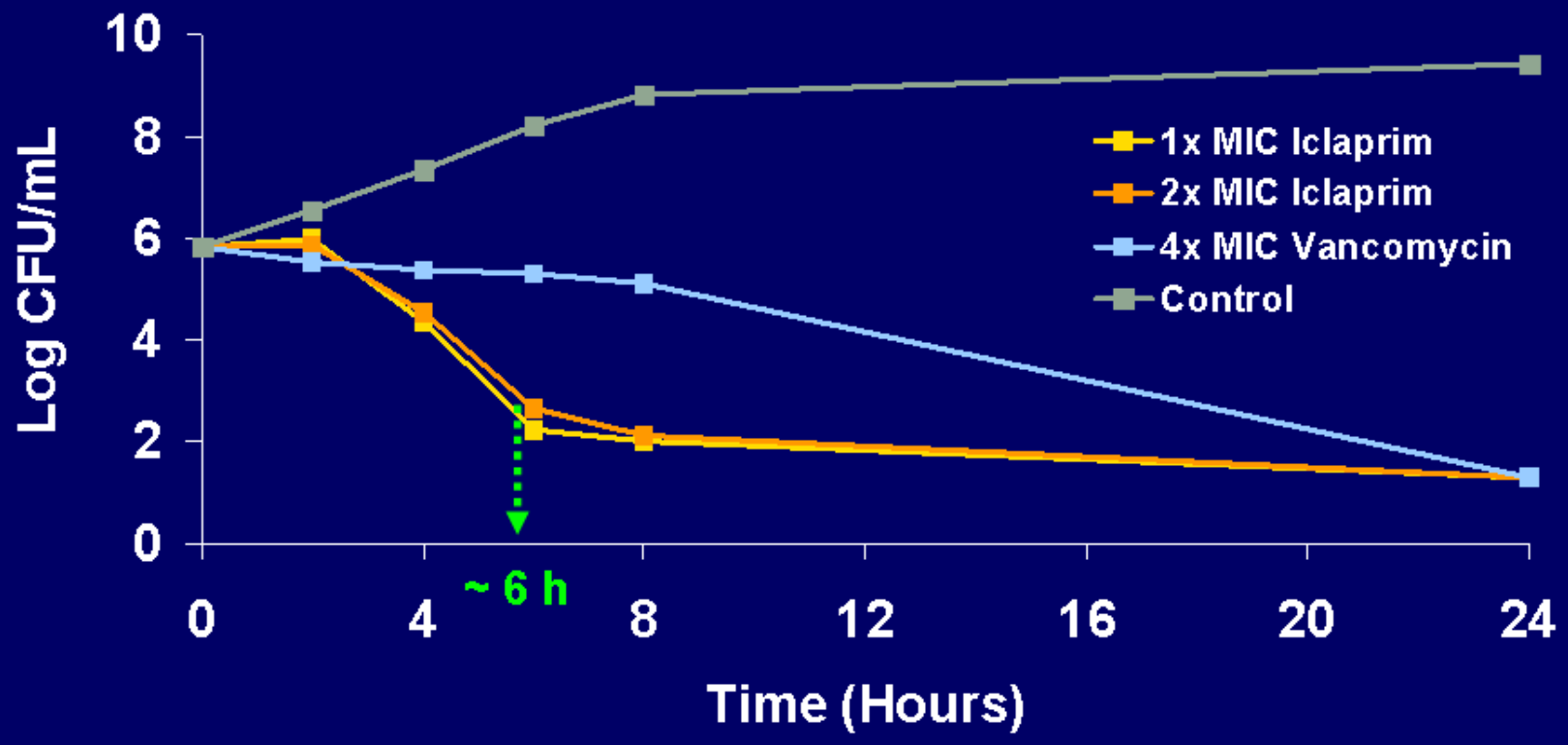
MRSA Phenotype	MIC ≤1 μg/mL	MIC Range (μg/mL)
h-VISA	23 / 24	0.06 - >8
DAP-NS	5 / 7	0.12 - >8
LZD-NS	37 / 37	0.03 - 1
CA-MRSA*	94 / 95	0.03 - 4

*Includes genotypically confirmed USA300 / PVL positive strains.

Sahm (Eurofins), Gemmell (Univ. of Glasgow), Mason (Texas) and internal reports.

Iclaprim Demonstrates a Rapidly Bactericidal Action

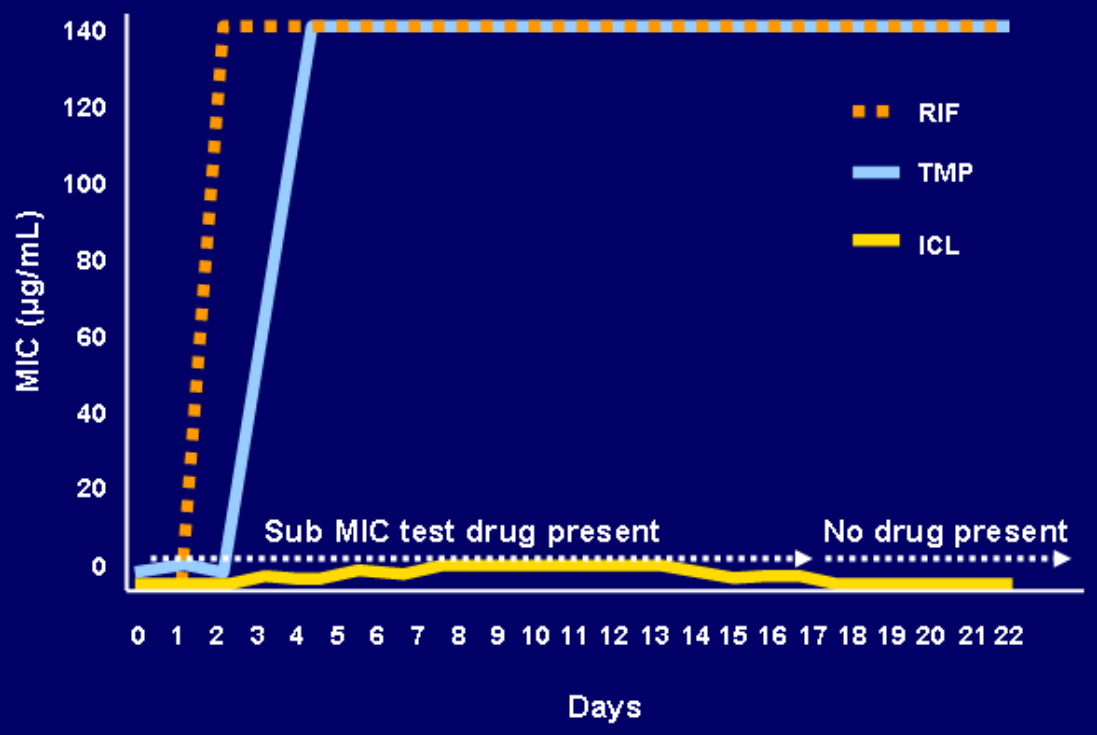
MRSA Strain 29[1] / VRSA (Van A)[2]



1. Weiss L, et al. *18th ECCMID* 2008; Abstract P588.
2. Pankuch GA, Appelbaum PC. *18th ECCMID* 2008; Abstract O98.

Low Propensity for Resistance Development

- Spontaneous mutation rate *S. aureus* $<10^{-10}$
- UV mutagenesis in *E. coli* frequency $<10^{-10}$
- Little or no change in MIC for up to 17 passages with iclaprim



***S. aureus* 29213 and MDR *S. aureus* 101**

Hawser S, et al. *42nd ICAAC* 2002; Abstract F2028.

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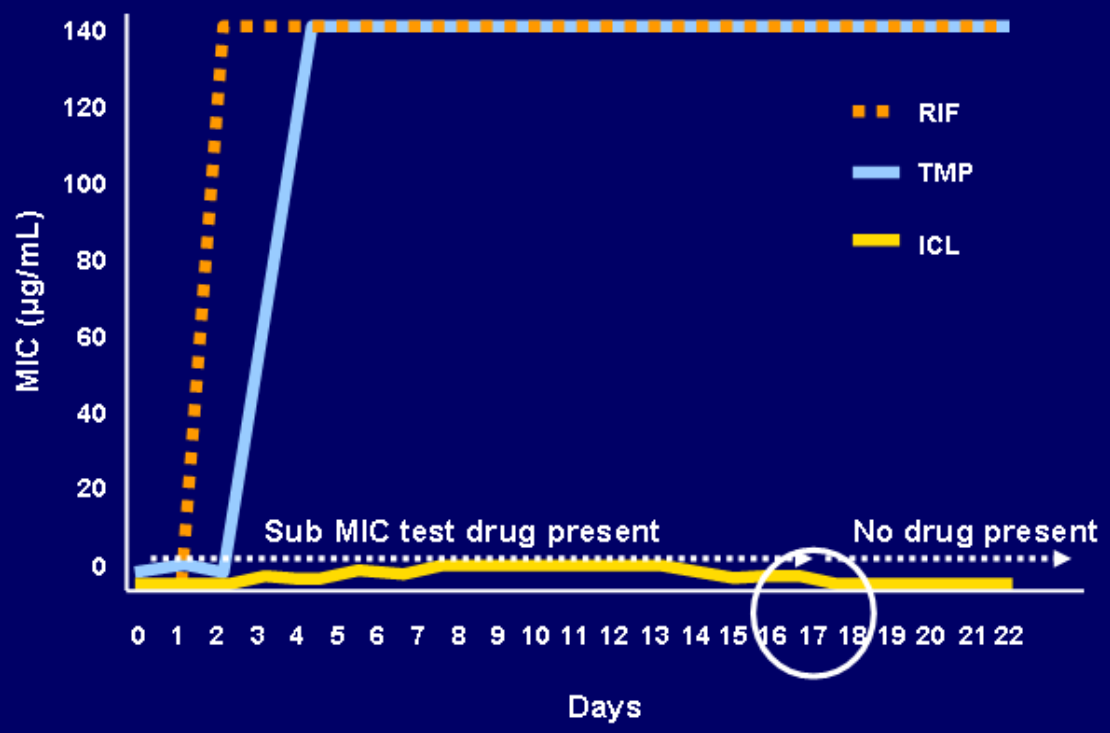


***S. aureus* 29213 and MDR *S. aureus* 101**

Hawser S, et al. *42nd ICAAC* 2002; Abstract F2028.

Consistent Efficacy in Established Murine Infection Models

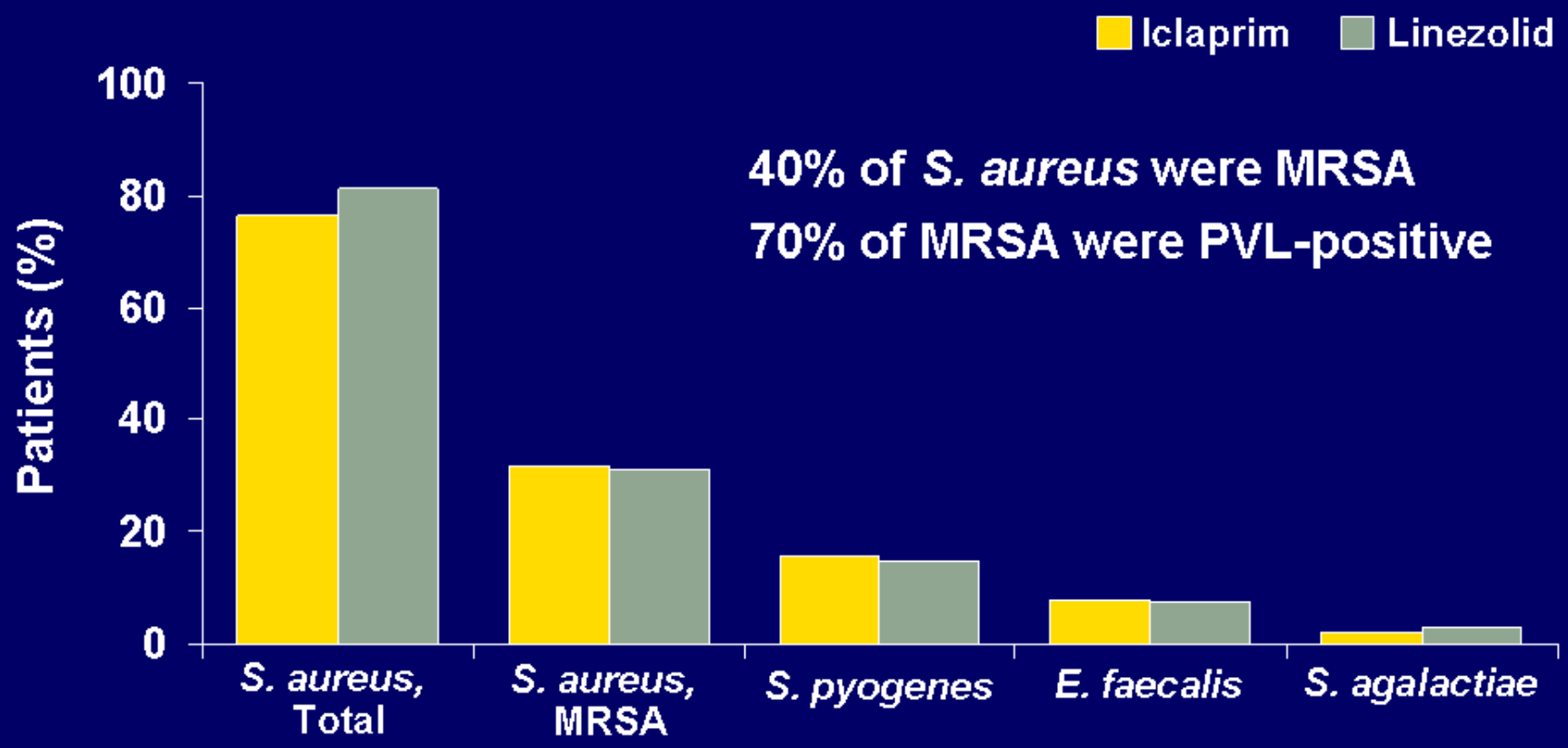
Infection Type	Strain	Route
Septicemia		
	MSSA	PO / iv
	MRSA / TMP-R	iv
Peritonitis		
	MRSA / TMP-R	iv
	PSSP / PISP	iv
Joint inflammation		
	MRSA	iv
Pneumonia		
	PISP / PRSP	iv
Pneumonia (PCP)		
	P. carinii	PO

Gemmell (Univ. of Glasgow), Statens Serum Institute (Denmark), Biosearch Italia (Italy), Dei Cas (France).

Clinical Microbiology

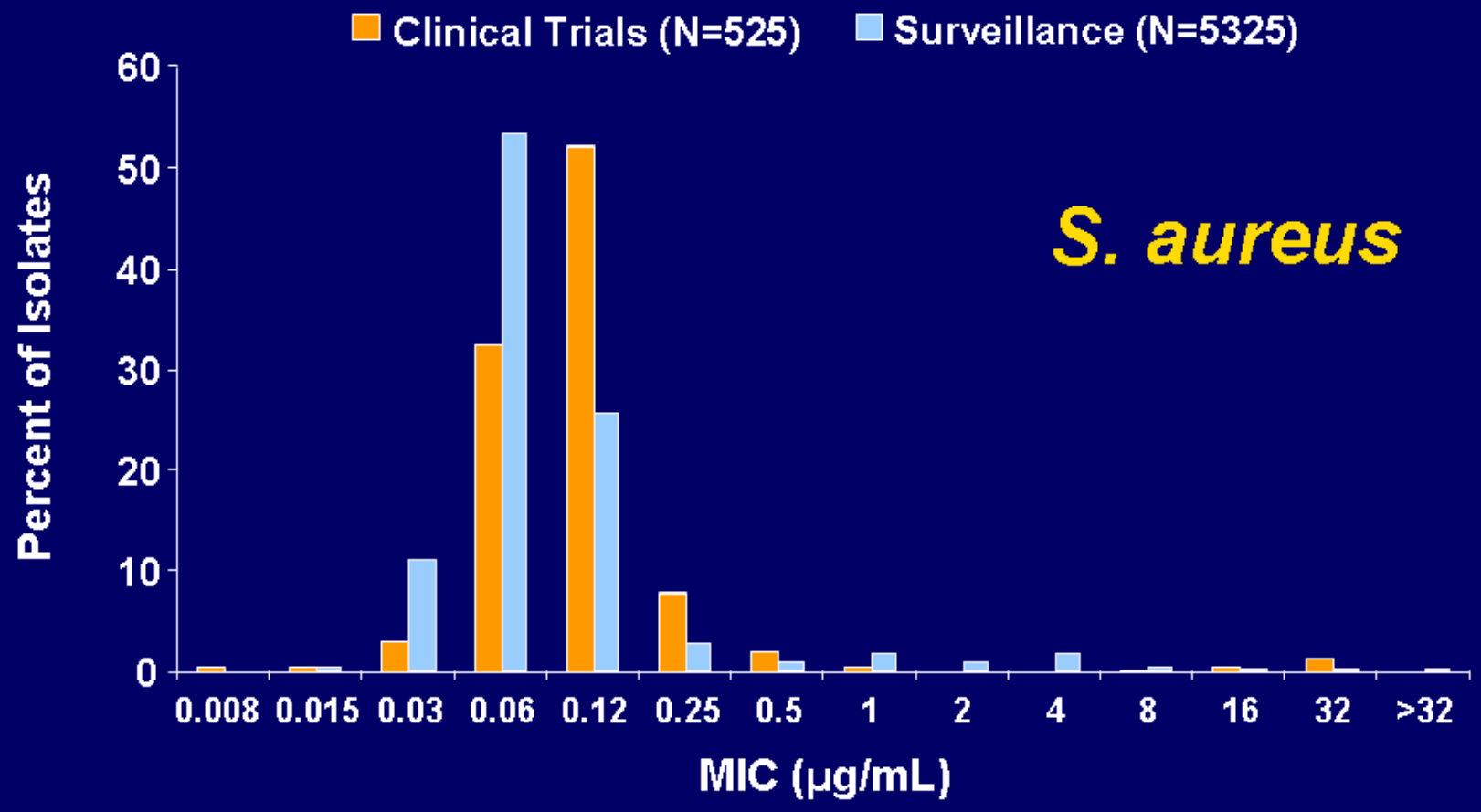
Causative Gram-positive Pathogens in Phase 3 Program are Representative of cSSSI

MITT Population* (Combined Phase 3 Data)



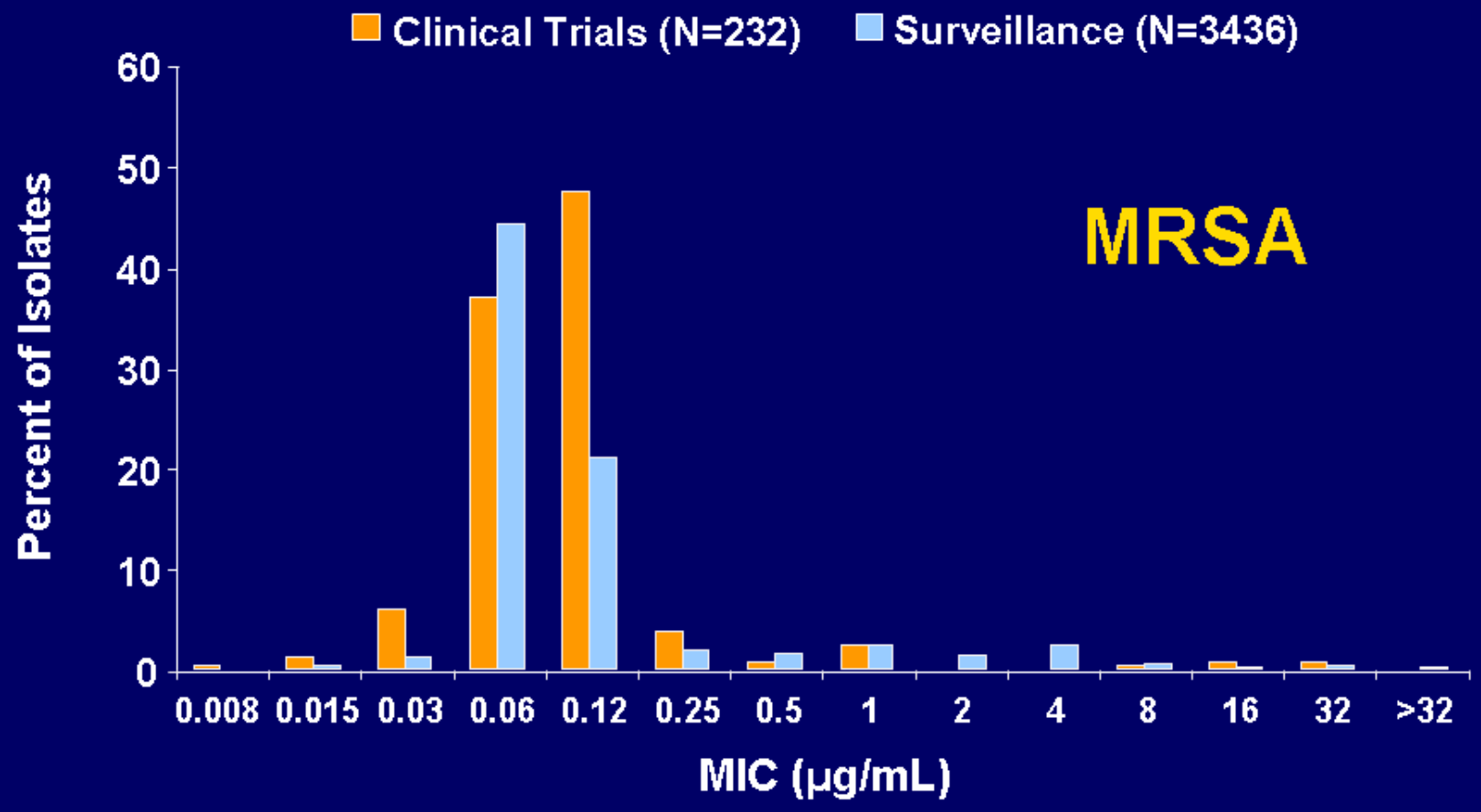
*MITT – ITT population with isolated Gram-positive BL pathogen.

