



ARPIDA AG

ICLAPRIM

CONCENTRATE FOR SOLUTION FOR INFUSION

ADVISORY COMMITTEE BRIEFING BOOK

Anti-Infective Drugs Advisory Committee Meeting

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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LIST OF ABBREVIATIONS

AE	Adverse event
ADME	Absorption/distribution/metabolism/excretion
ALT	Alanine aminotransferase
ASSIST	Arpida's Skin and Skin Structure Infection STudy
AST	Aspartate aminotransferase
ATCC	American Type Culture Collection
AUC	Area under the concentration curve (extent of exposure)
BMI	Body mass index
C _{max}	Maximum plasma concentration
CA-MRSA	Community-acquired, methicillin-resistant <i>Staphylococcus aureus</i>
CFR	Code of Federal Regulations
CFU	Colony forming units
CI	Confidence Interval
cSSSI	Complicated skin and skin structure infection
CYP450	Cytochrome P450
DHFR	Dihydrofolate reductase
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EMA	European Medicines Agency
EOT	End of treatment
ETA	Early Treatment Assessment
F/U	Follow-up
FDA	Food and Drug Administration
GAS	Group A streptococci
GBS	Group B streptococci
HED	Human Equivalency Dose
hVISA	Hetero-vancomycin-intermediate <i>Staphylococcus aureus</i>
hGISA	Hetero-glycopeptide-intermediate <i>Staphylococcus aureus</i>
ICH	International Conference on Harmonization
IDSA	Infectious Diseases Society of America
IND	Investigational New Drug
ITT	Intent To Treat
IV	Intravenous
LFT	Liver function test
MBC	Minimum Bactericidal Concentration
MCE	Modified Clinically Evaluable
ME _{MCE}	Microbiologically Evaluable MCE Population
ME _{PP}	Microbiologically Evaluable PP Population
MIC	Minimum inhibitory concentration
MIC ₉₀	Minimum inhibitory concentration required to inhibit 90% of individual strains of a given population of a bacterial species
MITT	Modified Intent To Treat
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MSSA	Methicillin-sensitive <i>Staphylococcus aureus</i>
N	Number
NDA	New Drug Application

NNIS	National Nosocomial Infections Surveillance
NOAEL	No observed adverse effect level
NS	Normal saline
OPAT	Outpatient parental antimicrobial therapy
PD	Pharmacodynamic
PG	Propylene glycol
PK	Pharmacokinetic
PK/PD	Pharmacodynamic/pharmacokinetic
Pres.	Presumed
PP	Per Protocol
PVL	Panton-Valentine Leukocidin
<i>q12h</i>	Every 12 hours
QTcB	QT interval according to Bazett's rule
QTcF	QT interval according to Fridericia's rule
RNA	Ribonucleic acid
ROW	Rest of the World
SAE	Serious adverse event
SAP	Statistical analysis plan
SIRS	Systemic Inflammatory Response Syndrome
T _{max}	Time to reach maximum concentration
TEAE	Treatment-emergent adverse event
TMP	Trimethoprim
TMP-R	Trimethoprim-resistant
TMP-S	Trimethoprim-sensitive
TMP-SMX	Trimethoprim-sulfamethoxazole
TOC	Test of cure
VISA	Vancomycin-intermediate <i>Staphylococcus aureus</i>
VRSA	Vancomycin-resistant <i>Staphylococcus aureus</i>
WBC	White blood cell

1. EXECUTIVE OVERVIEW

1.1 Brief Background

Iclaprim is a diaminopyrimidine derivative belonging to the class of selective dihydrofolate reductase (DHFR) inhibitors and represents a new, second generation of this well-established antibacterial class (Figure 1-1; Kompis et al, 2005). The only member of this class approved for marketing, trimethoprim (TMP), is one of the most widely used antibiotics in the world. Like TMP, iclaprim exhibits little or no activity against human DHFR at a concentration 4–5 orders of magnitude higher than that observed against bacterial DHFR.

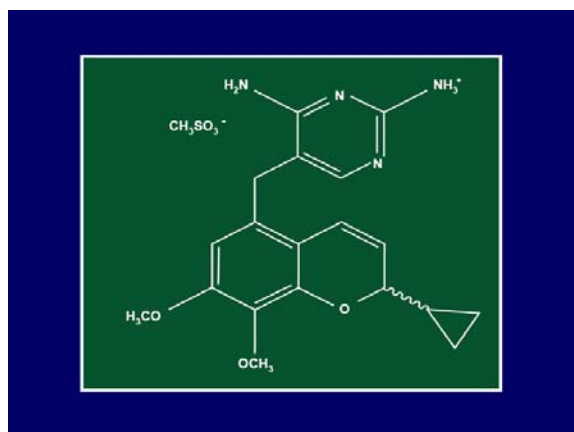


Figure 1-1: Structure of Iclaprim

The diaminopyrimidines have not evolved beyond TMP, which is considered to be a safe, efficacious drug and is used in combination with sulfamethoxazole. After several decades of trimethoprim-sulfamethoxazole (TMP-SMX) use, epidemiological studies showed that TMP-SMX resistance among *Staphylococcus aureus* (*S. aureus*) isolates from wound specimens was 1.6% in 2007 (N>95,000), while among methicillin-resistant *S. aureus* (MRSA), the prevalence of resistance was 1.9% (N>4,000) (Tillotson et al., 2008). The predominant resistance mechanism in *S. aureus* involves a single amino acid mutation (F98Y) in the DHFR enzyme. Based on the knowledge of this resistance mechanism and X-ray crystallographic information, modeling

approaches led to the design and synthesis of iclaprim, which exhibits a significantly stronger binding to microbial DHFR and the mutated F98Y *S. aureus* enzyme, compared with TMP (Figure 1-2). As a consequence, iclaprim exhibits a potent, bactericidal activity against Gram-positive pathogens (including multidrug-resistant pathogens such as MRSA) as well as a low propensity for resistance development. These properties obviate the need for combination with a sulfonamide, which is often associated with undesirable side effects.