Similar MICs Against *S. aureus* from Phase 3 Clinical and Surveillance Studies



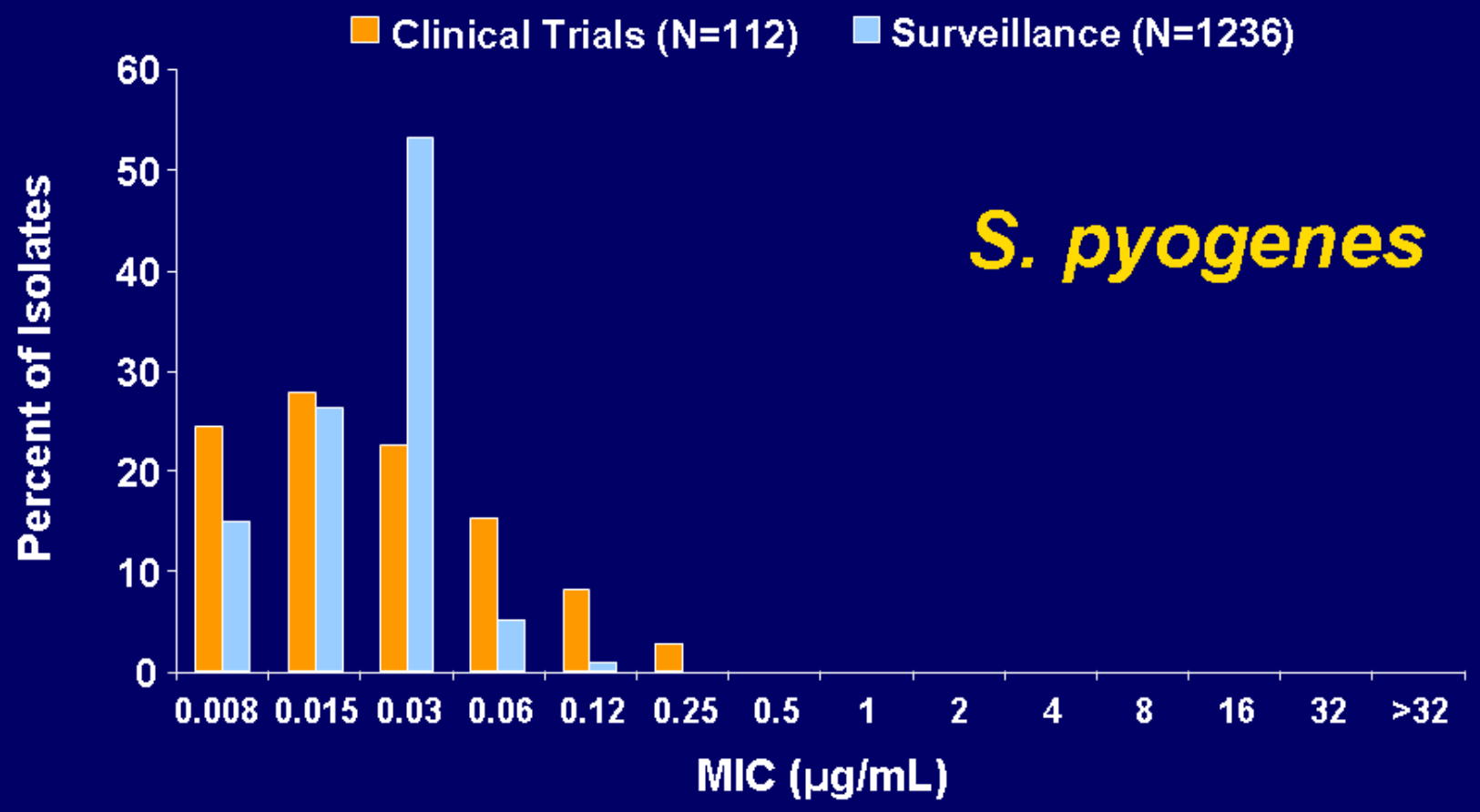
No change in baseline MICs observed for Gram-positive pathogens during clinical program

Similar MICs Against MRSA from Phase 3 Clinical and Surveillance Studies



No change in baseline MICs observed for Gram-positive pathogens during clinical program

Similar MICs Against *S. pyogenes* from Phase 3 Clinical and Surveillance Studies



No change in baseline MICs observed for Gram-positive pathogens during clinical program

Clinical Efficacy and Safety

Wayne Dankner, MD

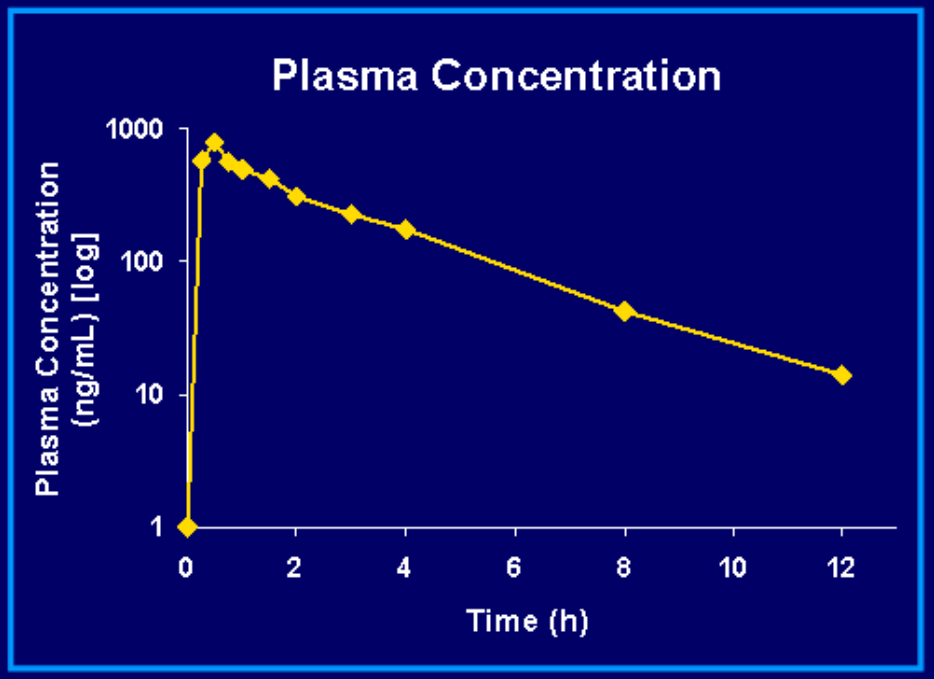
cSSSI Clinical Program Overview

- 14 Phase 1 trials (ascending dose, ADME, ECG, drug-drug interaction, and special populations)
  - Well tolerated
- Phase 2 trial vs vancomycin
  - Efficacious and well tolerated
- Two Phase 3 pivotal trials vs linezolid
  - High clinical cure rates
  - Good safety profile

Pharmacokinetic Profile of Iclaprim

0.8 mg/kg, 30-min Infusion

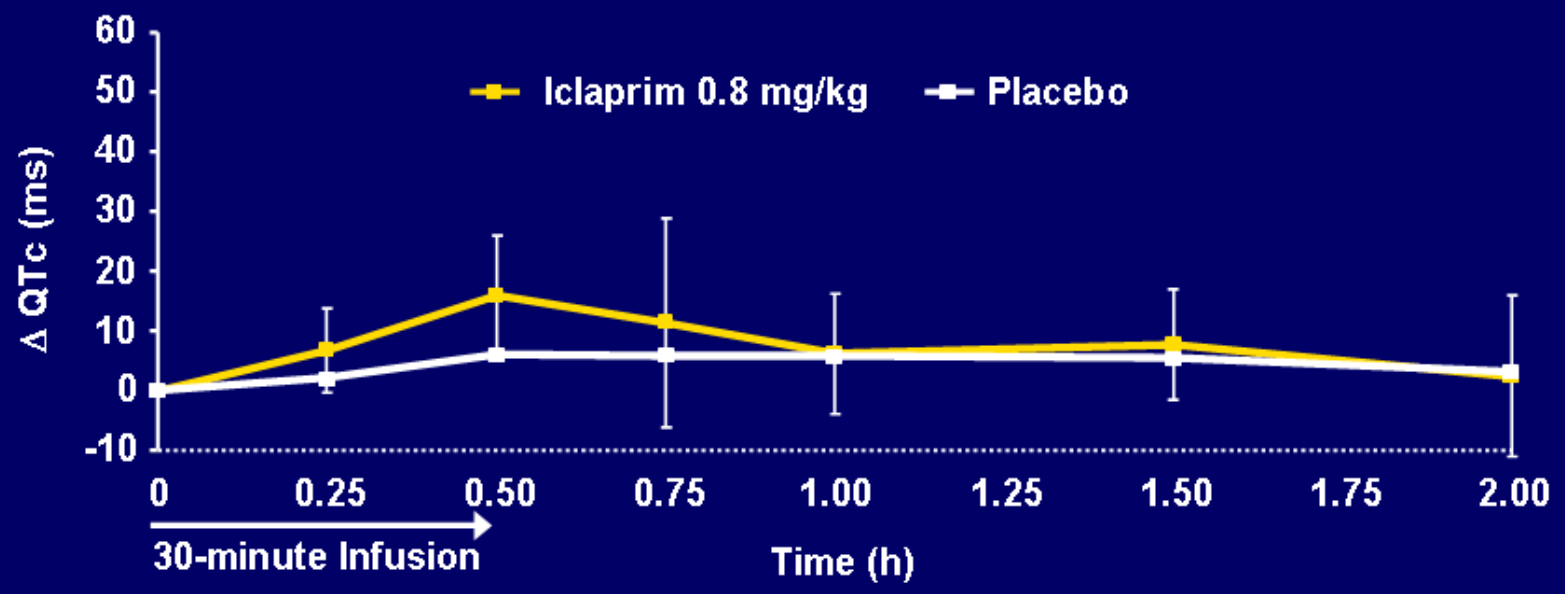
PK parameter	Mean (SD)
	N=22
C_{max} (ng/mL)	831 (245)
$AUC_{0-\infty}$ (ng.h/mL)	2082 (710)
$t_{1/2}$ (h)	2.5 (1.2)
V_{ss} (mL/kg)	1392 (324)



Well tolerated (4x therapeutic dose), no drug-related SAEs

- Dose proportional AUC and C_{max}
- No accumulation after multiple administration
- Rapid and extensive tissue distribution

Formal ECG Trials Show a Small, Rapidly Reversible, T_{max}-Related QTc Effect



- Dose-dependent increase in QTc
- Mean maximal increase about 10 ms at 0.8 mg/kg
- No gender difference

Low Potential for Drug-Drug Interactions

No clinically relevant interactions with:

- Ketoconazole (CYP3A4 inhibitor)
- Omeprazole (CYP2C19 inhibitor)
- Warfarin
- Digoxin

Special Patient Populations

Recommendations for Dose Adjustment

	Group	Definition	Dose Adjustment
Renally impaired	Mild	CrCL <80 and ≥50 mL/min	No
	Moderate	CrCL <50 and ≥30 mL/min	No
	Severe	CrCL <30 and >0 mL/min	No
	ESRD	On dialysis	No
Hepatically impaired	Mild	Child-Pugh grade A	No
	Moderate	Child-Pugh grade B	Dose reduction by up to 50%
Obese	Mild / Moderate	BMI ≥30 and <40	No
	Severe	BMI ≥40	Dose limitation of 100 mg

Phase 2 Dose-Finding Study in cSSSI

- Two doses of iclaprim vs vancomycin in hospitalized patients with cSSSI (92 patients)
- Both 0.8 mg/kg and 1.6 mg/kg doses of iclaprim were well tolerated, no drug-related SAEs
- High microbiological cure rates, incl. MRSA
- Clinical efficacy 92.9% for both 0.8 mg/kg iclaprim and 1 g vancomycin

Phase 3 dose: 0.8 mg/kg, q12h

Phase 3 ASSIST Program

Study Design and Results

Study Design: Clinical

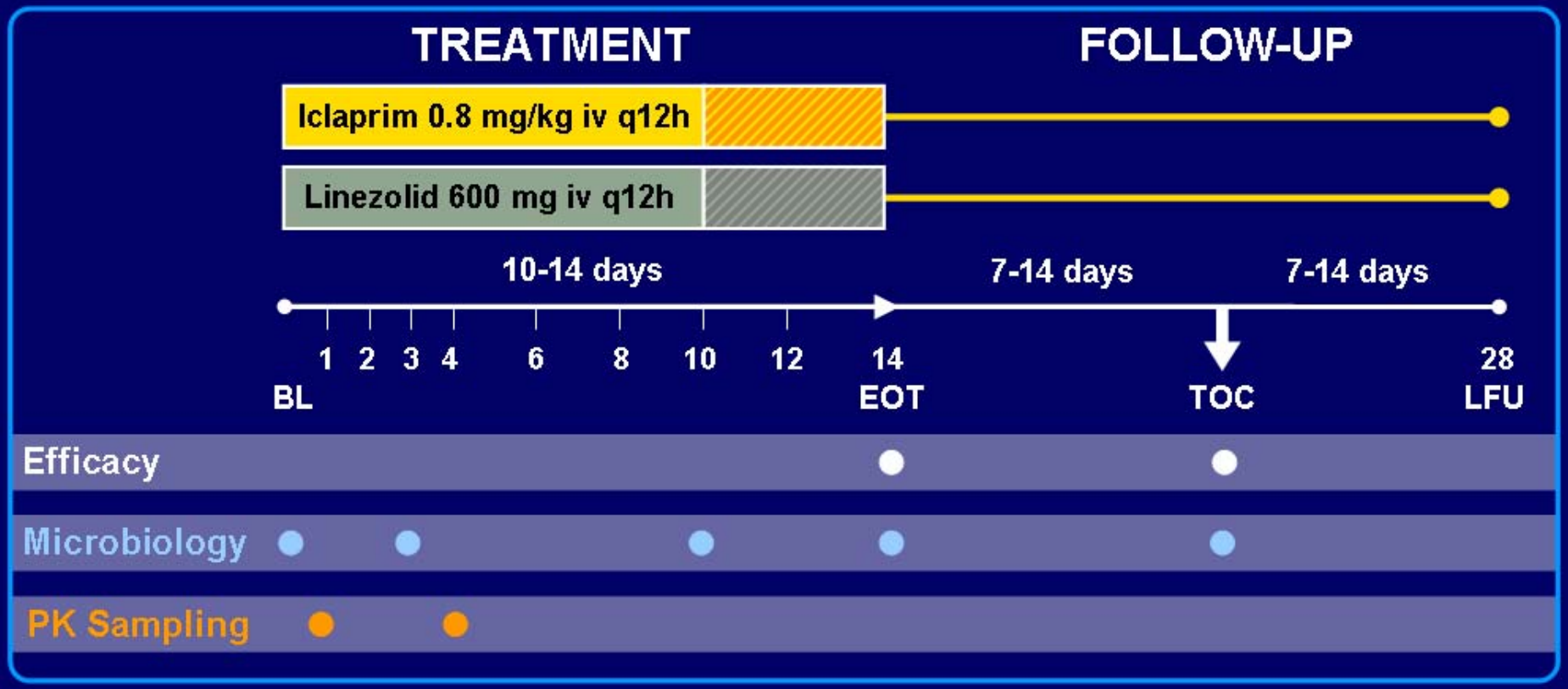
- Two independent non-inferiority studies with essentially identical design
- Hospitalized patients with cSSSI
- Randomized, double-blind, and multicenter
- Linezolid as comparator for both studies
- Only concomitant antibiotics permitted were aztreonam (Gram-negatives) and metronidazole (anaerobes)
- Independent Data Monitoring Committee established for both pivotal trials

Study Design

- ASSIST-1 and ASSIST-2 each had a pre-specified lower limit of the 95% CI for the iclaprim-linezolid treatment difference: -12.5%
- Prospectively planned to combine data from two studies for additional powering
- Primary end point = clinical cure at TOC
- Co-primary populations
  - Intent-to-treat (ITT) all patients who received one dose of study drug per protocol
  - Per protocol (PP) excludes all patients with any protocol violation

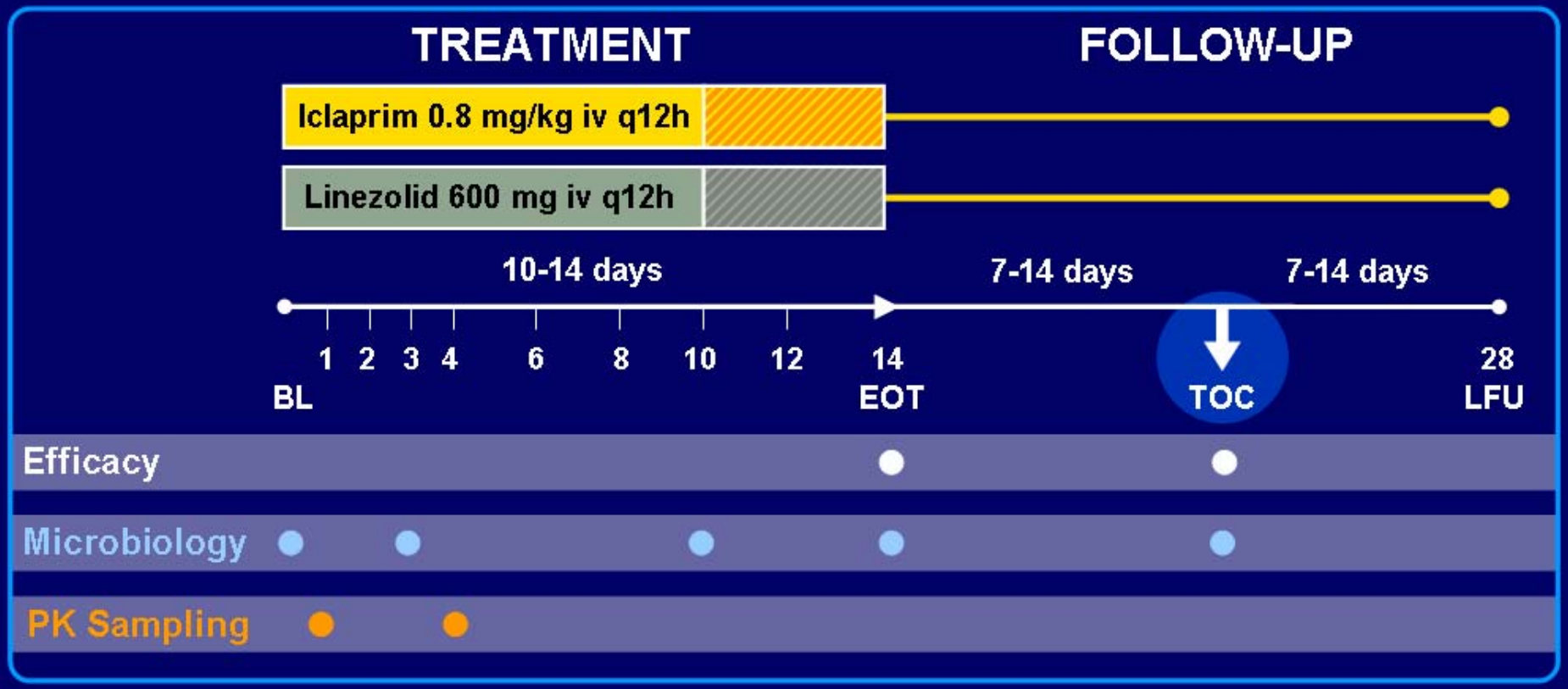
Study Design of ASSIST-1 and ASSIST-2

Phase 3



Study Design of ASSIST-1 and ASSIST-2

Phase 3



High Proportion of Patients Completed Treatment in Both Study Arms

ASSIST- 1 43 centers in 5 countries

ASSIST- 2 59 centers in 9 countries

	Iclaprim		Linezolid	
	ITT	Completed	ITT	Completed
USA	195	168 (86%)	190	158 (83%)
ROW	305	283 (93%)	301	283 (94%)
Total	500	451 (90%)	491	441 (90%)