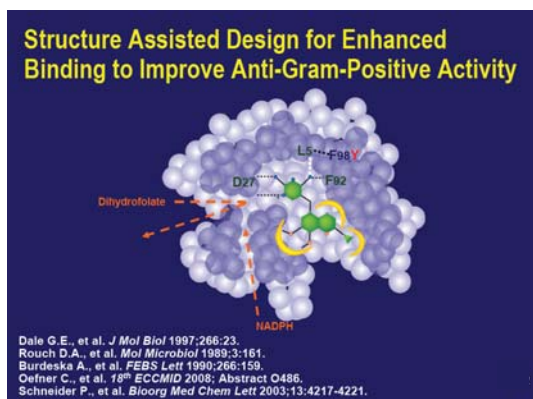


Figure 1-2: Iclaprim X-Ray Structure

Based on its potent antimicrobial activity against Gram-positive pathogens, iclaprim has been developed to address the increasing medical need for “difficult-to-treat” pathogens and, in view of the emerging resistance to current therapies, to provide an alternative treatment option to clinicians for the treatment of complicated skin and skin structure infections (cSSSI).

The development program of iclaprim consisted of 48 pharmacology, pharmacokinetic (PK), and toxicology pre-clinical studies., 14 Phase 1 studies have shown that iclaprim was well-tolerated in human subjects (ie, healthy, renal-/hepatic-impaired, and obese subjects) and has a low potential for drug-drug interactions . A Phase 2 study found that iclaprim was well-tolerated in cSSSI patients and exhibited high clinical and microbiological cure rates that compared favorably with

vancomycin. Finally, two pivotal Phase 3 studies demonstrated that iclaprim exhibited a good safety profile and exhibits high clinical cure rates that were non-inferior to linezolid.

The emergence of resistance to antibacterial drugs currently in clinical use heightens the urgency for new antibiotics that are active against drug-resistant strains and newly emerging pathogens. MRSA presents a major challenge to antibiotic therapy, as its prevalence is steadily increasing in the hospital as well as in institutional and community settings. As highlighted in a recent “Call to Action” publication from the Infectious Diseases Society of America (IDSA)’s Antimicrobial Availability Task Force, there is a convergence of increasing drug resistance and decreasing antibiotic development (Spellberg et al., 2008). Indeed, it is generally acknowledged that the current antibiotic pipeline is insufficient to satisfy the growing clinical need (Figure 1-3). The IDSA stressed the critical need to develop new, diverse antibiotics of various classes and decrease the selective pressure driving resistance, which is exacerbated by the limited number of agents available to treat individual disease entities, such as cSSSI.

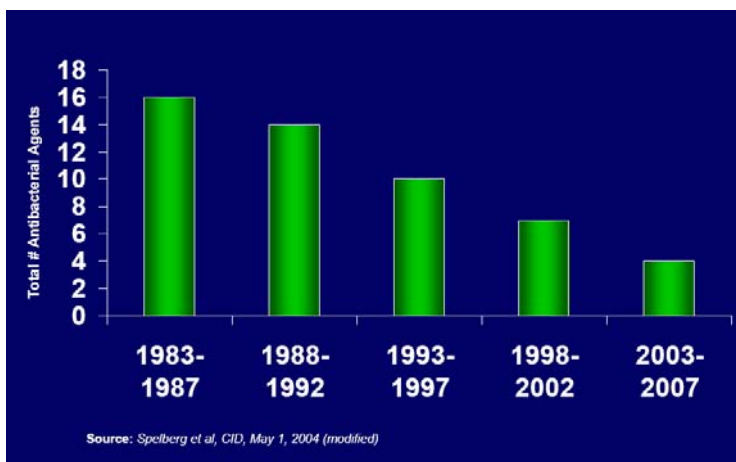


Figure 1-3: Antibacterial Agents Approved, 1983-2007

According to the National Nosocomial Infections Surveillance (NNIS, 2003), MRSA currently accounts for >60% of all *S. aureus* infections in both in-patients and out-patients (Figure 1-4). MRSA, by nature, is resistant to all β -lactams and exhibits reduced susceptibility, often referred to as the “MIC Creep,” to the glycopeptides drug class (eg, vancomycin). The reduced susceptibility to vancomycin has been implicated in a increasing number of clinical failures (Steinkraus et al., 2007). Decreased susceptibility to vancomycin also has been shown to cause reduced susceptibility to the more recently approved lipoglycopeptide daptomycin (Sader and Jones, 2006; Cui et al., 2006). Moreover, there is the potential for the emergence of resistance to linezolid, as demonstrated by case reports in which resistance developed during treatment with this agent (Gales et al., 2006; Hentschke et al., 2008).

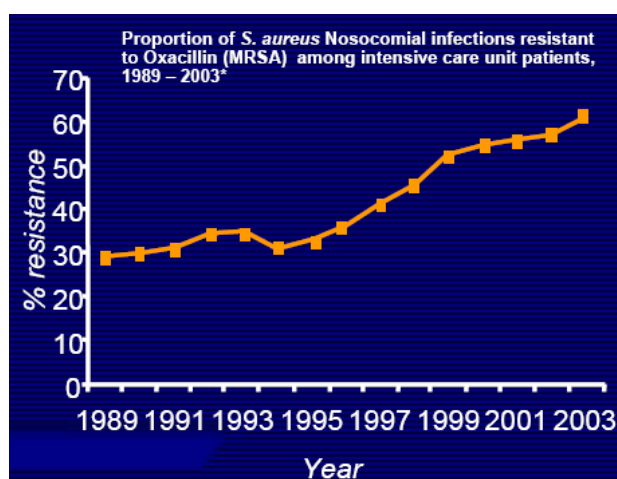


Figure 1-4: Proportion of Oxacillin-resistant *S. Aureus* (MRSA) Nosocomial Infections,

As a folate synthesis inhibitor, iclaprim has a differentiated mechanism of action that distinguishes it from currently approved cell-wall inhibitors, glycopeptides and β -lactams, and protein synthesis inhibitors, linezolid and tigecycline (Figure 1-5). Similarly, its mechanism is differentiated from other late-stage development products (glycopeptides or β -lactams) that target the cell wall. Importantly, Iclaprim has also been shown to be active against MRSA, as well as those pathogens

with reduced susceptibility to glycopeptides and lipoglycopeptides, quinolones, macrolides, and protein synthesis inhibitors.

Figure 1-5: Iclaprim vs. Current US Food and Drug Administration (FDA)-Approved Drugs For cSSSI

Property	Iclaprim (ARPIDA)	vancomycin (generic)	Tygacil (Wyeth)	Cubicin (Cubist)	Zyvox (Pfizer)
<i>MoA</i>	Folate Syn.	Cell wall	Prot. Syn.	Cell wall/Mem.	Prot. Syn.
<i>Action</i>	Rapidly cidal	Slowly cidal	Static	Rapidly cidal	Static
<i>MRSA MIC₉₀</i>	0.12	1 - 2	0.25	0.5	1 - 2
<i>Resistance</i>	Low*	VRE/VISA VRSA	Low	Emerging	Emerging
<i>Dosing</i>	Twice-a-day	Twice-a-day	Twice-a-day	Once-a-day	Twice-a-day
<i>Distribution</i>	High	Low	High	Low	High
<i>Potential for Oral</i>	Yes	No	No	No	Oral Formulation
<i>Adverse events</i>	Small & Transient QT	Nephrotoxicity	35% Nausea	Myopathy	Myelosuppression, Serotonin Syndrome

MIC₉₀ : Minimum Inhibitory Concentration = the lowest concentration of an antimicrobial that will inhibit the growth of 90% of microorganisms of a certain type
 * : based on serial passage experiments and frequency of mutation

In summary, iclaprim has several favorable characteristics that could be expected to provide advantages for the treatment of cSSSI:

- A differentiated mechanism of action distinct from all other currently approved options for the treatment of cSSSI and from those that are currently under late stage development ([Section 2.1](#))
- Potent, cidal, antimicrobial activity against clinically relevant Gram-positive bacteria, (including MRSA and those with reduced susceptibility to current treatment options) involved in cSSSI and other infections commonly seen in hospital settings ([Section 2.3](#));

- Good distribution in major organs and tissues and key lung compartments (Andrews et al 2007);
- A low propensity for development of resistance ([Section 2.2](#));
- A favorable safety profile ([Section 6.2](#));

1.2 Regulatory Guidance

In February 2005, an Investigational New Drug (IND) application for iclaprim was filed with the US Food and Drug Administration (FDA) and came into effect one month later. On August 8, 2005, iclaprim was granted fast-track product designation status by the US FDA for the indication of cSSSI because:

- it is being developed to treat potentially life-threatening conditions, including infections attributed to MRSA;
- it may offer an alternative treatment for those patients who may not be able to tolerate currently existing therapies; and
- it may offer potential benefit in the treatment of community-acquired MRSA infections.

Prior to initiation of the two Phase 3 clinical studies, the sponsor discussed and sought guidance on the study design with both the US FDA and the European Medicines Agency (EMA), and the final design was in accordance with published guidelines for antimicrobial drugs. Based on the regulatory discussions with the FDA and EMA, linezolid was chosen as a comparator for the two pivotal Phase 3 trials in cSSSI as unlike vancomycin, which is often considered sub-optimal for non-MRSA infections, linezolid is approved for the treatment of both MRSA and non-MRSA infections. The two pivotal, double-blind, non-inferiority trials were essentially identical in design

so that the combined data from the two independent studies could be pooled for additional statistical powering in analyzing efficacy parameters. The independent, pivotal Phase 3 trials were statistically powered to demonstrate non-inferiority to the comparator (linezolid) with a delta of -12.5%. (additional powering of the combined data was expected to achieve a delta of -10%). The FDA reviewed the proposed statistical analysis plan before the studies were unblinded.

In March 2008, a new drug application (NDA) was submitted to FDA for iclaprim in the treatment of patients with cSSSI. The recommended dose is 0.8 mg/kg administered twice daily for 8 14 days by intravenous (IV) infusion. The NDA (22-269) was accepted for filing on March 18, 2008.