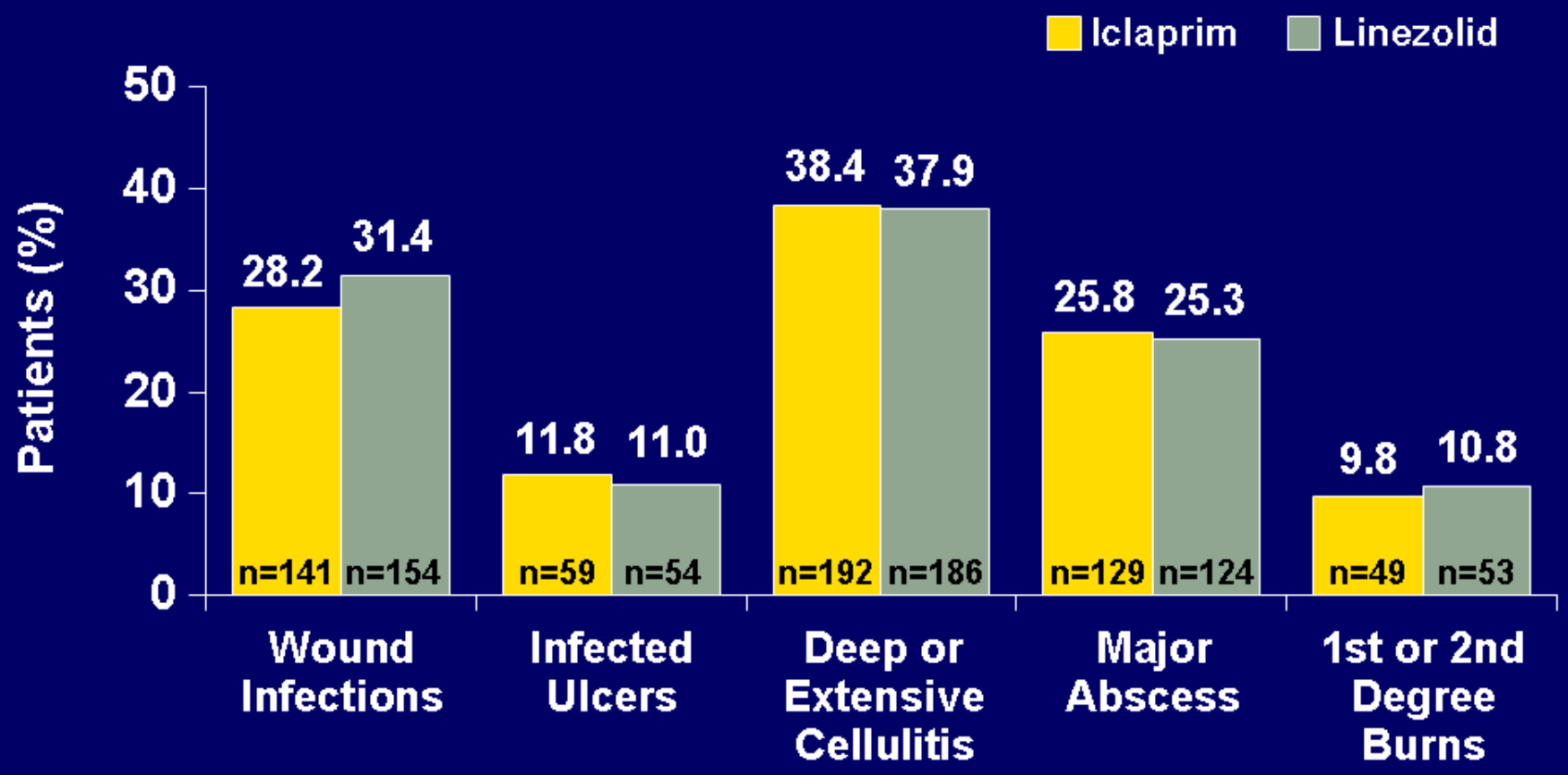
US patients comprised 39% of the total population

Demographics Similar Between Studies

	ASSIST-1	ASSIST-2	Combined
Age			
<65	416 (83.7%)	436 (88.3%)	852 (86.0%)
65-75	55 (11.1%)	35 (7.1%)	90 (9.1%)
>75	26 (5.2%)	23 (4.7%)	49 (4.9%)
Gender			
Male	338 (68.0%)	313 (63.4%)	651 (65.7%)
Female	159 (32.0%)	181 (36.6%)	340 (34.3%)
Ethnicity			
Caucasian	454 (91.3%)	368 (74.5%)	822 (82.9%)
Black	13 (2.6%)	34 (6.9%)	47 (4.7%)
Hispanic	25 (5.0%)	76 (15.4%)	101 (10.2%)
Other	5 (1.0%)	16 (3.2%)	21 (2.1%)

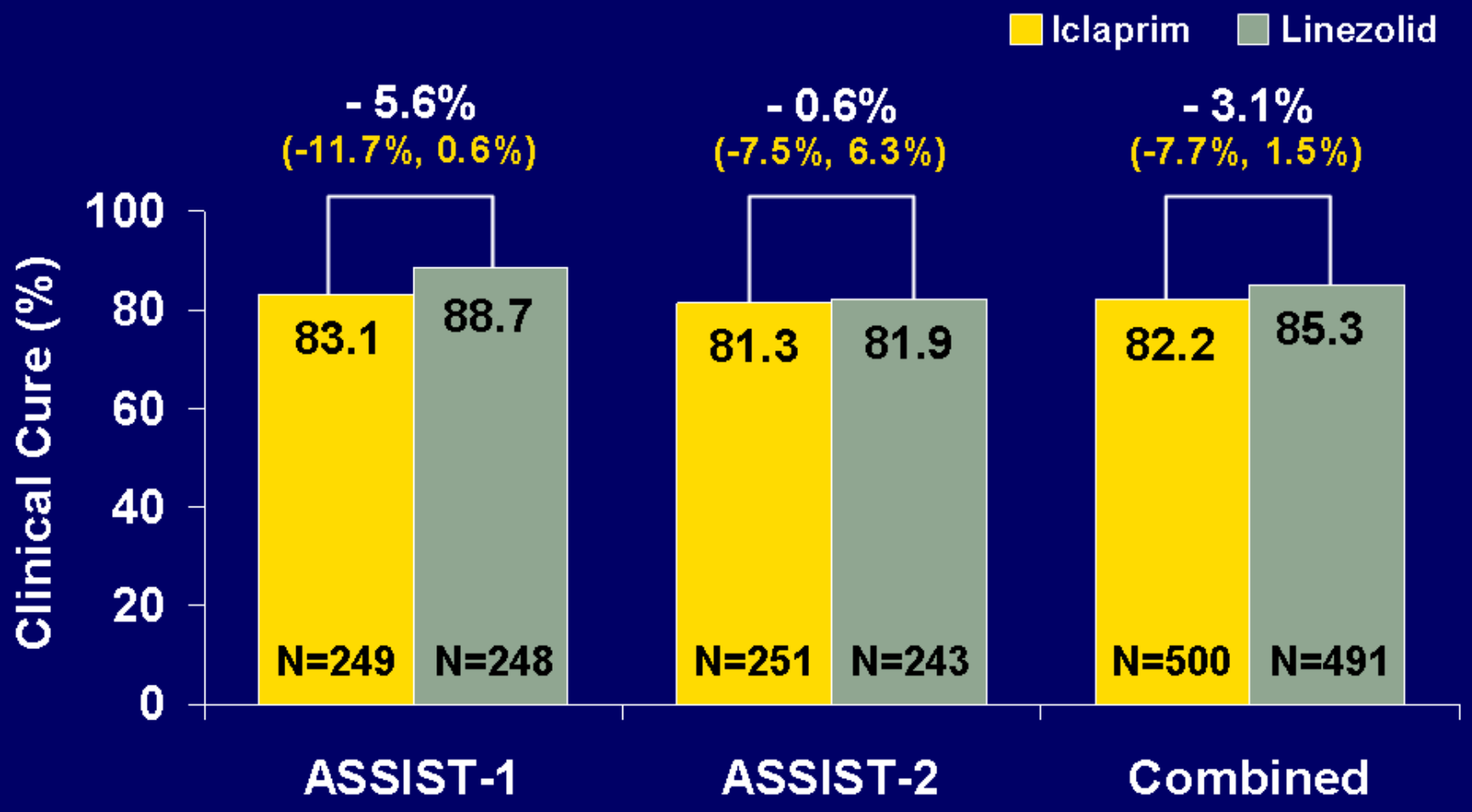
Type of cSSSI Infections

ITT Population (Combined Data)



High Clinical Cure Rates at TOC

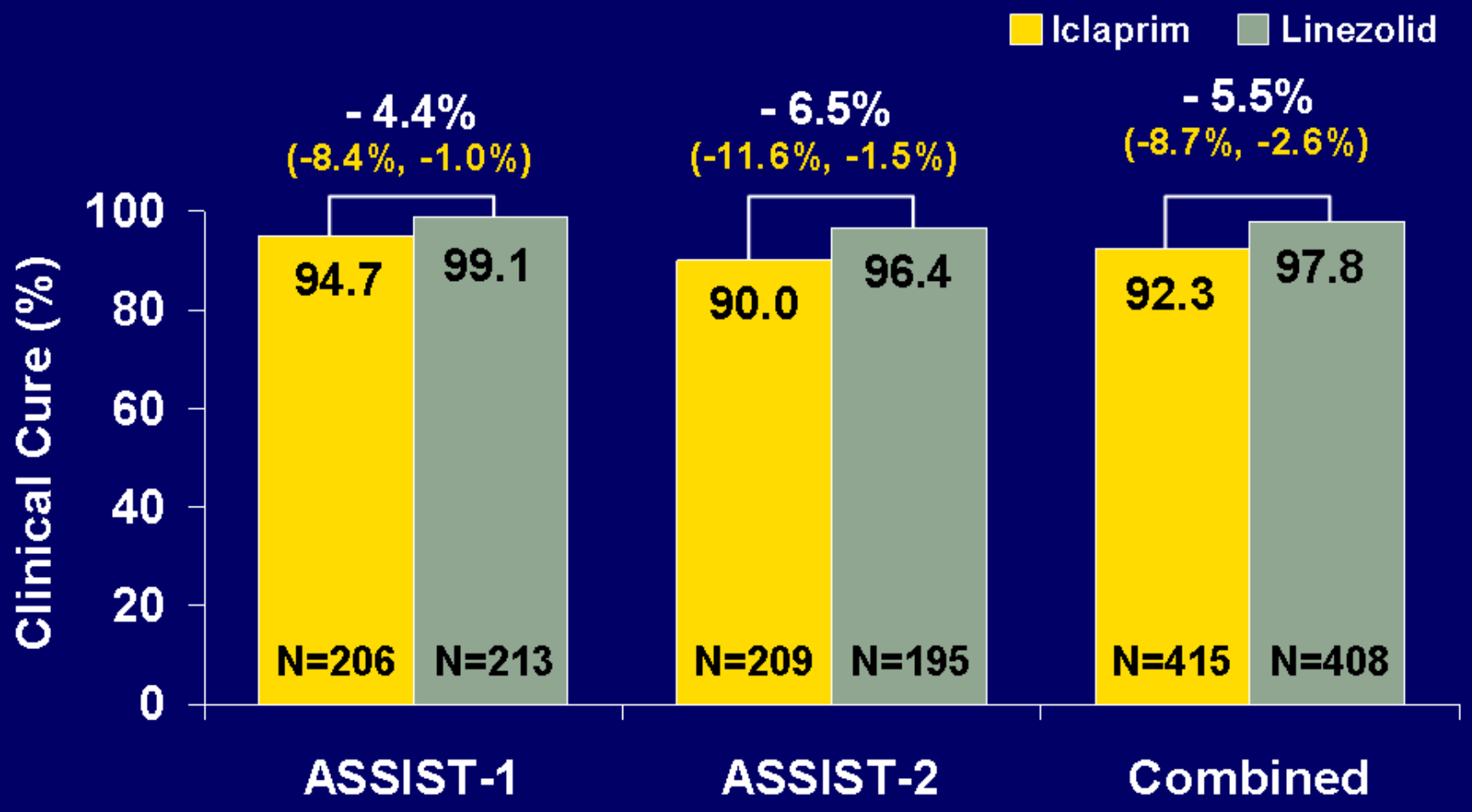
ITT Population



Confidence intervals were computed using the Newcombe-Altman formula.

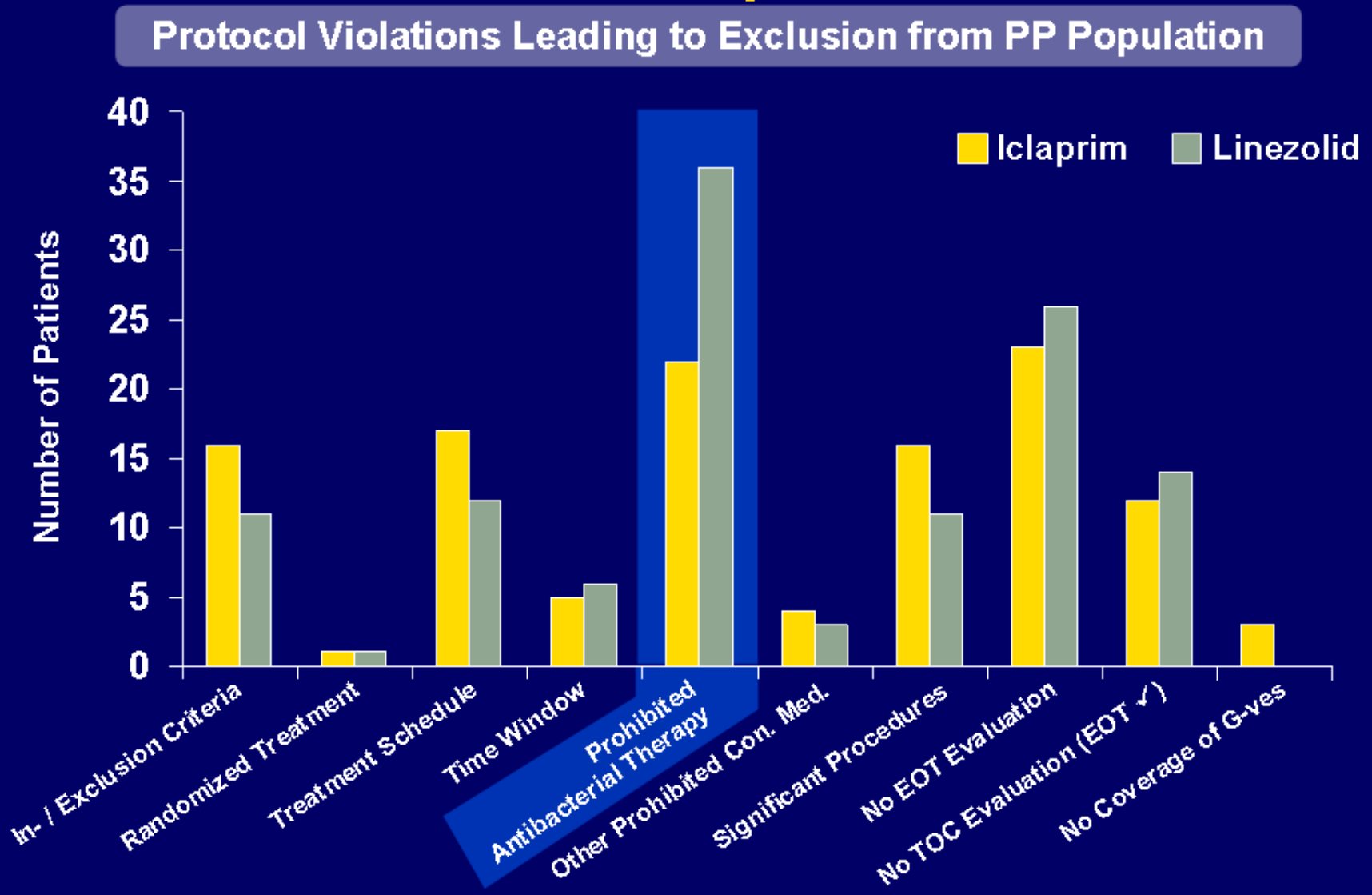
High Clinical Cure Rates at TOC

PP Population



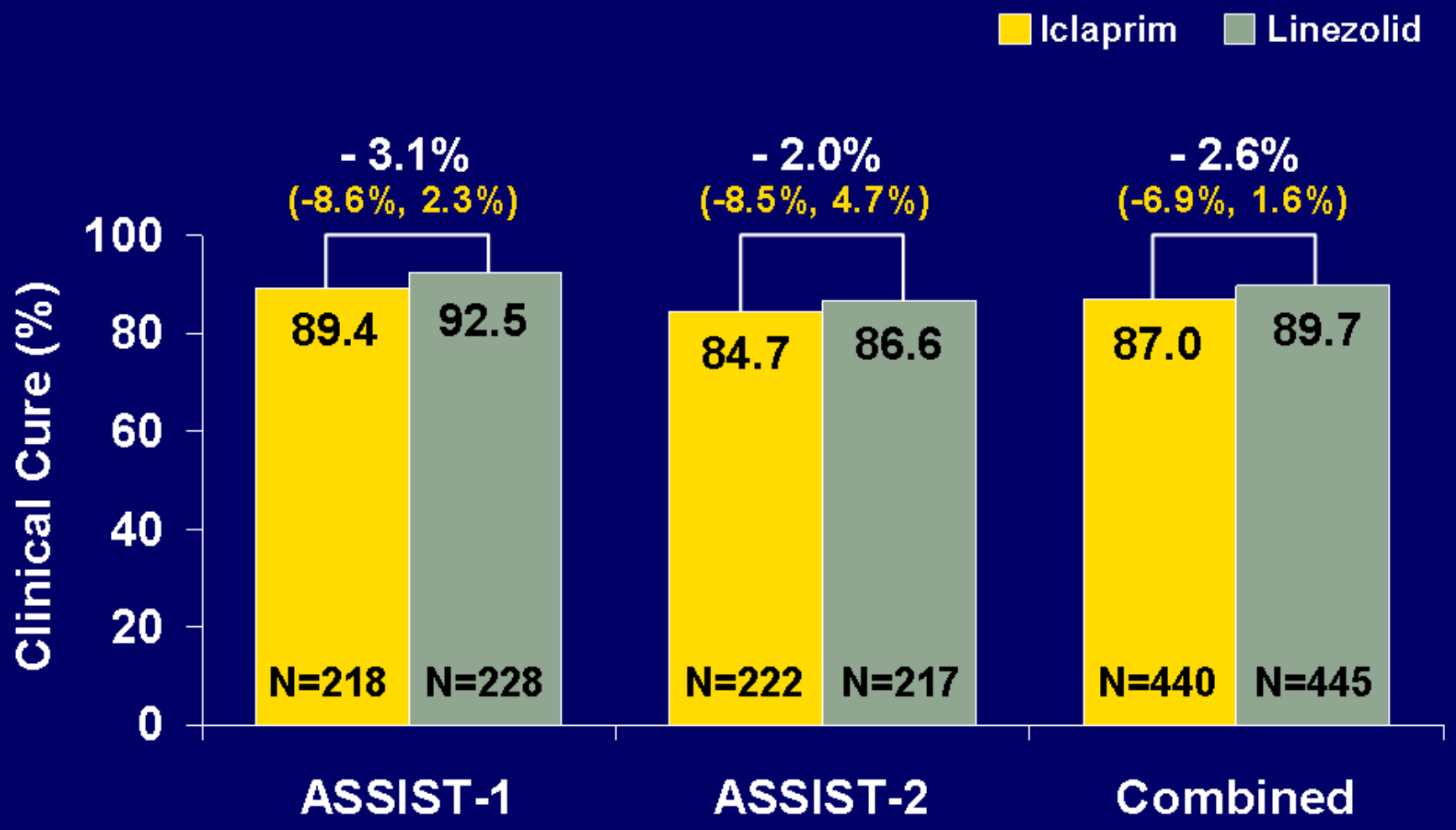
Confidence intervals were computed using the Newcombe-Altman formula.