1.3 Complicated Skin and Skin Structure Infections

SSSIs comprise a large component of cutaneous diseases, are caused by bacterial pathogens, and are treated according to whether they are complicated or uncomplicated. Uncomplicated infections include mild, often self-limited, infections, while complicated infections involve the skin and deeper tissues such as subcutaneous tissues, fascia, and skeletal muscle. By definition, cSSSIs are associated with higher morbidity and some occurrence of mortality. They usually require immediate medical treatment, which often involves surgical intervention and hospitalization. For this patient population, administration of IV antibiotics with suitable Gram-positive coverage is important. In areas where the prevalence of MRSA is high or in high-risk patients, an effective empiric therapy against MRSA is required.

cSSSIs may be community-acquired, healthcare-related, or nosocomial as the result of hospitalization itself or surgical intervention. If not appropriately treated, cSSSI, which is the most frequent hospital infection, can lead to increased morbidity and systemic dissemination with the attendant risk of distant organ involvement and possible mortality. Surgical-site infection is reportedly the third most common nosocomial form, accounting for approximately 14% to 25% of

all new infections. According to reports from the SENTRY Antimicrobial Surveillance Program, *S. aureus* is the most common pathogen involved in community- and hospital-acquired SSSIs worldwide, particularly among high-risk populations such as the elderly (Mathai et al., 2001). More recently, the widespread emergence of Panton-Valentine leukocidin gene (PVL)-positive MRSA isolates has further exacerbated the problem (Boyle-Vavra and Daum, 2007; Chastre, 2008; Balis et al., 2007).

The IDSA has well-defined therapeutic guidelines for SSSI management (Stevens et al., 2005). If no MRSA is suspected, it recommends the empiric use of methicillin-sensitive *S. aureus* (MSSA)- and streptococci-active compounds such as β -lactams (ie, isoxazolyl penicillins or cephalosporins) and macrolides as first-line agents when infections are not likely to respond well to local measures or incision and drainage. A different approach is required in the presence of deep-seated MRSA infections, when there is some predisposing risk factor for MRSA infection, macrolide or penicillin-resistant streptococci are suspected, or patients have severe penicillin hypersensitivity. For these situations, the use of a glycopeptide (eg, vancomycin) or linezolid (in combination with rifampicin) is recommended. The IDSA also recommends daptomycin as an alternative for penicillin-hypersensitive patients.

Important factors that have created the need for new anti-MRSA drugs include: (i) the increasing prevalence of MRSA combined with the emergence of strains with decreased susceptibility to glycopeptides (vancomycin-intermediate *S. aureus* [VISA]/hetero-vancomycin-intermediate *S. aureus* [hVISA]/hetero-glycopeptide-intermediate *S. aureus* [hGISA]) or full-blown glycopeptide resistance (vancomycin-resistant *S. aureus* [VRSA]), which can have also a negative impact on susceptibility to other cell wall-acting drugs such as daptomycin; (ii) the over-dependence on

glycopeptides, combined with the emergence of glycopeptide resistance in enterococci; and (iii) the potential for the emergence of resistance to linezolid, the first available alternative to the glycopeptides, especially among *S. aureus* (Gales et al., 2006; Hentschke et al., 2008).

1.4 Iclaprim – Addressing Important Medical Needs

Emerging issues include reduced susceptibility not only to vancomycin but also to daptomycin and linezolid. Strains resistant to linezolid, daptomycin, and vancomycin have shown *in vitro* susceptibility to iclaprim. Moreover in the Phase 3 trials, iclaprim showed high clinical cure and microbiological eradication rates for *S. aureus* (including MRSA), and no on-treatment MIC increases were observed. Indeed, iclaprim has been shown *in vitro* to have a low propensity for resistance development.

Resistance patterns in MRSA-associated cSSSI are continuously evolving, and the community-acquired MRSA (CA-MRSA) USA300 clone is no longer just a cause of community-acquired infections, but it is also rapidly emerging as a cause of healthcare-associated infections (Al Rawahi et al., 2008). Iclaprim may have advantages over other antibiotics, especially in the treatment of CA-MRSA infections. The MICs of iclaprim for either nosocomial MRSA, CA-MRSA or MSSA strains are essentially equivalent, with MIC₉₀s ranging from 0.12 to 0.25 µg/mL. The drug's mode of action as a folate-synthesis inhibitor, which simultaneously affects bacterial DNA, RNA, and protein synthesis, likely leads to an overall reduction in toxin production and release, factors that can be of paramount importance, especially against CA-MRSA, and could constitute an important advantage over cell wall-acting antibiotics.

The safety profile of iclaprim compares favorably with those of currently marketed systemic antibiotics used for the treatment of cSSSI. In contrast to the currently approved drugs, no monitoring may be required, and patients with renal dysfunction do not need dose adjustments.

1.5 Antibacterial Activity of Iclaprim

- Iclaprim exhibits rapid bactericidal activity, a post-antibiotic effect, and a low propensity for resistance emergence (Figure 1-6);

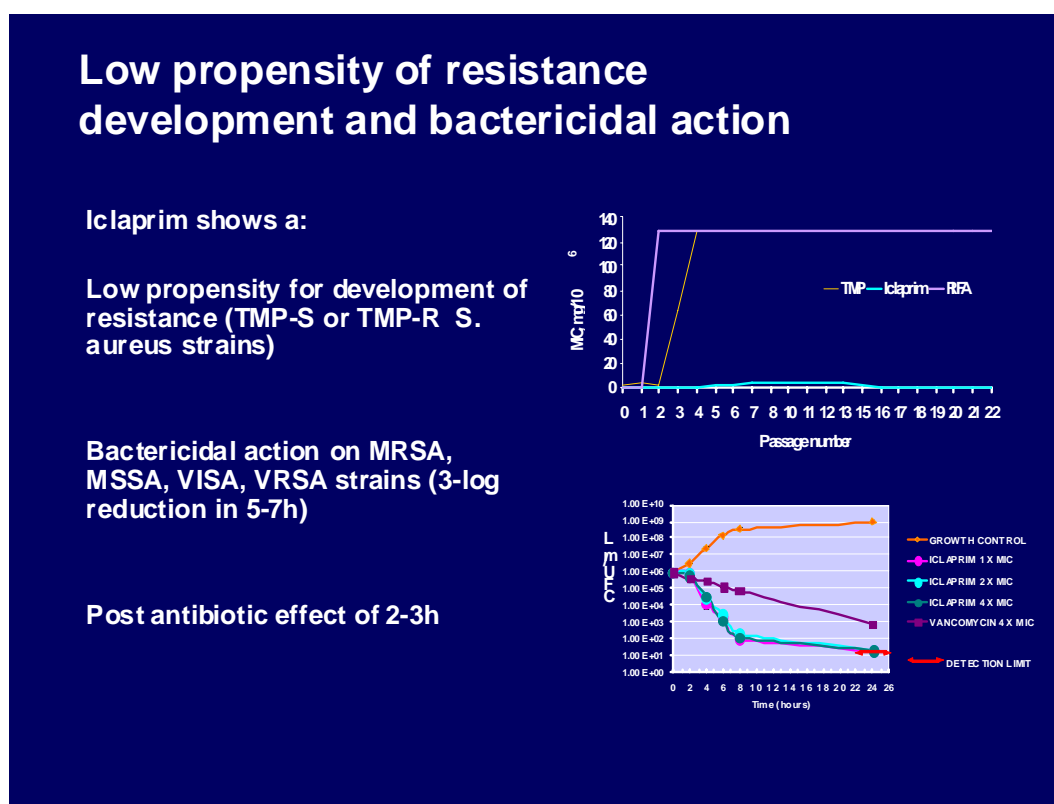


Figure 1-6: Low Propensity of Resistance Development

- Against more than 5,000 recent surveillance isolates of *S. aureus*, including nosocomial and community acquired MRSA and multidrug-resistant strains, the MIC₉₀ of iclaprim was 0.12 µg/mL. Similar MIC distribution was seen in the pivotal clinical studies (Figure 1-7);

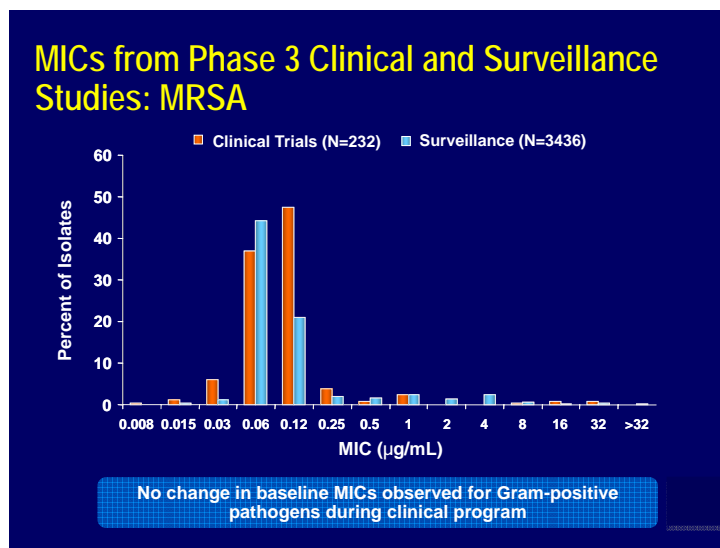


Figure 1-7: MICs from Phase 3 Clinical and Surveillance Studies

- The MIC₉₀ of iclaprim also was 0.12 µg/mL for 1,600 surveillance isolates of β-hemolytic streptococci, which included more than 1,200 *Streptococcus pyogenes* strains, for which the MIC₉₀ was lower (≤0.03 µg/mL), and 350 *Streptococcus agalactiae* strains;
- Checkerboard experiments demonstrated that iclaprim showed no antagonism with over 30 different antibiotics. Iclaprim exhibited synergy with sulfonamides, as would be expected for a folate synthesis inhibitor;
- Iclaprim is efficacious in various animal infection models via intravenous, subcutaneous, and oral routes of administration.

1.6 Safety Pharmacology

Safety pharmacological testing of iclaprim in non-clinical studies led to the following conclusions:

- Consistent with its lack of interaction with mammalian DHFR at levels up to 10⁴ times higher than those required to inhibit bacterial DHFR, no biologically significant adverse

effects on the central nervous, cardiovascular, or respiratory systems were seen at human equivalent doses (HED) 5 to 10 times above the human therapeutic dose ([Section 3](#)); and

- Iclaprim inhibited selectively the hERG channel activity at concentrations that can be achieved in humans; the potential of iclaprim for cardiac QT interval prolongation was thoroughly evaluated in clinical Phase 1 and Phase 3 studies ([Section 3](#));

1.7 Toxicology

- Iclaprim was well tolerated in rats and marmosets at doses approximately 6 times greater than the HED; ([Section 3](#))
- Neither female nor male fertility was affected by IV treatment; ([Section 3](#))
- Iclaprim showed class-specific propensity for teratogenic effects with unknown relevance for humans ([Section 3](#)); and
- Iclaprim is not mutagenic, clastogenic, or phototoxic ([Section 3](#)).