Marked Imbalance in Prohibited Antibiotics Between Treatment Groups



Sensitivity Analysis per ICH E9

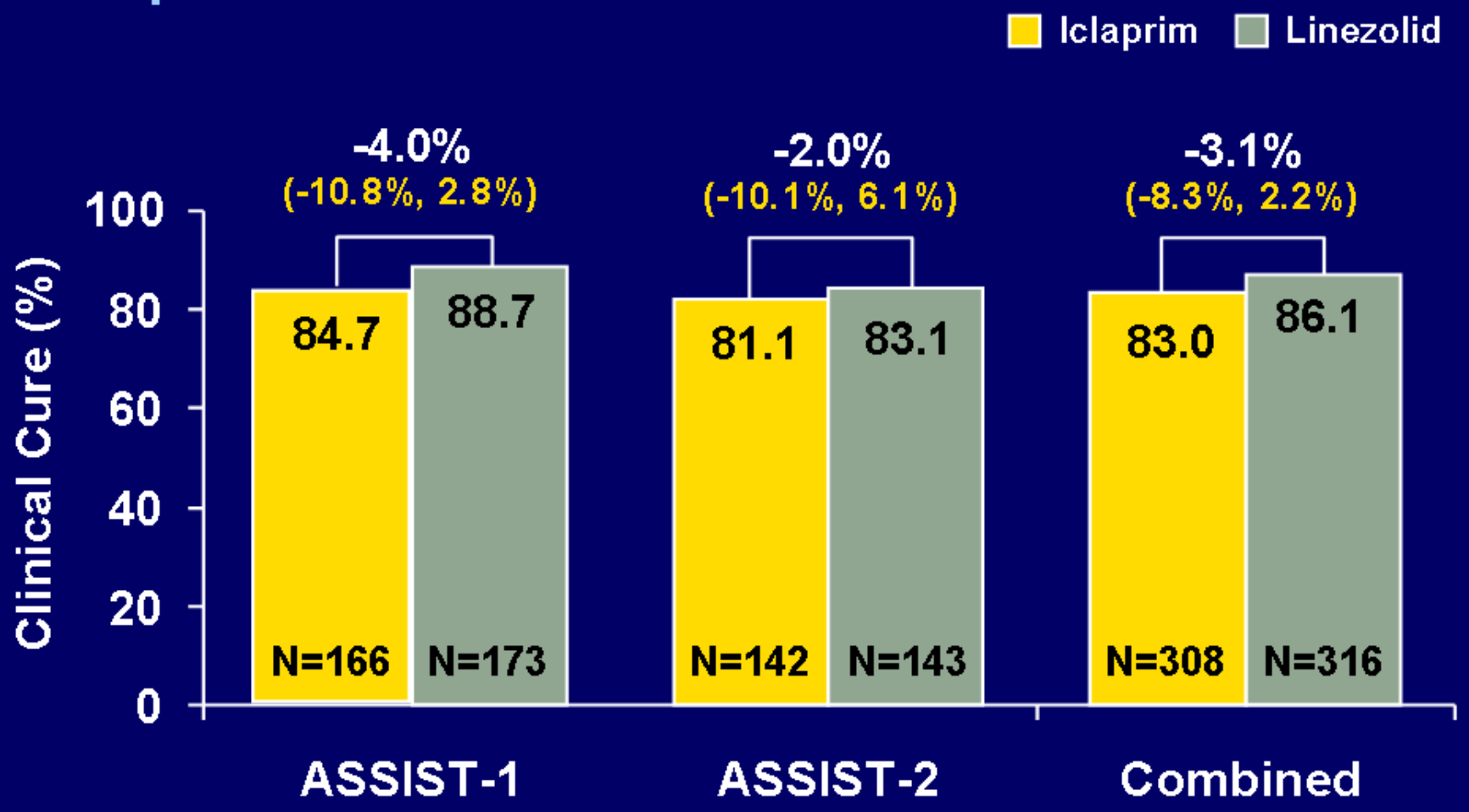
MCE Population



Confidence intervals were computed using the Newcombe-Altman formula.

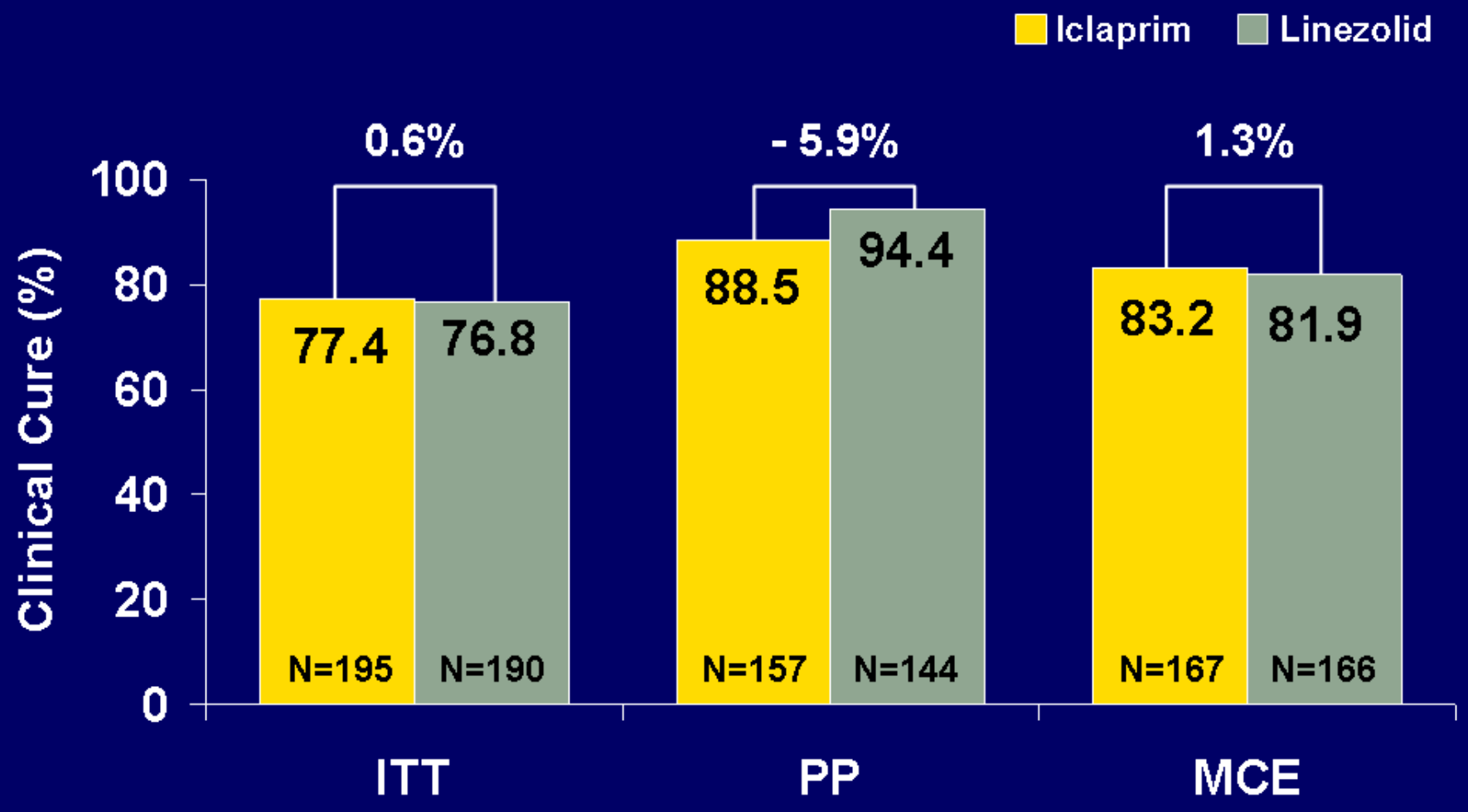
Clinical Cure Rates at TOC – No Abscesses

ITT Population



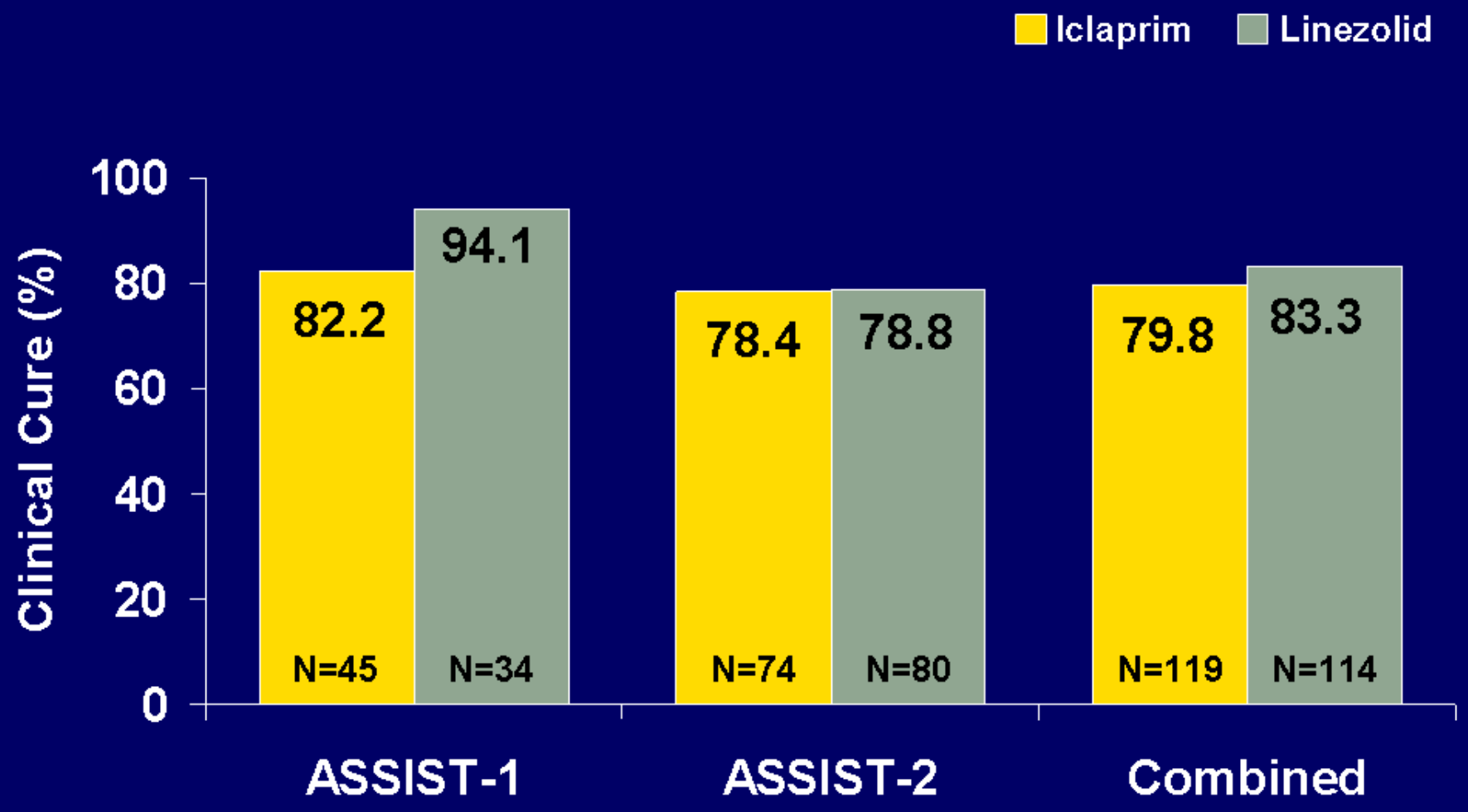
High Clinical Cure Rate in US Population

Combined Data



Clinical Cure at TOC

MITT Patients with MRSA as BL Pathogen (Combined Data)



Examination of FDA Reclassifications of Cures

ASSIST-1

Patient/ Tx	CRF	FDA	BL Pathogen	Comments	Days Since Last Dose
113-03 Icla	Cure	Fail	MRSA	New/recurrent infection documented 14 days after TOC visit. Presumed eradication at EOT and TOC	22
302-12 Icla	Cure	Fail	*S. pyogenes*	New/recurrent infection documented 4 days after TOC visit. Presumed eradication at EOT and TOC	11
303-17 Icla	Cure	Fail	MSSA + *S. agalactiae*	Infection documented at TOC visit but on opposite buttocks. Original site of infection responded to study medication	7

Examination of FDA Reclassifications of Cures

ASSIST-2

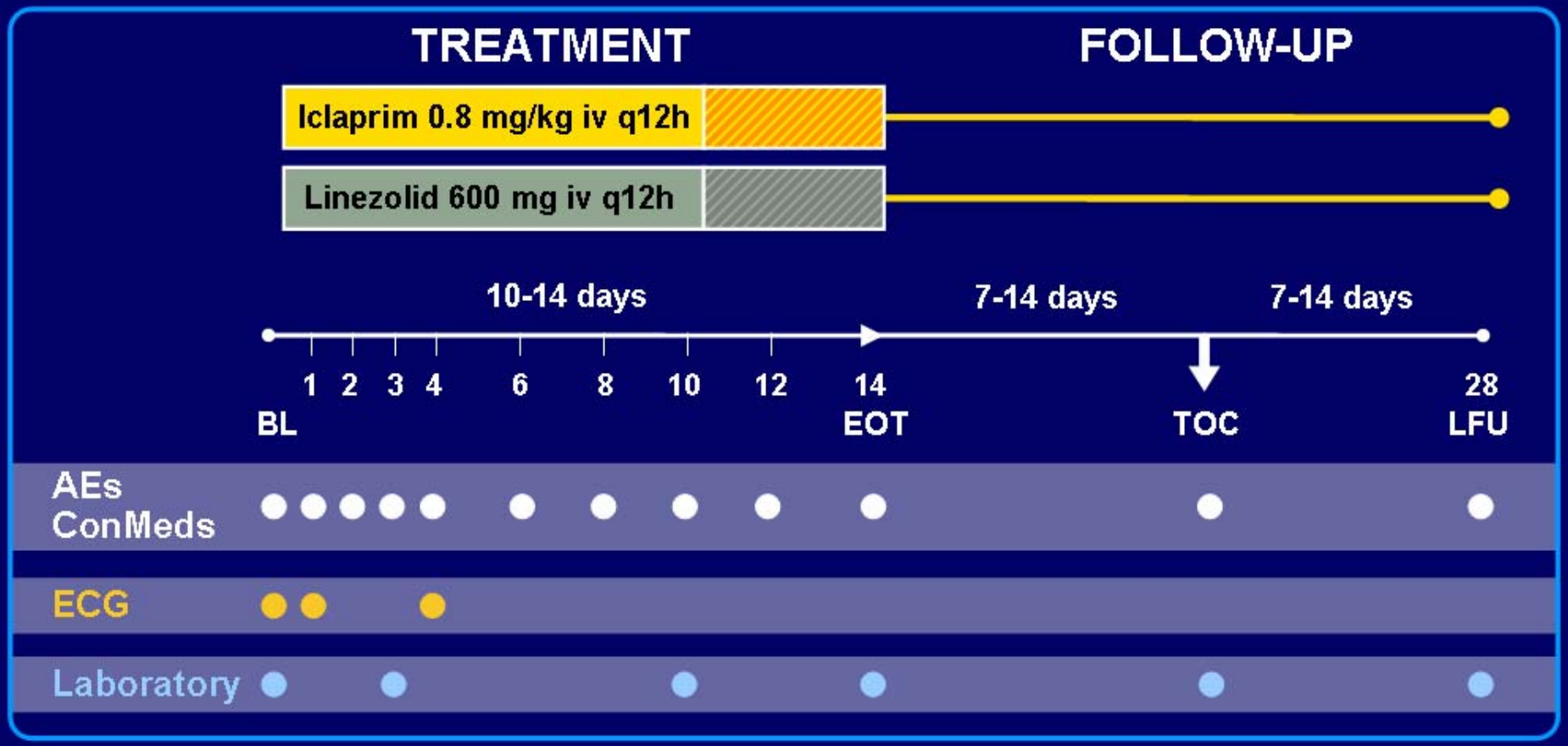
Patient/ Tx	CRF	FDA	BL Pathogen	Comments	Days Since Last Dose
616-03 Icla	Cure	Fail	MRSA	Received oral TMP-SMX for new/recurrent abscess 2 days after TOC	9
649-02 Icla	Cure	Fail	Viridans Group Strep	Recurrent right hand infection 12 days after TOC	28
624-34 Icla	Cure	Indeter-minate	MRSA	Received 24 hrs of oral TMP-SMX without resolution of abdominal wall infection followed by a single dose of Clindamycin before entry into study	-
616-14 Lin	Cure	Indeter-minate	MRSA	Received dose of cefazolin (post-operatively) on Study Day 2. No activity against MRSA	-

Clinical Efficacy Summary

- All populations achieved predefined non-inferiority margin in each independent study and NI margin in Combined analysis between -8% and -9%
- High clinical cure rates observed with iclaprim in the independent studies and in the Combined analysis
- Iclaprim shows comparable cure rates to linezolid (Phase 3) and vancomycin (Phase 2)
- Combined analysis of the US population also demonstrates high clinical cure rate
- High cure rates for patients with MRSA as baseline pathogen
- No changes of iclaprim MICs while on therapy

Clinical Safety

Safety Monitoring



Both ASSIST studies were evaluated on an ongoing basis by an independent DMC

Adverse Event Profile Similar to Linezolid

ITT Population (Combined Data)

	All AEs		Possibly / Probably Related AEs	
Patients (%)	Iclaprim (N=500)	Linezolid (N=491)	Iclaprim (N=500)	Linezolid (N=491)
Any AE	49.0	50.7	22.6	27.9
Any SAE	4.0	3.3	0.2	-
Any severe AE	6.8	6.9	1.4	1.8
Any AE causing study drug discontinuation	2.2	1.2	1.2	1.2
Deaths	1.2	0.4	-	-

Examination of Deaths Assessed by FDA as Possibly Drug Related

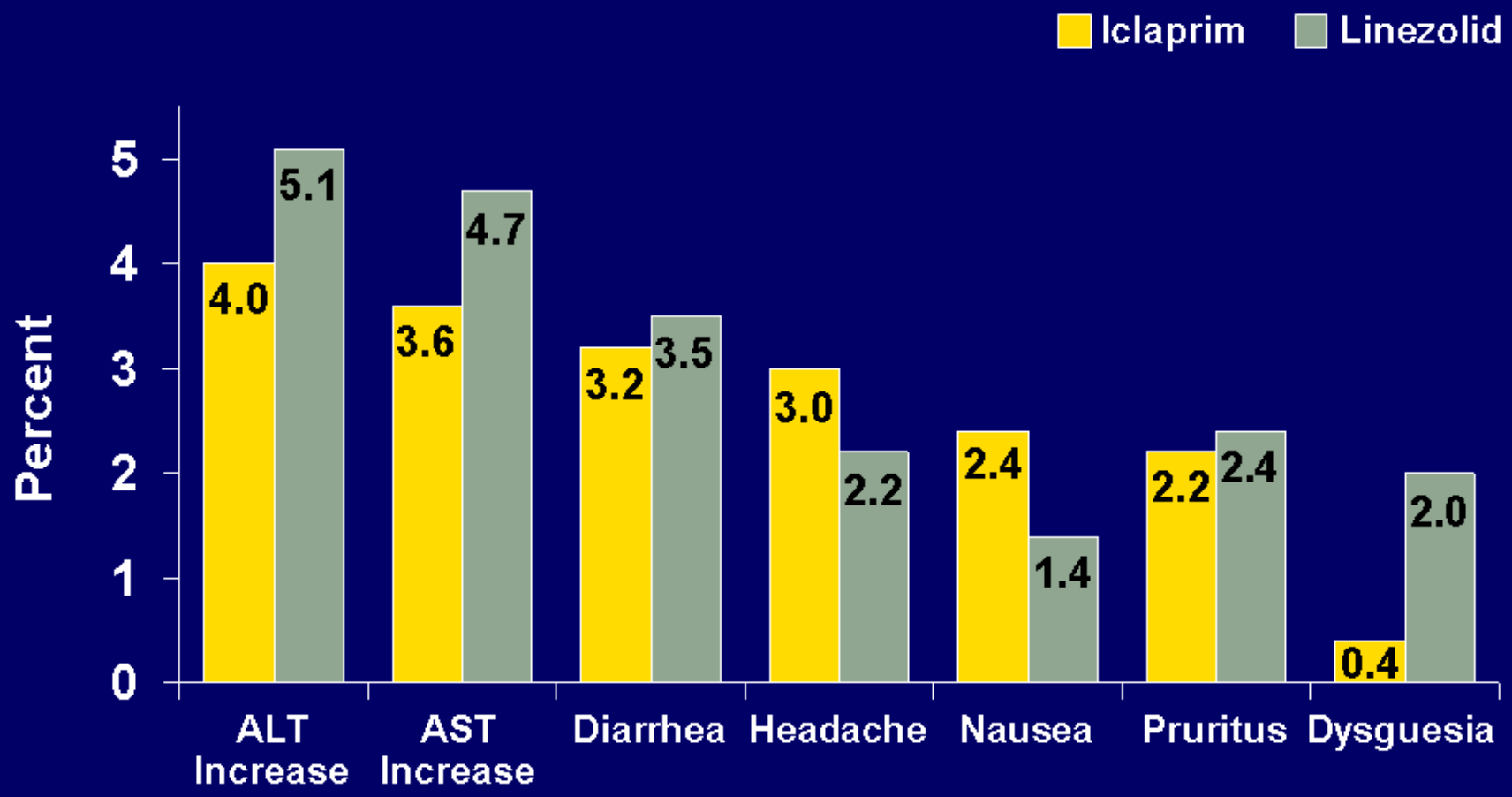
Patient	Preferred Term	Rationale for Assessing Deaths as Non-Drug Related	
		Time of Death	Clinical Course
306-27 Iclaprim	Anemia Sudden Death	7 days post EOT	No QTc change Day 1 and 4
306-34 Iclaprim	Erysipelas Septic Arthritis Acute Renal Failure	12 days post EOT	No change in serum creatinine from BL to EOT
306-33 Iclaprim	Anemia Hypoalbuminemia - Peripheral Edema - Swelling of the Face Acute Cardiac failure	Day 12 of therapy	Significant co-morbidities and extensive wound that led to metabolic derangement
304-38 Linezolid	Kidney Infection Acute Renal Failure Pulmonary Embolism	10 days post EOT	No change in serum creatinine from BL to EOT

Examination of Non-Fatal SAE Assessed by FDA as Possibly Drug Related

Patient	Preferred Term	Rationale for Assessing SAE as Non-Drug Related
133-01 Iclaprim	Acute Renal Failure	Study drug discontinued on Day 2 of therapy ARF diagnosed 3 days later after receipt of vancomycin and NSAIDs. Normal creatinine at BL and 1 day after discontinuation of iclaprim

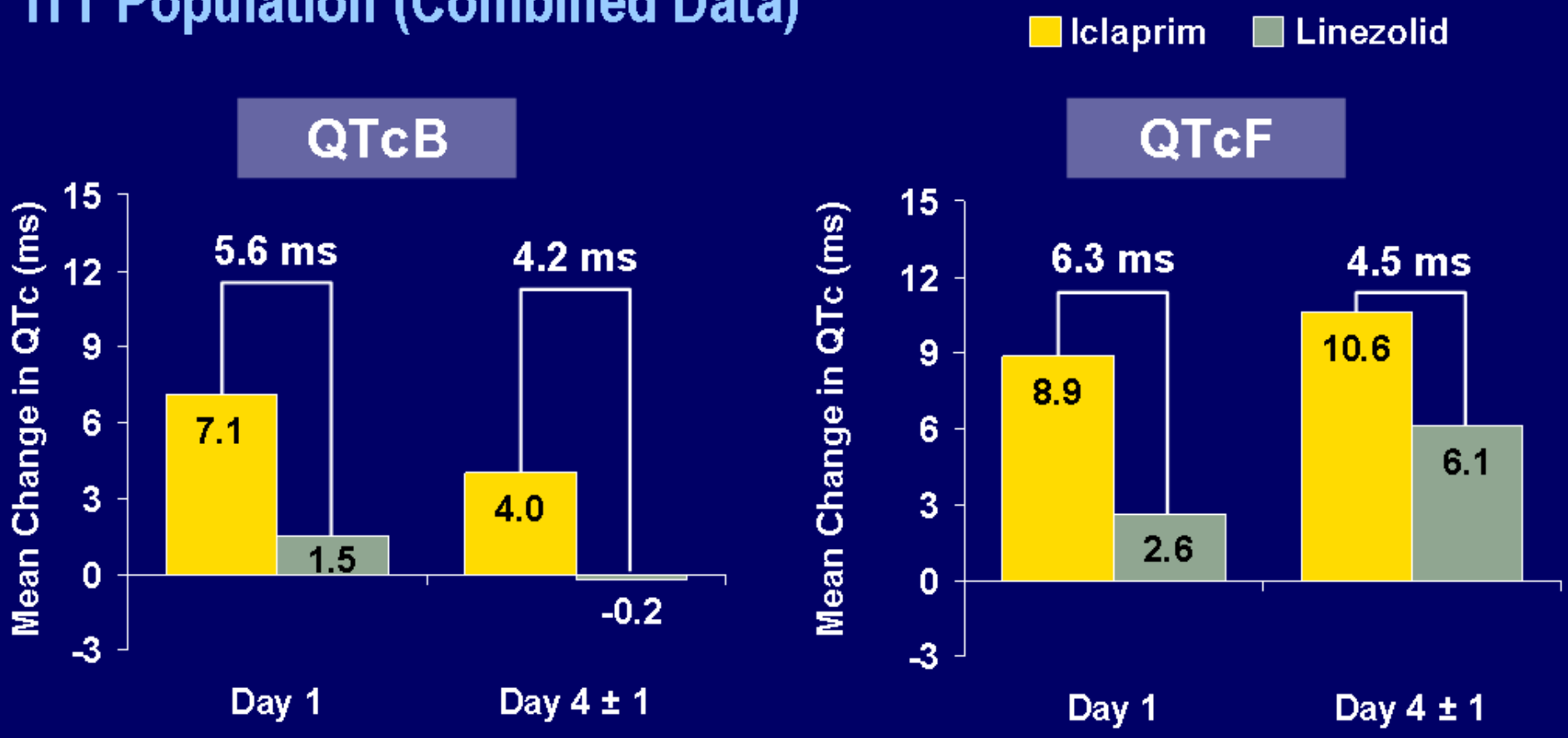
Incidence of Possibly / Probably Related AEs (>2%) Comparable with Linezolid

ITT Population (Combined Data)



Changes in QTc from BL to Day 1 and Day 4 Low (4-6 ms) Compared with Linezolid

ITT Population (Combined Data)



No difference associated with gender, age, BMI and cardiac history

Incidence of QTc Outliers (>60 ms) Low and Similar to Linezolid

Day 1 and Day 4 (QTcF)

	ICL (%)	LZD (%)
Change >30 ms (Day 1 / Day 4)	3.2 / 12.1	0.8 / 5.0
Change >60 ms (Day 1 / Day 4)	0.2 / 0.6	0.2 / 0.4

- Only 1 patient in iclaprim (ICL) group had a transient change in QTcF to 507 ms
- 1 patient was withdrawn from treatment in linezolid (LZD) group for exceeding protocol defined criterion of QTc >520 ms and increase above baseline of >60 ms
- No arrhythmogenic events associated with QTc prolongation were observed in either group

Safety Summary for Iclaprim

- Well tolerated at a dose of 0.8 mg/kg
- Safety profile was comparable with linezolid
- QTc prolongation (4-6 ms), similar to that reported for oral moxifloxacin
- No arrhythmogenic events associated with QTc prolongation

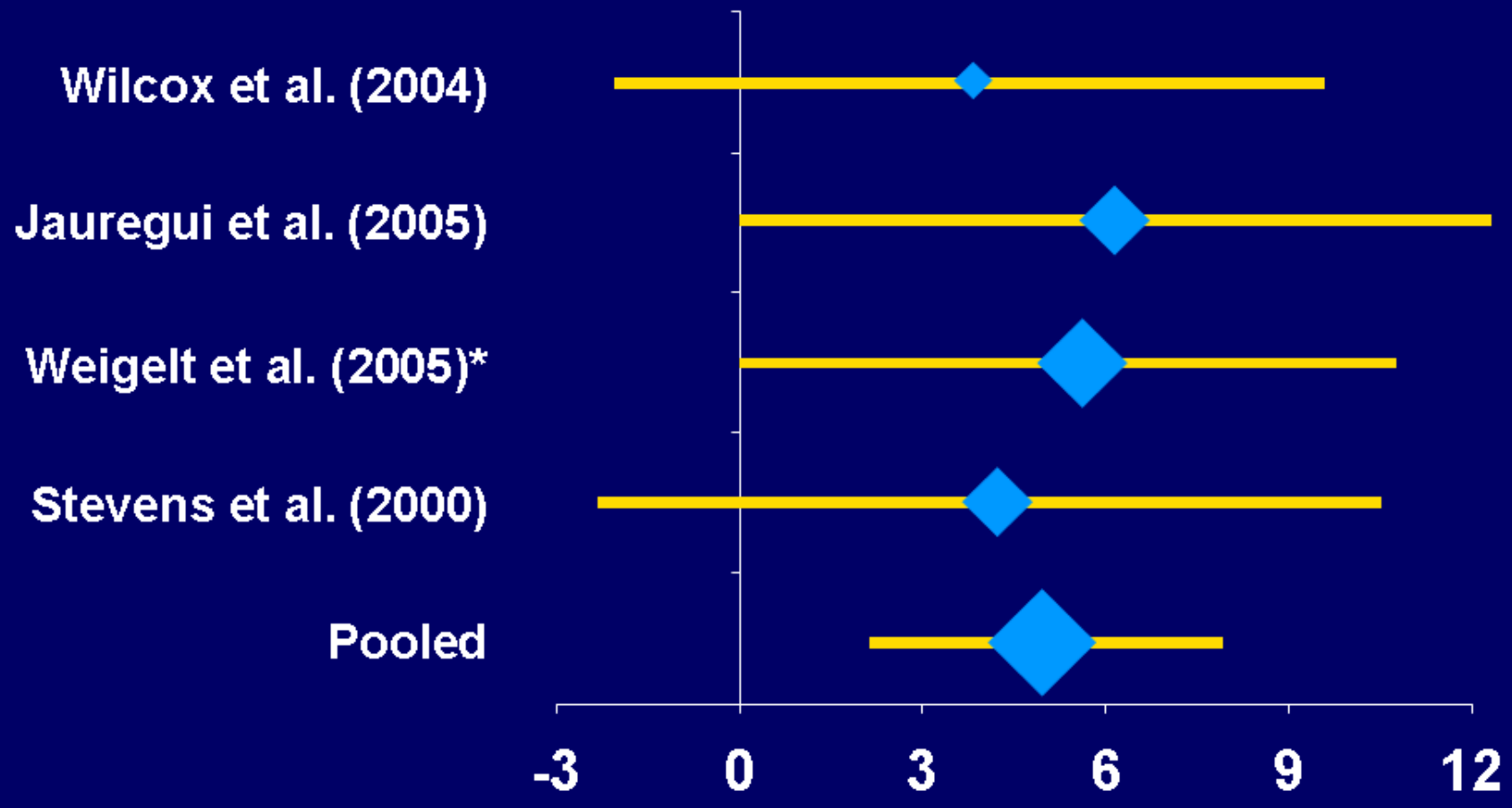
Evidence to Support a Different NI Margin if Linezolid is the Comparator

LJ Wei, PhD

- 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 streptoccoci [2]

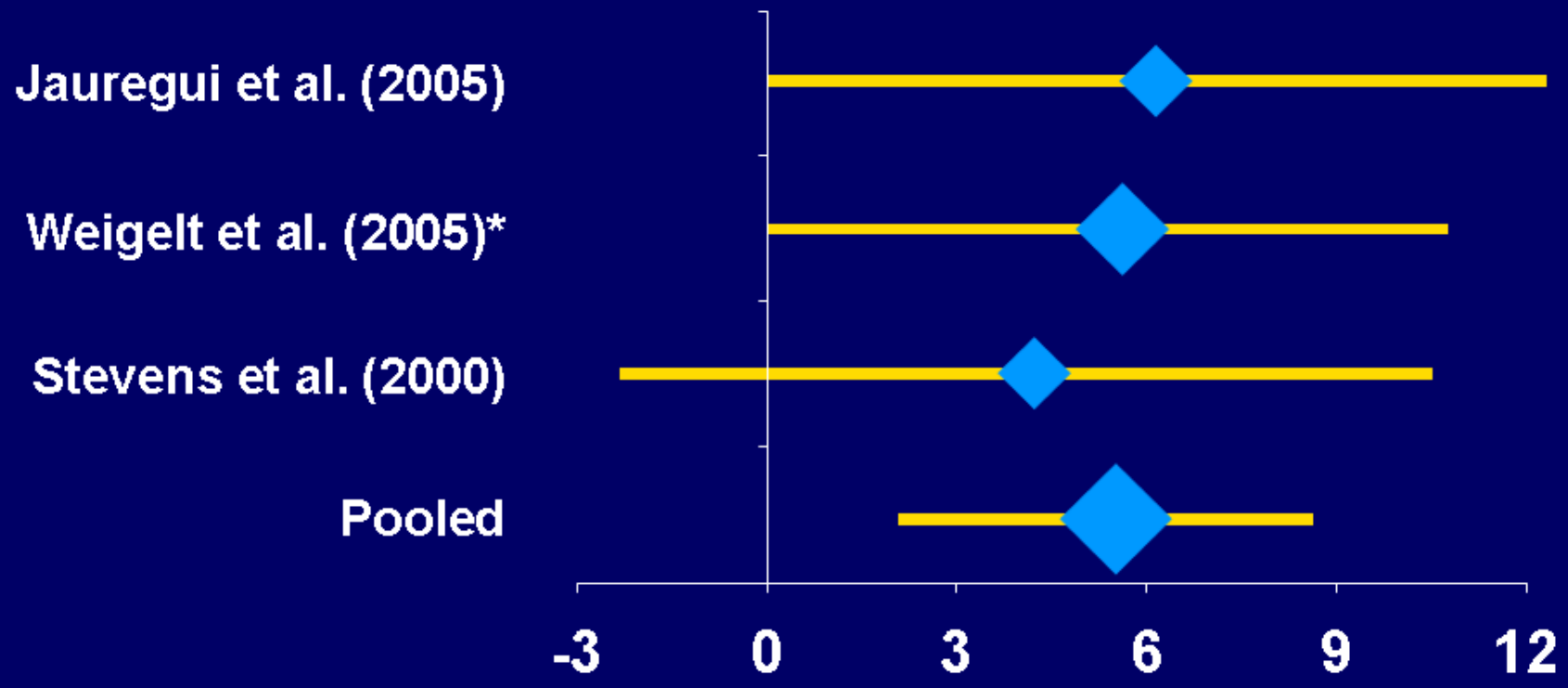
1. Medical reviewer comment Cubicin NDA 21-572.
2. Linezolid approved label.

Randomized, Parallel-Group Trials of Linezolid in cSSSI: Cure Rate Differences (%)



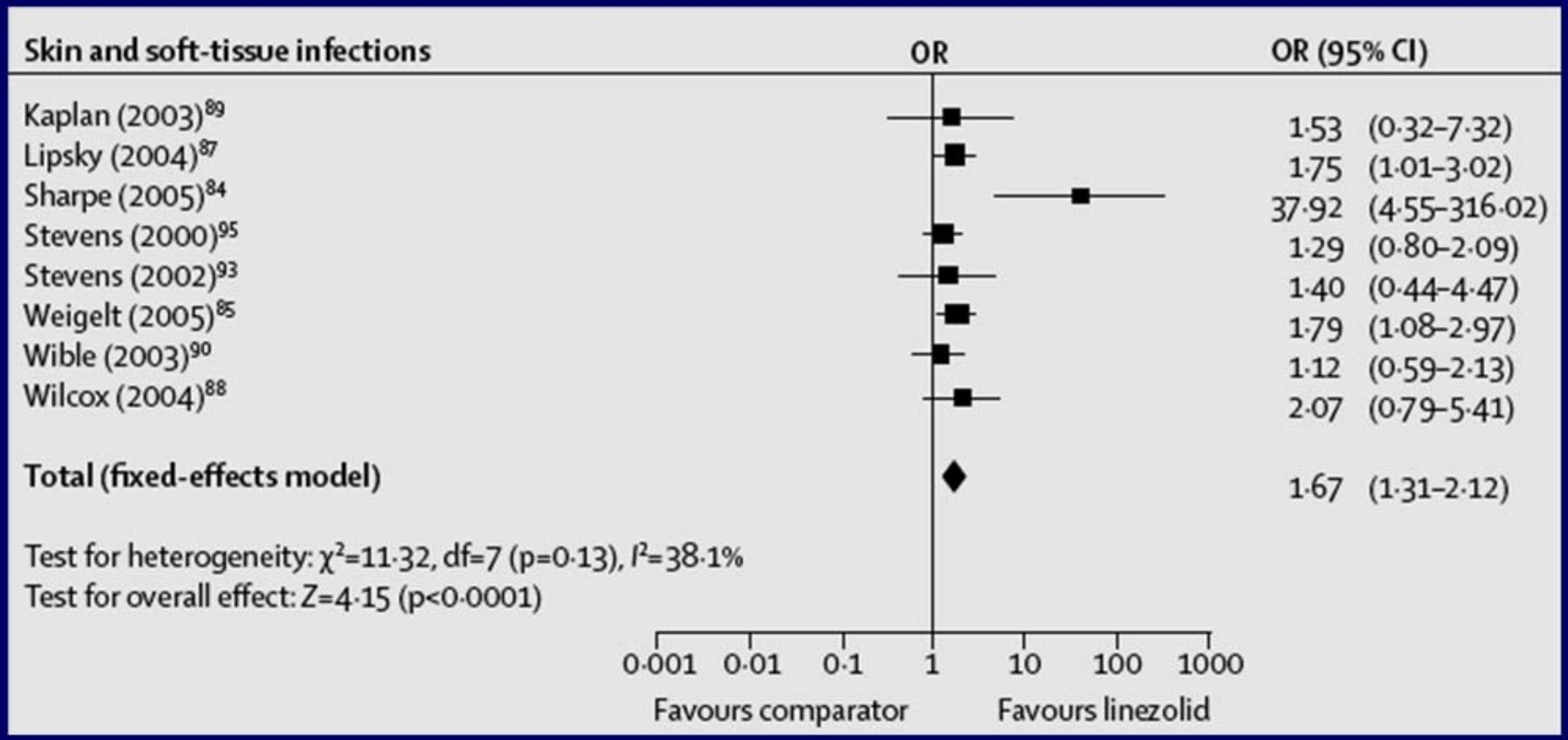
*Linezolid vs vancomycin.

Randomized, Parallel-Group Trials of Linezolid in cSSSI: Cure Rate Differences (%)



*Linezolid vs vancomycin.

Linezolid vs Glycopeptide or β-lactam for Treatment of Gram-positive Bacterial Infections: Meta-analysis of Randomized Controlled Trials in SSSI



Falagas, et al, *Lancet Infectious Diseases*. 2008.