1.8 Clinical Pharmacology

The pharmacokinetic (PK) profile of IV iclaprim was thoroughly investigated and characterized in 14 Phase 1 studies. The PK parameters for iclaprim at the therapeutic dose of 0.8 mg/kg, 30-minute infusion, are shown in Table 1-1. The kinetic profile was linear at doses from 0.4 to 3.2 mg/kg (Figure 1-8).

Dose Infusion Time	0.8 mg/kg, 30-minute infusion
No. of Subjects	N = 22
C_{max} (ng/mL)	831.1 (245.1)*
AUC_{0-t} (ng.h/mL)	2058 (691.7)*
AUC_{0-∞} (ng.h/mL)	2082 (709.7)*
t_{1/2} (h)	2.52 (1.23)*
V_{ss} (mL/kg)	1392 (324.4)*

* Standard deviation in parentheses

Table 1-1: PK Mean Parameters – 0.8 mg/kg Dose

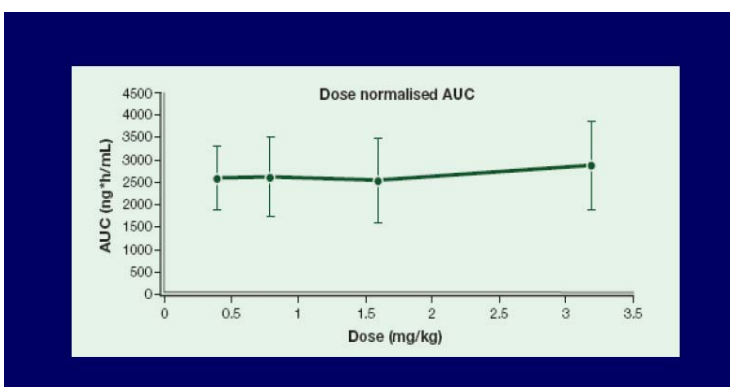


Figure 1-8: Linear PK - AUC Normalized to 0.8 mg/kg

Examination of the absorption, distribution, metabolism, and excretion (ADME) profile in clinical studies revealed:

- Rapid and extensive distribution into tissues and key lung compartments;(Andrews et al., 2007)
- No accumulation upon repeated *q12h* administration ([Section 4](#)) ; and
- Hepatic metabolism (CYP450 3A4 and 2C19) and renal excretion of metabolites.

In addition, the PK profile of iclaprim was examined in certain special populations, which led to the following conclusions:

- No dose adjustment is needed for patients with renal impairment; ([Section 4.3](#))
- A dose reduction of approximately 50% is recommended for patients with moderate hepatic impairment ([Section 4.3](#)); and
- A dose limit of 100 mg is advised for obese patients. ([Section 4.3](#))

The potential for drug-drug interactions was evaluated in four Phase 1 studies. Iclaprim was metabolized by CYP3A4 and CYP 2C19 and studies were therefore conducted with inhibitors of these two cytochromes, namely ketoconazole and omeprazole respectively. In addition, studies were also conducted with digoxin and warfarin. There were no clinically relevant changes in the PK parameters and consequently a low propensity for drug-drug interactions is expected. ([Section 4.4.2](#))

Finally, the conclusions from a population PK model (based on the determination of drug concentrations from approximately 95% of the Phase 3 study patients) were:

- The derived PK parameters fully corroborate findings from the Phase 1 PK studies;
- Influence of gender, age, and duration of treatment have only a minimal impact (<-10%) on the PK parameters AUC and C_{\max} ;
- Ethnicity and creatinine clearance have no effect on the population PK model;
- A high body mass index (BMI) requires dose adjustment (recommended dose limitation: 100 mg).

The influence of iclaprim on QT prolongation was investigated in two well-controlled Phase 1 studies. They showed:

- A linear, dose-dependent effect on QT prolongation;
- Maximal QT change was observed at the end of infusion (T_{\max});
- QT prolongation was transient and rapidly reversible; and
- The effect was independent of gender.

1.9 Phase 2 Study AR-100-SSTI-001

The Phase 2 study AR-100-SSTI-001 was a randomized, double-blinded, multicenter study that compared the safety and efficacy of two doses of IV iclaprim with IV vancomycin in cSSSI patients. Ninety-two patients enrolled in 7 active centers participated in this study which comprised 3 treatment arms: (1) iclaprim 0.8 mg/kg, (2) iclaprim 1.6 mg/kg, and (3) vancomycin 1 g. All treatments were administered *q12h* for 10 days.

Results from this study can be summarized as follows:

- Comparable rates of clinical efficacy of 92.9%, 90.3%, and 92.9% were observed at the test-of-cure (TOC) visit in the 0.8 mg/kg iclaprim, 1.6 mg/kg iclaprim, and 1 g vancomycin treatment arms, respectively;
- No differences between the treatment groups with respect to clinical cure by infection type or presence of surgical intervention were evident;
- Eradication rates of Gram-positive pathogens were 89.7% (0.8 mg/kg iclaprim), 80.0% (1.6 mg/kg iclaprim), and 72.0% (1 g vancomycin);
- *S. aureus* was the most frequently isolated baseline pathogen, and the eradication rates were 80% (0.8 mg/kg iclaprim), 72.2% (1.6 mg/kg iclaprim) and 58.8% (1 g vancomycin);

- Administration of both 0.8 and 1.6 mg/kg doses demonstrated good tolerability of the drug in cSSSI patients; and
- Results from this study provided a conclusive basis for the Phase 3 dose rationale (chosen dose and dosing regimen: 0.8 mg/kg dose *q12h*).

1.10 Phase 3 Studies ASSIST-1 and ASSIST-2

The design of the two pivotal Phase 3 studies ASSIST-1 and ASSIST-2 was discussed with and agreed to by the FDA. Historically, cSSSI studies are designed as non-inferiority trials so that human subjects will not be exposed to an unreasonable and significant risk of illness or injury (21 Code of Federal Regulations (CFR) 312.42; *Guidance for Industry – Antibacterial Drug Products: Use of Non-inferiority Studies to Support Approval, October 2007*) (Food and Drug Administration, 2007). Linezolid, rather than vancomycin, was as the comparator, as it has been shown to be superior to vancomycin for MRSA infections in cSSSI and may also be superior for non-MRSA infections (Weigelt et al., 2005). Indeed, linezolid is approved for use against MRSA and non-MRSA infections, and its twice-daily administration, like that of iclaprim, facilitates blinding. Such blinding is difficult when vancomycin and semi-synthetic penicillins (requiring 4 administrations *per diem*) are used to cover MRSA and non-MRSA infections, respectively.

The two pivotal, double blind, non-inferiority studies used essentially identical protocols, and the pre-defined non-inferiority margin against linezolid for each of the studies was set at -12.5%. Historically, cSSSI studies have been conducted using a non-inferiority design with an active comparator, and no placebo-controlled trials have been reported. The non-inferiority margin was conservatively chosen based on an estimated placebo effect and followed the International Conference on Harmonization (ICH) E9 and E10 guidelines (International Conference on Harmonization, 2008) For example, data from a recent, randomized Phase 2 cSSSI dose-finding

study for dalbavancin demonstrated that two doses of dalbavancin were 30% more effective than a single dose of dalbavancin, both for the intent-to-treat and clinically evaluable population (Jauregui et al., 2005). It is likely that a single dose of dalbavancin was still superior to placebo, although a placebo was not tested in the study. Based on this study, the minimal magnitude of efficacy of an effective antibiotic relative to placebo for cSSSI is expected to be 30%. To preserve 50% of the antibiotic efficacy, a non-inferiority margin of -15% is a reasonable margin for a non-inferiority clinical trial of antibiotics for cSSSI. The independent pivotal trials of iclaprim in cSSSI each had a pre-defined NI margin of -12.5%, which was chosen to add an additional, conservative “buffer zone” and ensure that the margin for each study was well within the expected antibiotic efficacy relative to placebo for cSSSI. The two trials were essentially identical in design so that the data from the two independent studies could be pooled for additional statistical powering in analyzing safety and efficacy parameters.

These studies enrolled a total of 991 patients in 11 countries for the intent-to-treat (ITT) population: 500 patients received iclaprim and 491 received linezolid. Thirty-nine percent of the randomized patients were from the US. A high percentage of patients in each treatment group had a severe infection at baseline (overall: 92.6%). *S. aureus* was the predominant pathogen isolated in these studies and was found in 60% of patients. Of these *S. aureus* isolates at baseline, close to 40% were MRSA and approximately 70% were PVL-positive.

1.10.1 Results of Phase 3 Clinical Studies

The protocol-defined primary endpoint of both individual studies ASSIST-1 and ASSIST-2 was clinical cure at the TOC visit in the intent-to-treat (ITT) and per protocol (PP) co-primary populations. Non-inferiority was tested with a one-sided alpha of 0.025 and a delta of 12.5%.

For both co-primary populations, the protocol-defined primary endpoint was reached in the 2 studies. For the combined population, the result was within 10% for both the ITT and PP populations (Table 1-2). Iclaprim achieved the pre-defined margin of $<-12.5\%$ for non-inferiority versus linezolid in both individual studies; for the combined studies, iclaprim met a $<-10\%$ non-inferiority margin.

Table 1-2: Clinical Cure at TOC – Primary Efficacy Populations ITT and PP and Supporting Population MCE

	ASSIST-1		ASSIST-2		Combined	
	Iclaprim	Linezolid	Iclaprim	Linezolid	Iclaprim	Linezolid
ITT	N = 249	N = 248	N = 251	N = 243	N = 500	N = 491
Clinical cure, n (%)	207 (83.1%)	220 (88.7%)	204 (81.3%)	199 (81.9%)	411 (82.2%)	419 (85.3%)
95% CI	78.0% – 87.3%	84.2% – 92.1%	76.0% – 85.6%	76.6% – 86.2%	78.6% – 85.3%	81.9% – 88.2%
Treatment difference (iclaprim - linezolid) and 95% CI	-5.6% [-11.7% to 0.6%]		-0.6% [-7.5% to 6.3%]		-3.1% [-7.7% to 1.5%]	
PP	N = 206	N = 213	N = 209	N = 195	N = 415	N = 408
Clinical cure, n (%)	195 (94.7%)	211 (99.1%)	188 (90.0%)	188 (96.4%)	383 (92.3%)	399 (97.8%)
95% CI	90.7% – 97.0%	96.6% – 99.7%	85.1% – 93.3%	92.8% – 98.3%	89.3% – 94.5%	95.9% – 98.8%
Treatment difference (iclaprim - linezolid) and 95% CI	-4.4% [-8.4% to -1.0%]		-6.5% [-11.6% to -1.5%]		-5.5% [-8.7% to -2.6%]	
MCE	N = 218	N = 228	N = 222	N = 217	N = 440	N = 445
Clinical cure, n (%)	195 (89.4%)	211 (92.5%)	188 (84.7%)	188 (86.6%)	383 (87.0%)	399 (89.7%)
95% CI	84.7 % – 92.9%	88.4% – 95.3%	79.4% – 88.8%	81.5% – 90.5%	83.6% – 89.9%	86.5% – 92.2%
Treatment difference (iclaprim - linezolid) and 95% CI	-3.1% [-8.6% to 2.3%]		-2.0% [-8.5% to 4.7%]		-2.6% [-6.9% to 1.6%]	