NI Margin: With Abscess

IDSA Recommendation	% in ASSIST	Active – Placebo	50% of Active	Retention of 50%	Retention of 60%	Retention of 70%
Wounds & Ulcers	39%	42%	21%	8%	7%	5%
Cellulitis	33%	28%	14%	5%	4%	3%
Abscesses	28%	14%	7%	2%	2%	1%
Non-inferiority Margin				15%	12%	9%

NI Margin: Without Abscess

IDSA Recommendation	% in ASSIST	Active – Placebo	50% of Active	Retention of 50%	Retention of 60%	Retention of 70%
Wounds & Ulcers	39%	42%	21%	11%	9%	7%
Cellulitis	33%	28%	14%	6%	5%	4%
Non-inferiority Margin				18%	14%	11%

Medical Need for a New Antibiotic: The Case for Iclaprim

Vance G. Fowler, Jr. MD, MHS

Medical Need for a New Antibiotic

- Increasing Clinical Need
- Declining Numbers of New Agents
- “Allen Wrench” Analogy

Medical Need for a New Antibiotic

- Increasing Clinical Need
- Declining Numbers of New Agents
- "Allen Wrench" Analogy

Increasing Frequency of SSTI

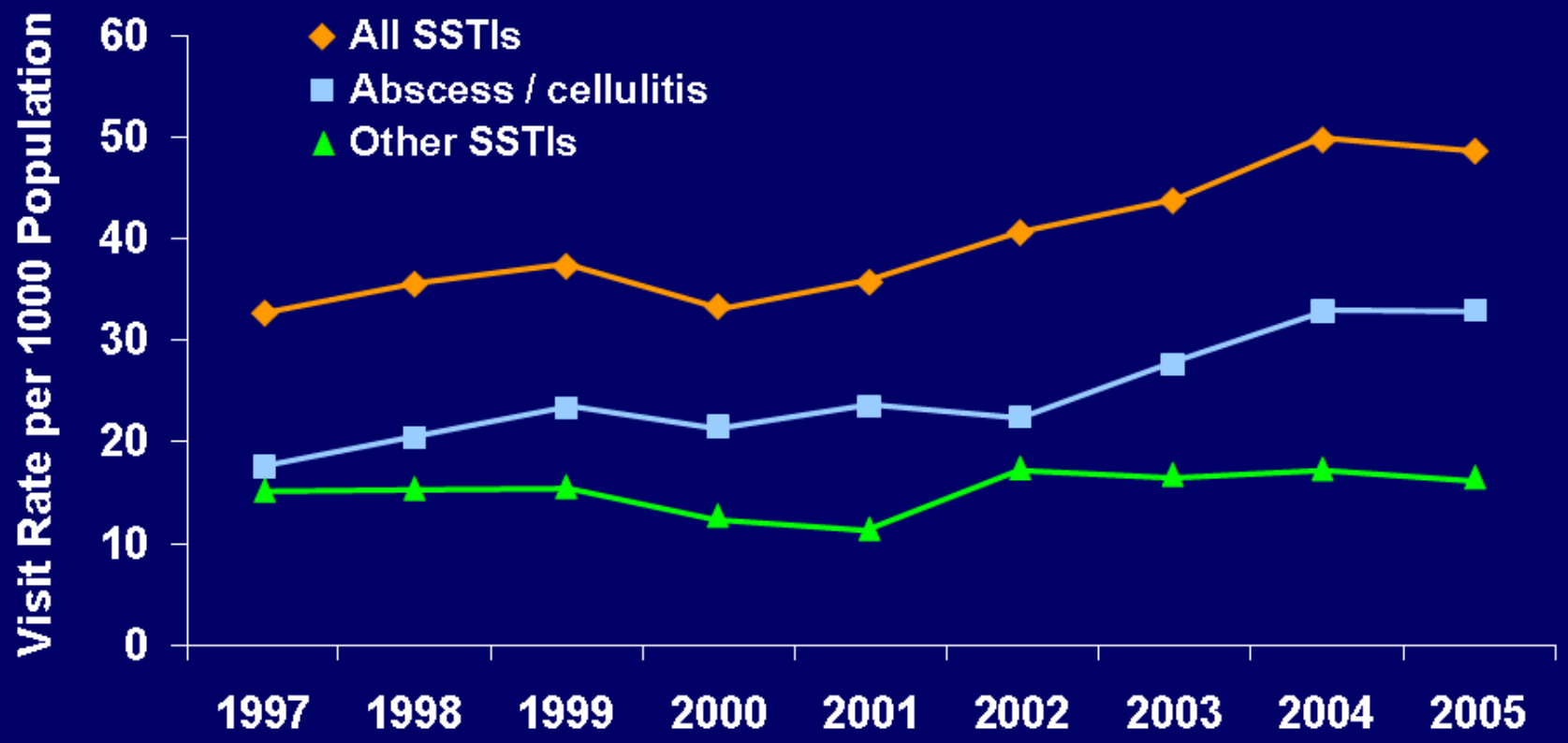


Figure 1. Annual rates of visits for skin and soft-tissue infections (SSTIs) in the US. A visit for abscess / cellulitis is based on codes 681.x and 682.x from the *International Classification of Diseases, Clinical Modification, Ninth Revision (ICD-9-CM)*. Visits for other SSTIs are based on *ICD-9-CM* codes 035, 611.0, 680.x, 683.x, 684.x, 686.x, 704.8, 728.0, 728.86, and 771.5.

Hersch et al. *Arch Intern Med* 2008; 168 (14): 1585-1591.

Medical Need for a New Antibiotic

- Increasing Clinical Need
- Declining Numbers of New Agents
- "Allen Wrench" Analogy

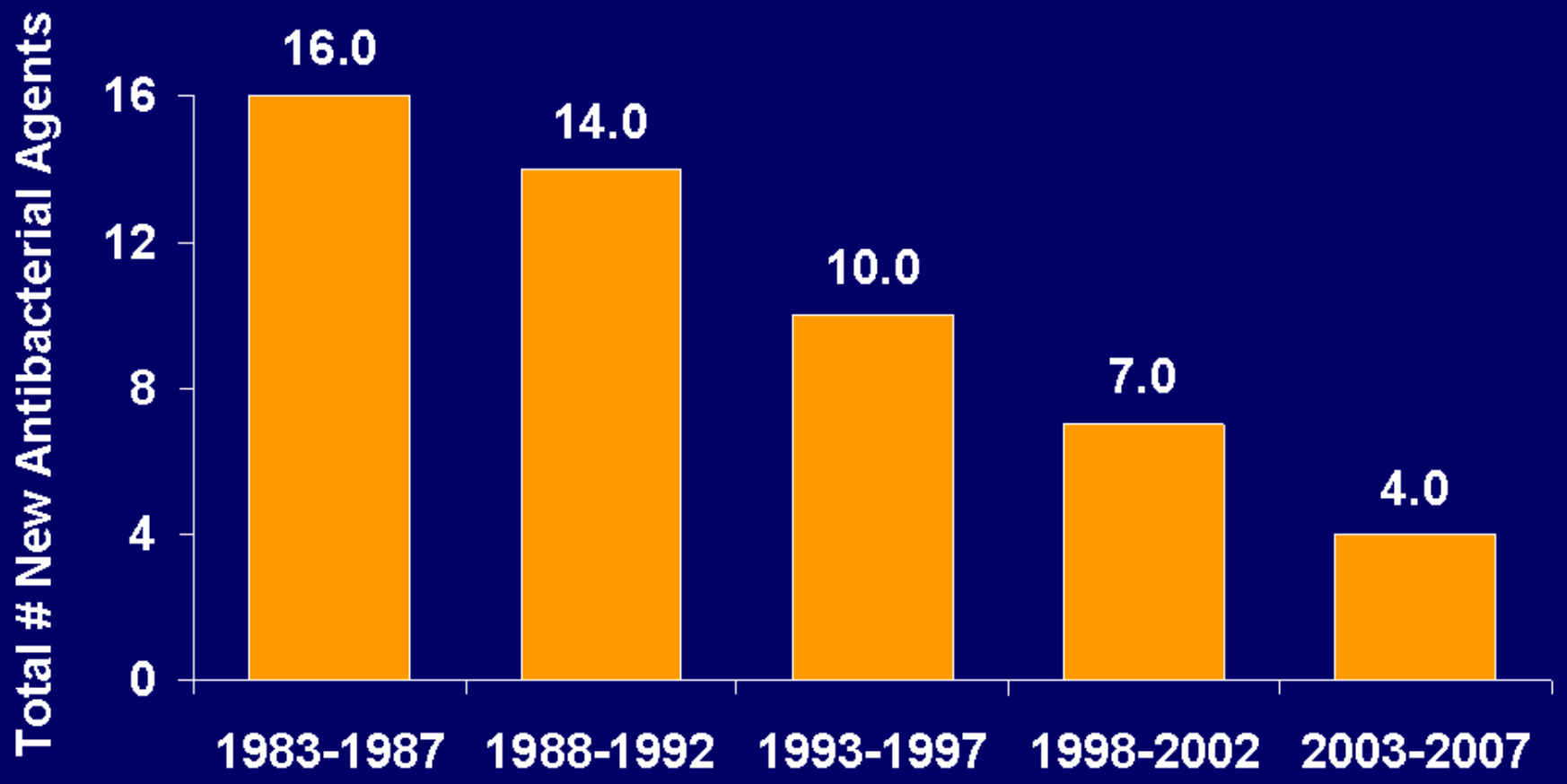
Rapid Emergence of Resistance in *S. aureus*

Antibiotic	Year of Introduction of First Significant Use	Year of Discovery of Resistance	Interval, Years
Penicillin	1944	1945	1
Methicillin	1959	1961	2
Linezolid	2000	2001	1
Daptomycin	2003	2005	2
Vancomycin			
Intermediately susceptible	1958; 1985	1997	39; 12
Resistant	1958; 1985	2002	44; 17

Table 1. History of antibiotic resistance in *S. aureus.*

Clinical Infectious Diseases 2007;45:601-8.

Total Approved Antibacterials: United States



Spellberg, et. al., *Clin Infect Dis* 2008; 46 (2);155-64

Medical Need for a New Antibiotic

- Increasing Clinical Need
- Declining Numbers of New Agents
- "Allen Wrench" Analogy

Allen Wrench Analogy

Allen Wrench Analogy

Allen Wrench Analogy: Approved Antibiotics for cSSSI

	Favors Use	Favors Avoidance
Vancomycin	Vast body of experience	"MIC Creep" Treatment failure
Quinupristin-dalfopristin	Failure / intolerance of other agents	Central line Arthralgias
Linezolid	Pneumonia (?) Oral administration	Myelosuppression MAO-I contraindication
Daptomycin	Bacteremia	Resistance Pneumonia
Tigecycline	Intra-abdominal infection	Nausea / vomiting

Why Iclaprim?

The Case for Iclaprim

Benefits

- Safe
  - "2nd generation" trimethoprim
  - Low potential for drug-drug interaction
  - No requirement for dose-adjustment for renal impairment
- Efficacious
  - High cure rates in cSSSI patients
- Durable
  - "Resistance to resistance"
- Good tissue / lung penetration
  - Future: CAP / HAP?
- Oral Bioavailability
  - Future: Oral formulation?

Risks

- QTc prolongation
  - Small (4-6 ms)
  - Transient
  - Rapidly reversible

Allen Wrench Analogy: The Case for Iclaprim

	Favors Use	Favors Avoidance
Iclaprim	■ Safe ■ Durable ■ Prospect for Oral Alternative to TMP / SMX	QTc
Vancomycin	Vast body of experience	"MIC Creep" Treatment failure
Quinupristin-dalfopristin	Failure / intolerance of other agents	Central line Arthralgias
Linezolid	Pneumonia Oral administration	Myelosuppression MAO-I contraindication
Daptomycin	Bacteremia	Resistance Pneumonia
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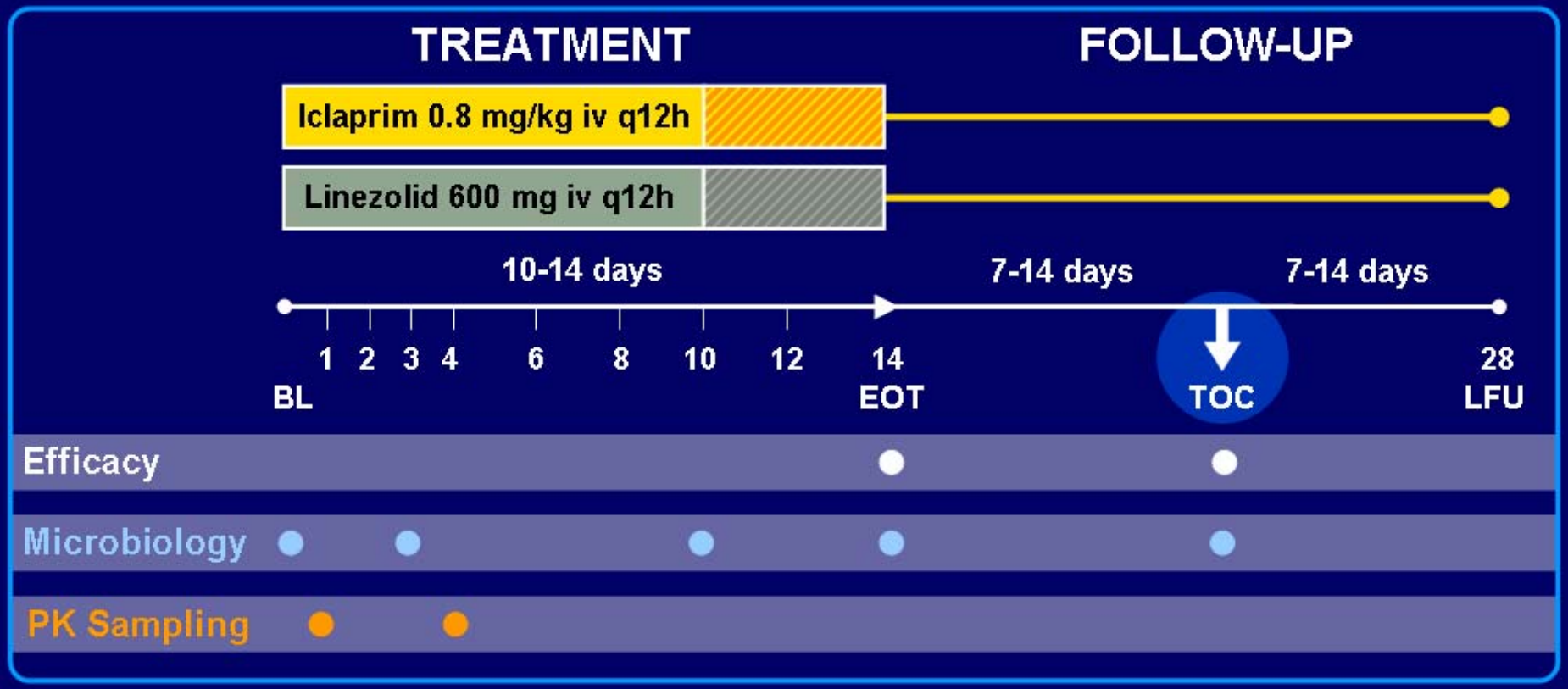
Concluding Remarks

Khalid Islam, PhD

Study Design of ASSIST-1 and ASSIST-2

Phase 3

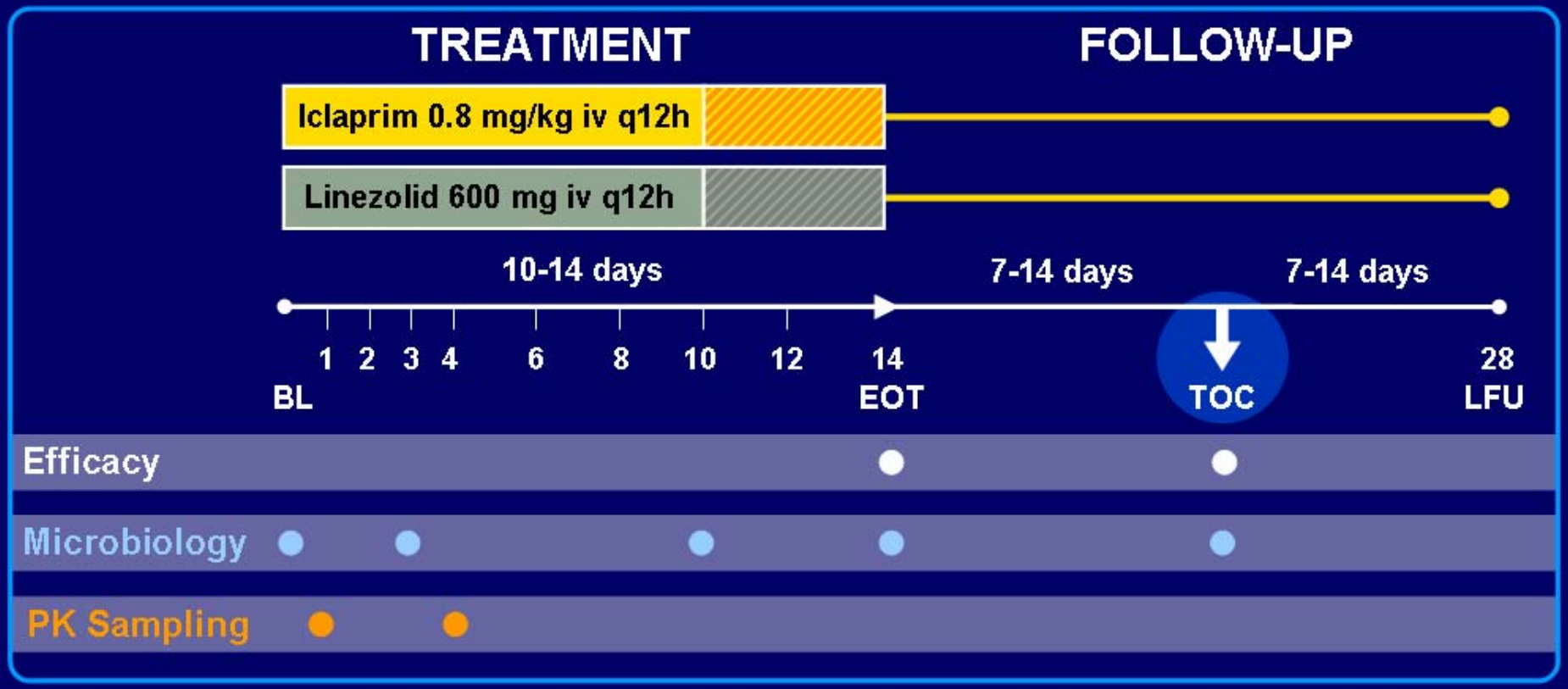


Examination of FDA Reclassifications of Cures

- Sponsor analysis differs from FDA analysis
- Primary end point was defined as clinical cure at Test of Cure (TOC) visit – 7-14 days after the End of Therapy (EOT)
- All patients reclassified by the FDA including those still considered as failures or indeterminates in the FDA addendum were defined as cures by investigator, medical monitor and Arpida on a blinded basis at the TOC visit

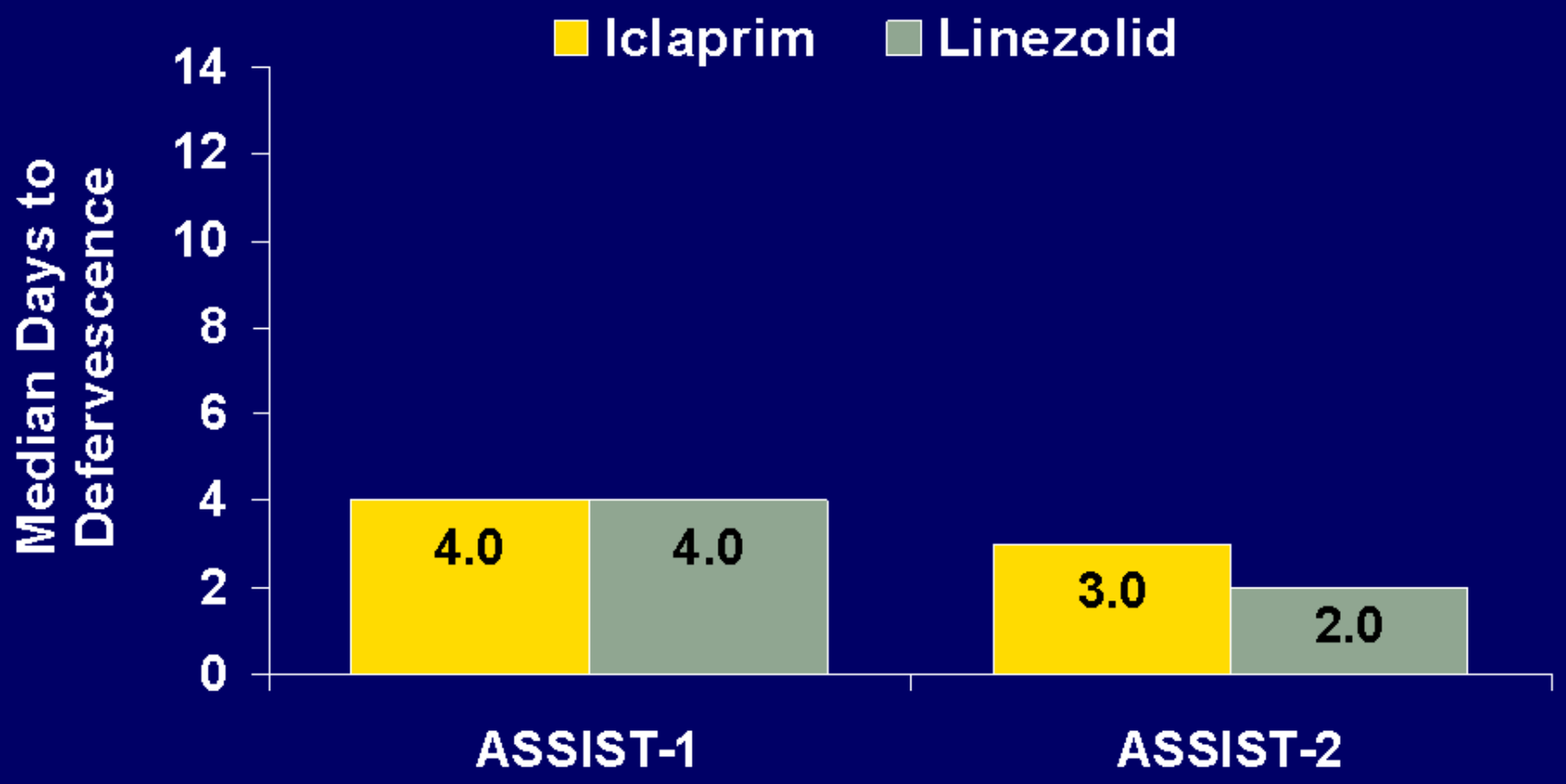
Study Design of ASSIST-1 and ASSIST-2

Phase 3



Time to Defervescence

ITT Population*

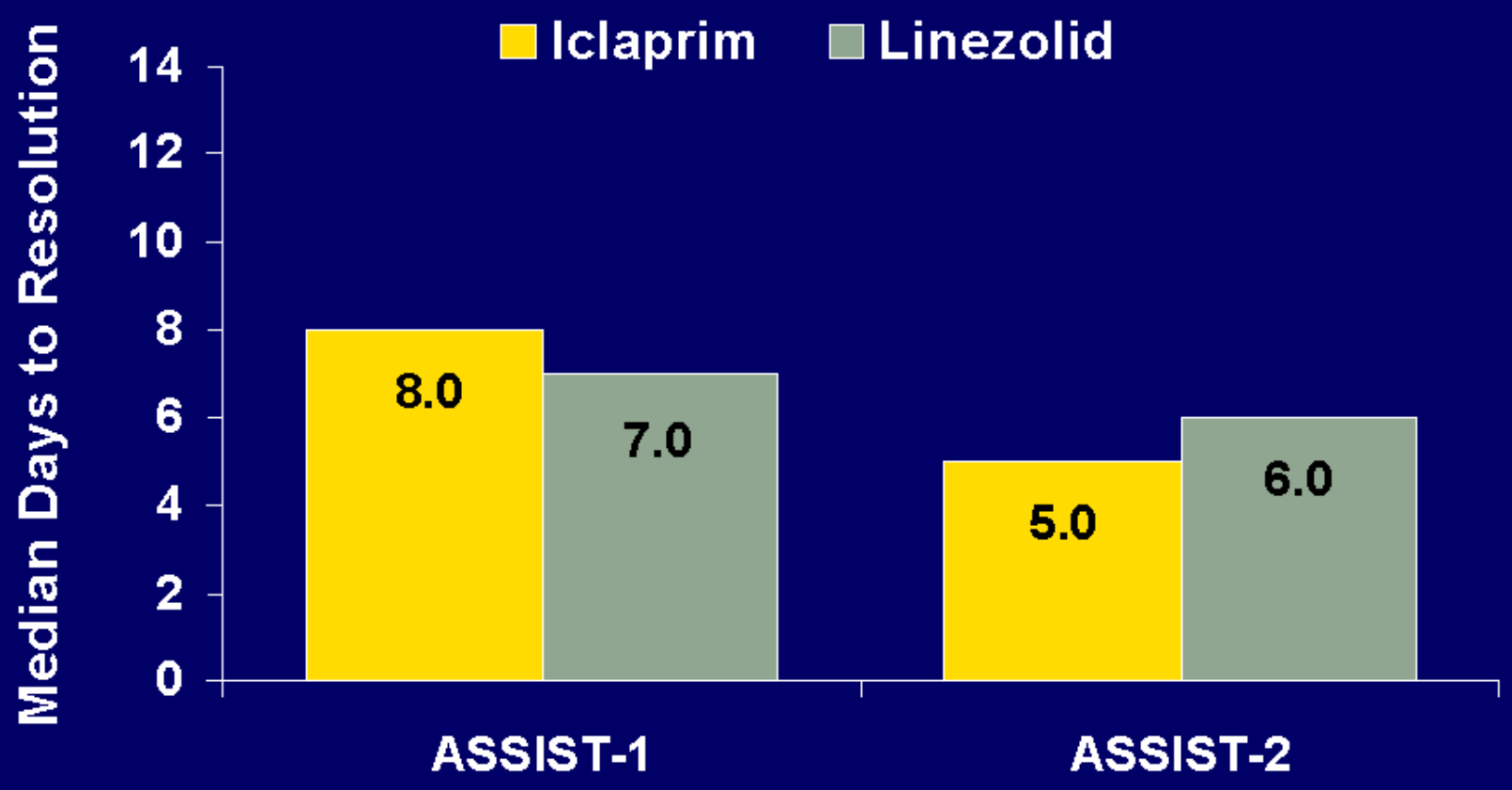


*Same results for PP Population.

From Kaplan-Meier analysis, point estimate.

Time to Resolution of Signs and Symptoms of cSSSI

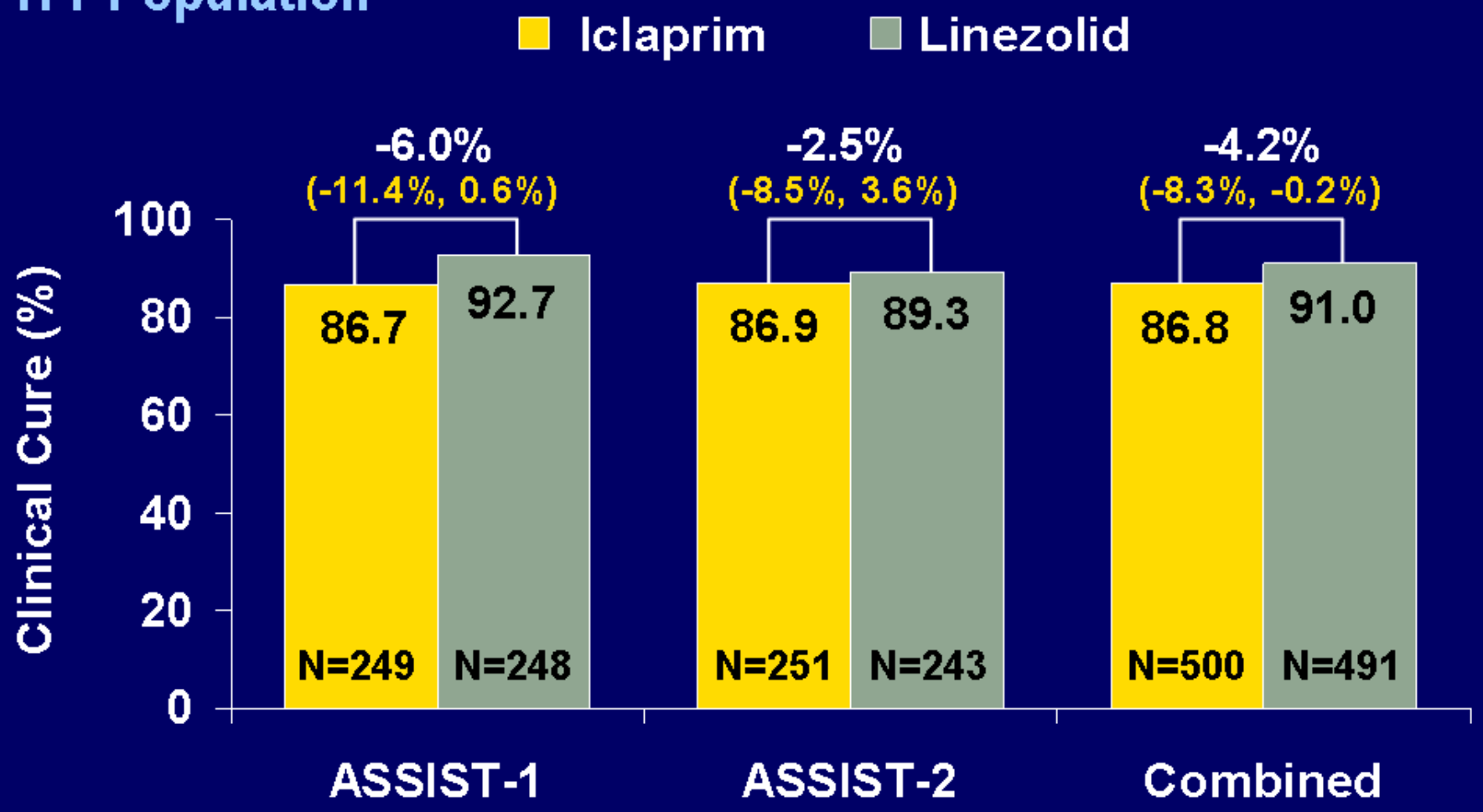
ITT Population*



*Same results for PP Population.

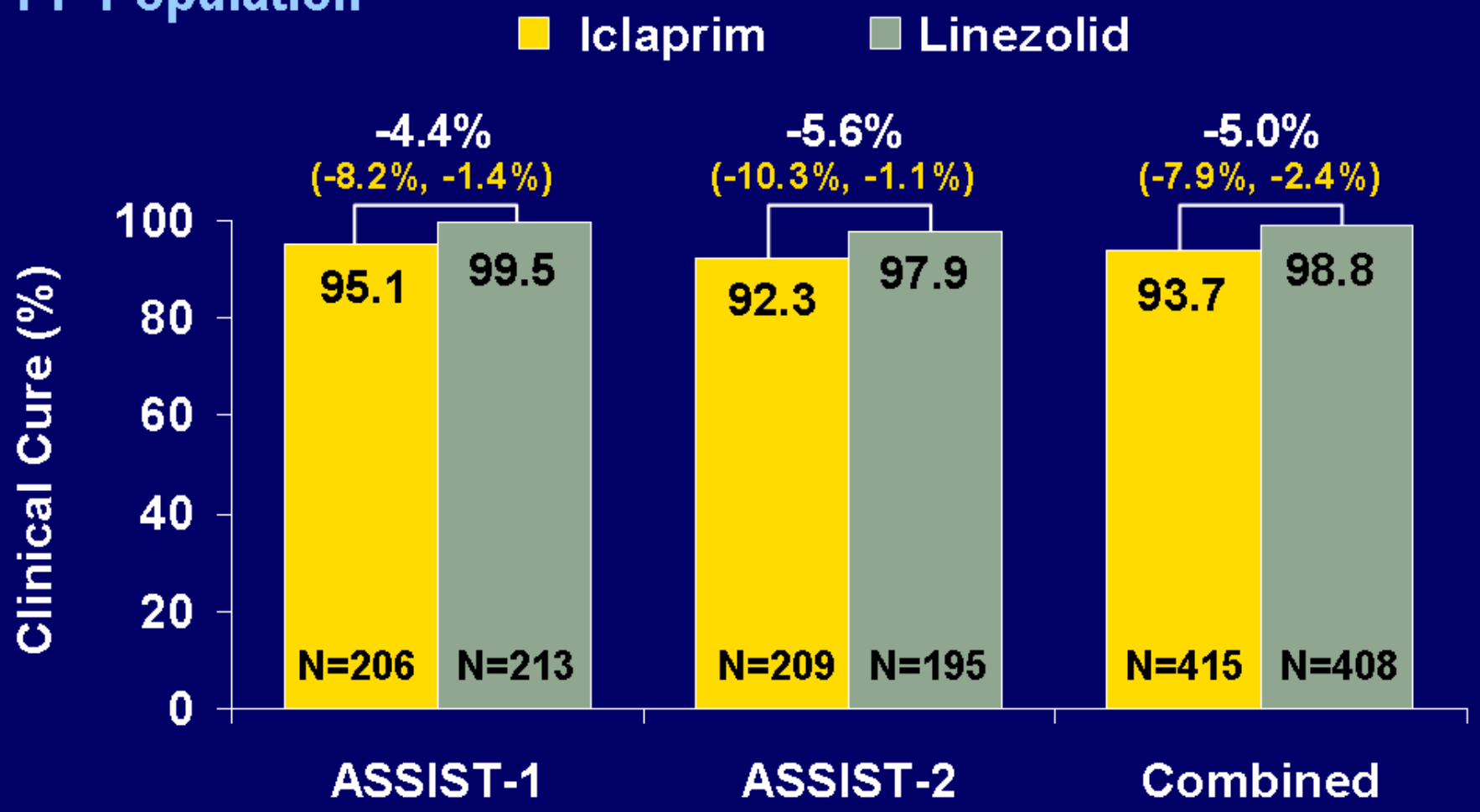
Clinical Cure at EOT

ITT Population



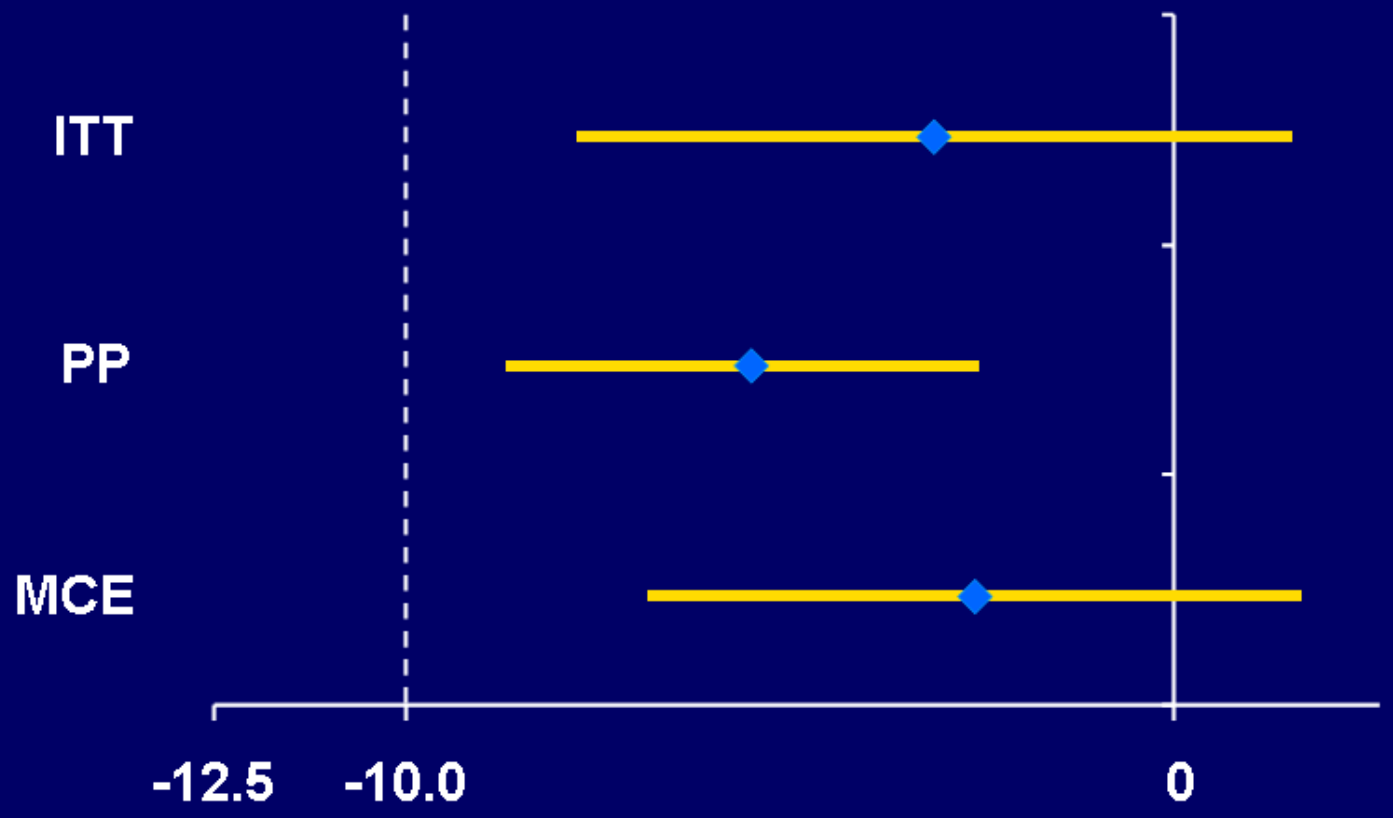
Clinical Cure at EOT

PP Population



Primary Analysis Results in ITT, PP and MCE Populations

Combined



NDA 22-269

ICLAPRIM: Concentrate for Solution for Infusion

Indication: Complicated Skin and Skin Structure Infections (cSSSI)

Anti-Infective Drugs Advisory Committee Meeting

November 20, 2008

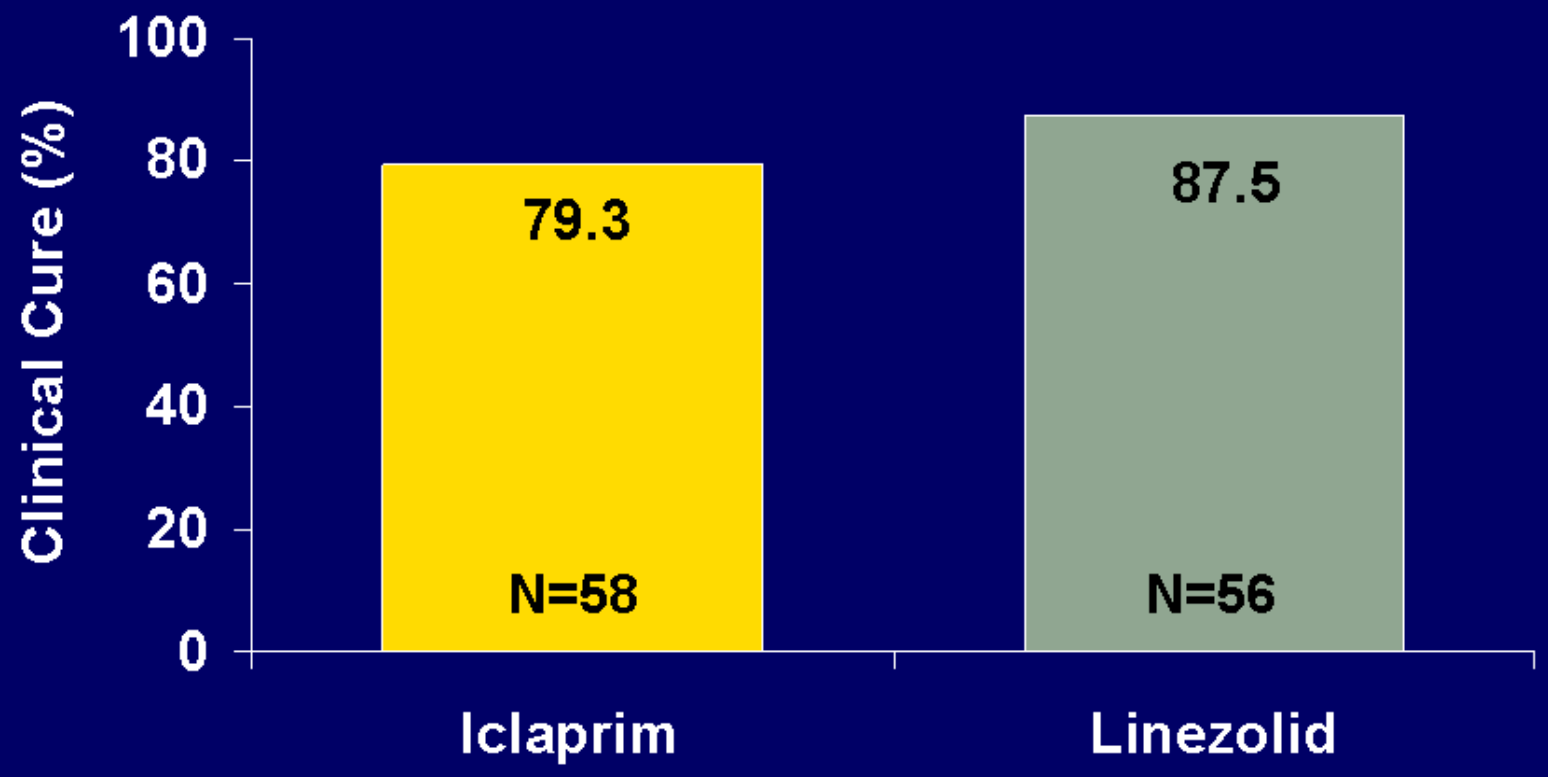
Demonstrates a PAE, SME and PA-SME

Strain	MIC (ug/ml)	10xMIC PAE	0.2xMIC	
			SME (hours)	PA-SME (hours)
MSSA (ATCC 25923)	0.06	2.1	1.4	>6.1
MRSA 3817	0.06	1.2	>3.8	>3.8
MRSA 6	0.06	1	>4.2	>4.2
S. agalactiae 24706	0.25	1.5	>6.4	>6.4
S. pyogenes GAS1	0.06	0.7	>5.3	>5.3

Zampolina Internal Report

Clinical Cure at TOC

Patients with *S. pyogenes* as BL Pathogen (Combined Data)



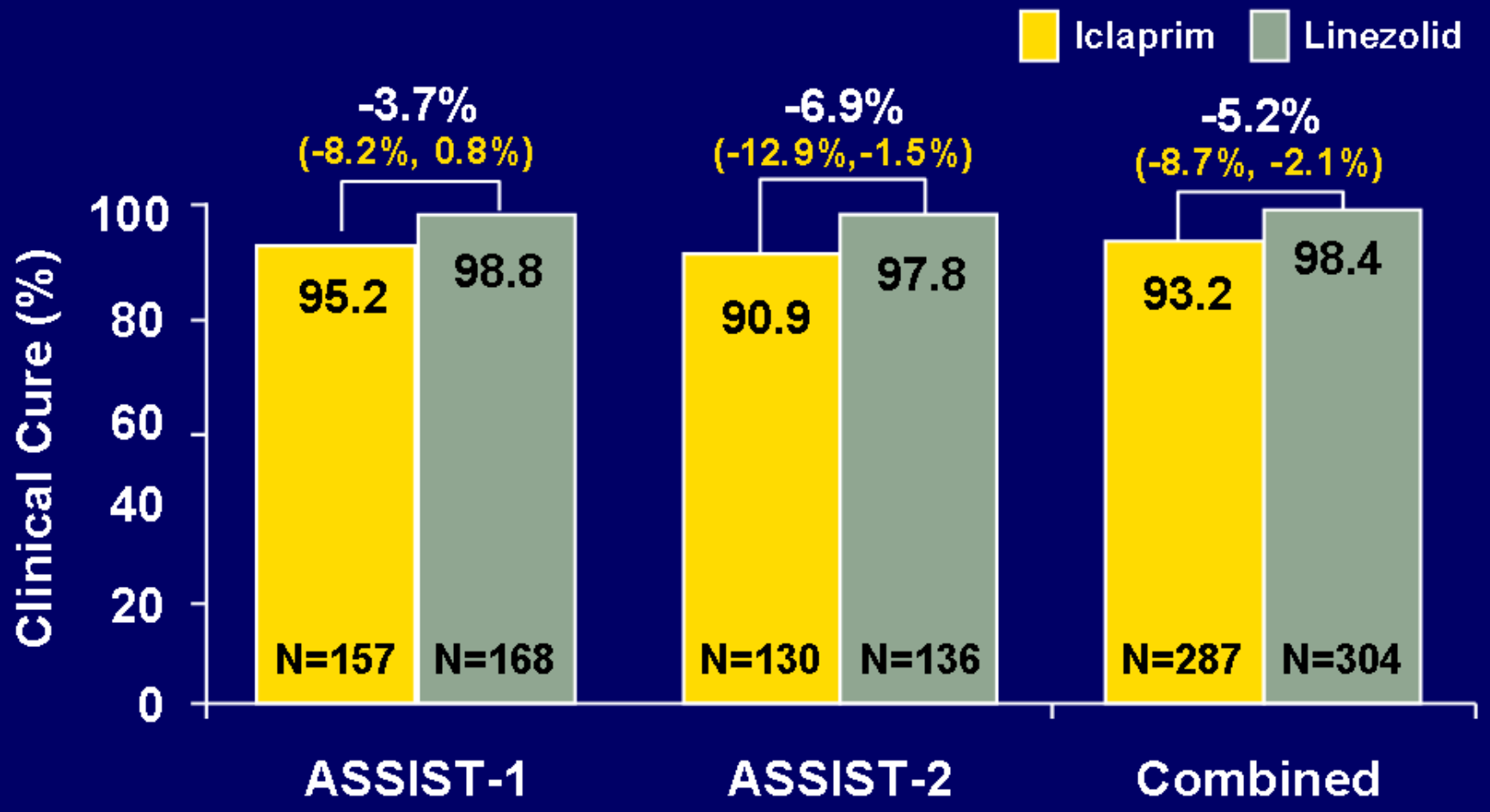
Patient Cure Rate for *S. pyogenes* by Infection Types

MITT Combined

	ICL	LIN
Ulcers	5 (100%)	5 (60%)
Burns	7 (86%)	9 (89%)
Abscess	7 (71%)	8 (100%)
Cellulitis	38 (74%)	28 (86%)
Wound Infections	10 (80%)	15 (87%)

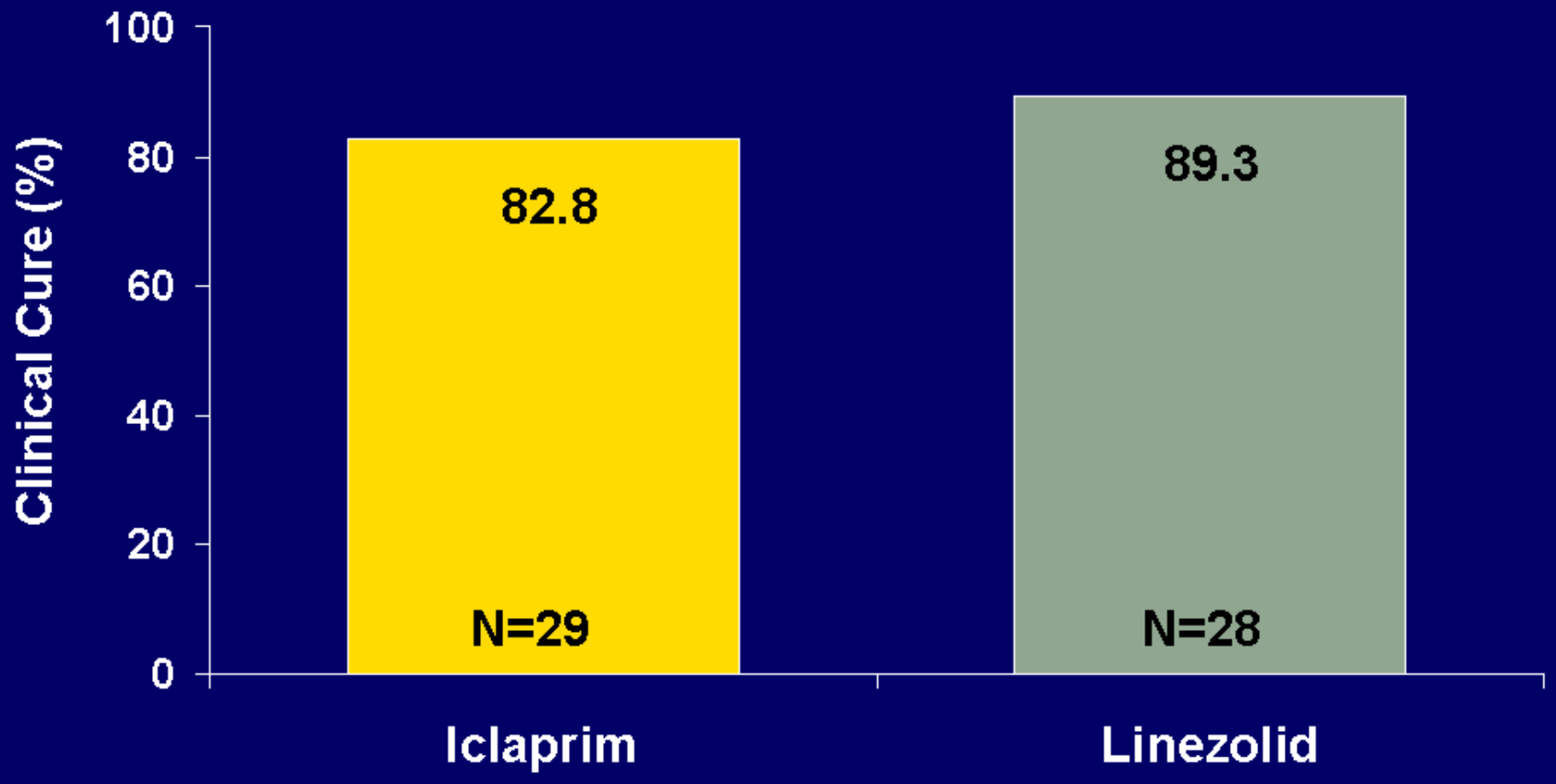
Clinical Cure Rates at TOC – No Abscesses

PP Population

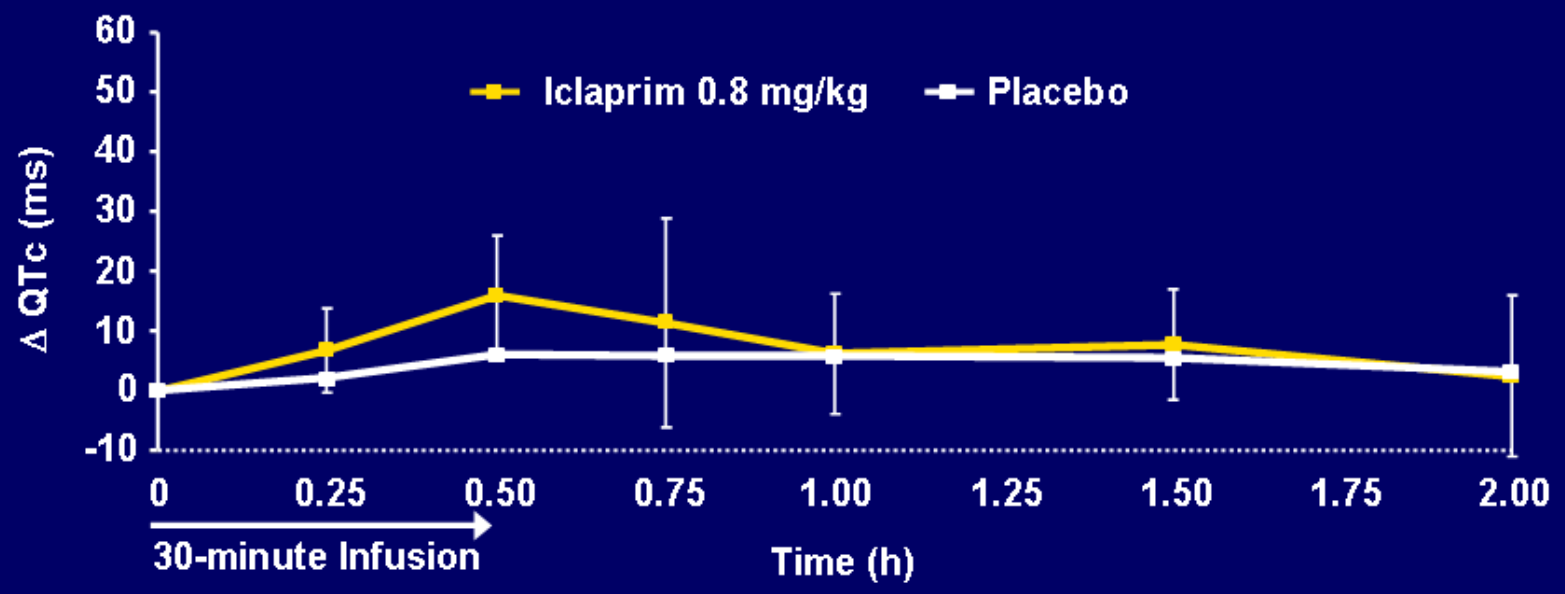


Clinical Response at TOC

E. faecalis (Combined Data)



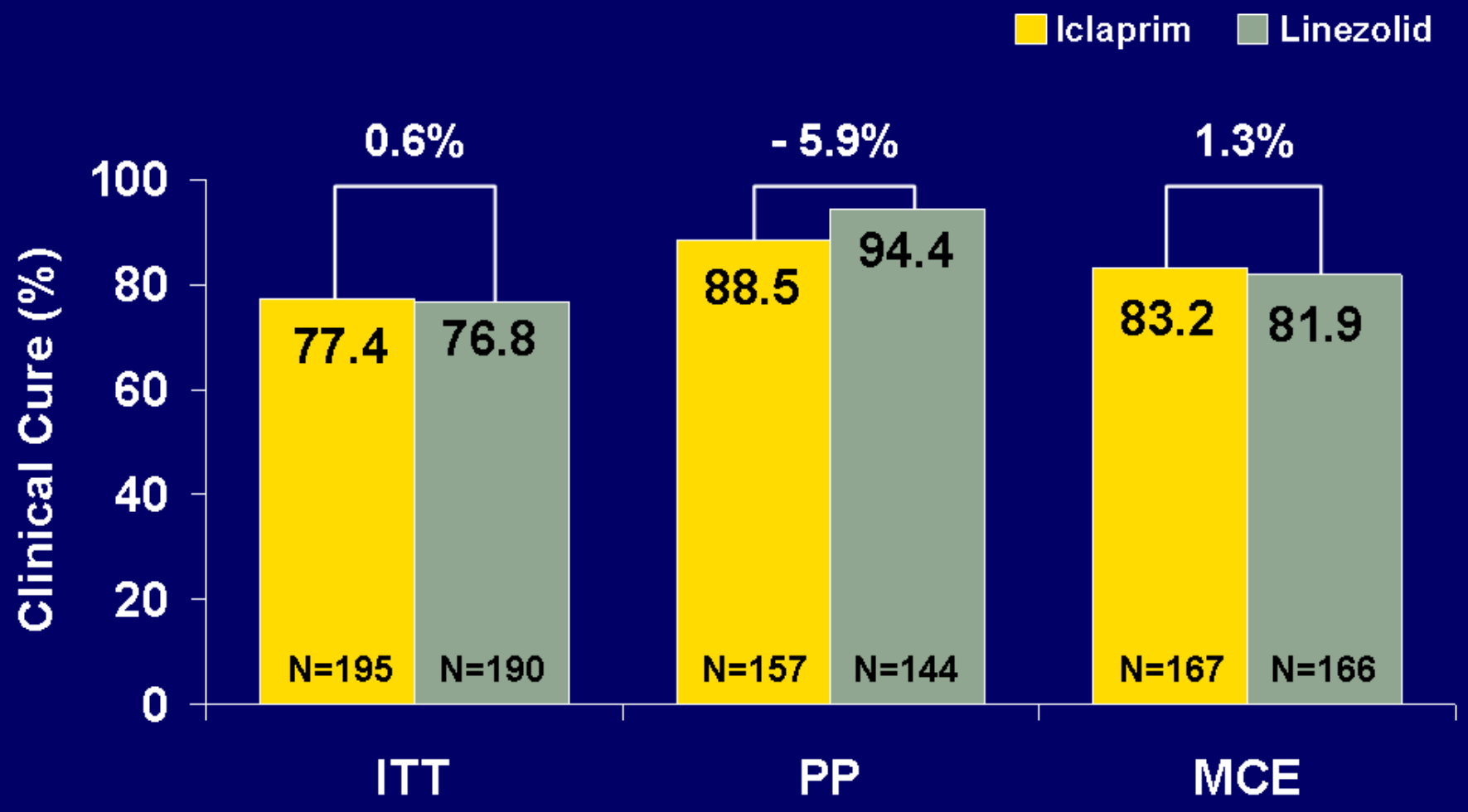
Formal ECG Trials Show a Small, Rapidly Reversible, T_{max}-Related QTc Effect



- Dose-dependent increase in QTc
- Mean maximal increase about 10 ms at 0.8 mg/kg
- No gender difference

High Clinical Cure Rate in US Population

Combined Data



ECG Summary of QTc Values, Absolute Values

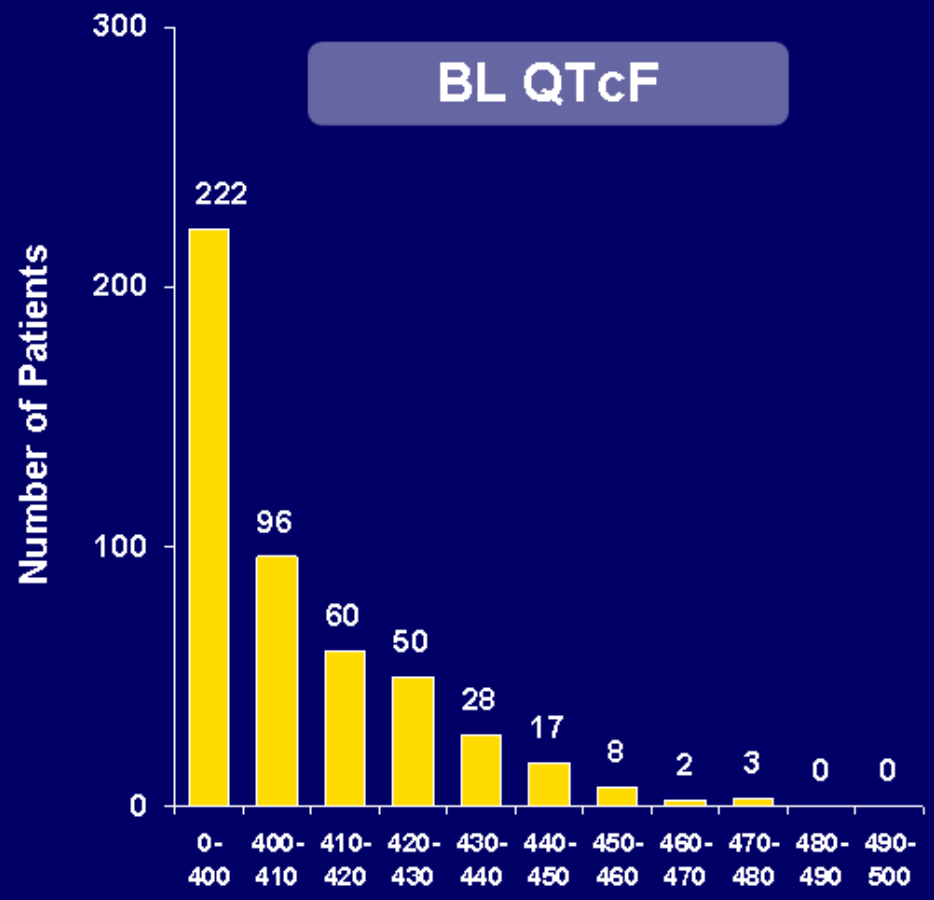
ITT Population

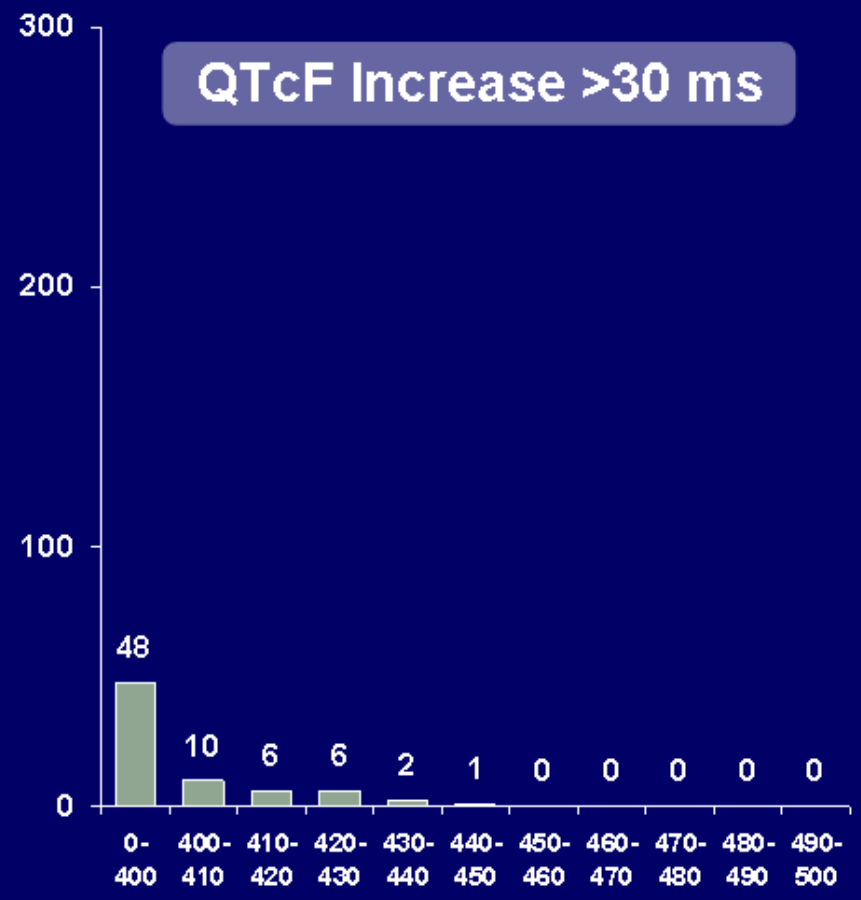
		ASSIST-1		ASSIST-2*	
		Iclaprim N=250 N (%)	Linezolid N=247 N (%)	Iclaprim N=250 N (%)	Linezolid N=244 N (%)
Screening					
QTcB	>500 ms	0	2 (0.8%)	0	0
QTcF	>500 ms	0	0	0	0
Day 1 Predose					
QTcB	>500 ms	0	1 (0.4%)	0	1 (0.4%)
	>510 ms	0	1 (0.4%)	0	1 (0.4%)
	>520 ms	0	0	0	1 (0.4%)
QTcF	>500 ms	0	0	0	1 (0.4%)
	>510 ms	0	0	0	1 (0.4%)
	>520 ms	0	0	0	1 (0.4%)
Day 1 Postdose					
QTcB	>500 ms	1 (0.4%)	0	3 (1.2%)	0
	>510 ms	1 (0.4%)	0	0	0
QTcF	>500 ms	0	0	0	0
Day 4 Postdose					
QTcB	>500 ms	1 (0.4%)	2 (0.8%)	2 (0.8%)	0
	>510 ms	1 (0.4%)	1 (0.4%)	1 (0.4%)	0
QTcF	>500 ms	0	0	1 (0.4%)	0
	>510 ms	0	0	0	0

*Where BL values were missing but a screening ECG was carried out, these data have been included in the BL.

Distribution of QTcF in Iclaprim Arm

BL QTcF of Patients Treated with Iclaprim (Combined)





Toxicology in Rats and Marmosets (Cont'd)

- Reproductive toxicity
  - No effect on fertility in rats (iv)
- Developmental toxicity
  - Potential for teratogenic effects observed (rats and minipigs, oral); known class effect for folate antagonists
- Genotoxicity
  - No mutagenic / clastogenic effects observed