ITT – Intent to Treat; PP – Per Protocol; MCE – Modified Clinically Evaluable

During analysis, an imbalance was noted between the two arms with respect to the number of patients excluded from the PP analysis due to the use of additional antibiotics prohibited by the study protocol. Specifically, 4.4% of ASSIST-1 and ASSIST-2 patients received prohibited antibiotics in the iclaprim treatment arm, compared with 5.6% and 9.1% of linezolid-treated patients in the ASSIST-1 and ASSIST-2 studies, respectively (Table 1-3). Analysis of primary data did not reveal the exact reason for the more frequent addition of prohibited antibiotics to patients in the linezolid arm. However, the lack of adequate clinical response may be the likely explanation for the use of additional prohibited antibiotics.

Given the imbalance in the use of prohibited antibiotics, a sensitivity analysis was performed to explore the possible effect on the study results (ICH E9). Importantly, all protocol violations were defined prior to database lock and unblinding. This additional analysis yielded the modified clinically evaluable (MCE) population and included those patients who were excluded from the PP population only because they had received prohibited concomitant antibiotic therapies. The clinical cure rates in the MCE population were similar to those in the ITT population, and demonstrated non-inferiority of iclaprim to linezolid within a delta of $<-10\%$ (Table 1-3).

Table 1-3: Summary of Major Protocol Violations – ITT Population

	ASSIST-1		ASSIST-2	
Protocol Violation	Iclaprim N = 250	Linezolid N = 249	Iclaprim N = 251	Linezolid N = 243
Any major protocol violation	44 (17.6%)	36 (14.5%)	42 (16.7%)	48 (19.8%)
Deviation from inclusion/exclusion criteria	8 (3.2%)	5 (2.0%)	8 (3.2%)	6 (2.5%)
Deviation from randomized treatment	0	1 (0.4%) ^b	1 (0.4%)	0
Deviation from study treatment schedule	9 (3.6%)	5 (2.0%)	8 (3.2%)	7 (2.9%)
Deviation from time window schedule	0	1 (0.4%)	5 (2.0%)	5 (2.1%)
<i>Other systemic antibacterial therapy</i>	<i>11 (4.4%)</i>	<i>14 (5.6%)</i>	<i>11 (4.4%)</i>	<i>22 (9.1%)</i>
Other prohibited concomitant medication administered	2 (0.8%)	2 (0.8%)	2 (0.8%)	1 (0.4%)
Significant procedures (eg surgery, debridement)	10 (4.0%)	7 (2.8%)	6 (2.4%)	4 (1.7%)
EOT/TOC clinical evaluation not performed	20 (8.0%)	19 (7.6%)	16 (6.4%)	22 (9.1%)
No effective therapy against Gram-negative organisms	2 (0.8%)	0	1 (0.4%)	0

Results from the Phase 3 studies ASSIST-1 and ASSIST-2, as well as from the combined Phase 3 analysis, were:

- The clinical cure rate at the TOC visit for iclaprim was high, above 80% and 90% in the ITT and PP populations, respectively, and was comparable to results seen with linezolid in both ASSIST-1 and ASSIST-2 and the combined analysis ([Section 5.2.7.2](#));
- The lower bound of the confidence interval (CI) was within the pre-defined non-inferiority margin of -12.5% in ASSIST-1 and ASSIST-2 for the co-primary populations.

For the combined data set, this difference was well within the pre-defined non-inferiority margin of -10% ([Section 5.2.7.2](#));

- Sensitivity analysis of the MCE population in ASSIST-1, ASSIST-2, and the combined data set demonstrated the lower bound of the CI for the treatment difference was <-10% in all studies. ([Section 5.2.7.2](#));
- No significant differences in efficacy were observed in subgroups stratified by age, ethnicity, or gender.
- Of the 500 patients randomized to iclaprim in the combined Phase 3 data set, 287 had a baseline isolate of *S. aureus*; of these 119 (41.5%) were MRSA. Overall in the iclaprim treatment arm, 82.2% of patients with *S. aureus* at baseline and 79.8% of patients with MRSA at baseline were considered as clinically cured (modified ITT [MITT] population: ITT with a baseline pathogen isolated) ([Section 5.2.7.2](#)); and
- In the combined Phase 3 analysis, the overall eradication rates of baseline pathogens in the MITT population were 76.0% and 81.1% for iclaprim and linezolid, respectively. Similarly, eradication rates by iclaprim for *S. aureus* and MRSA were high with 77.7% and 76.4%, respectively, and were similar to those observed with linezolid (81.0% and 78.7%). ([Section 5.2.7.2](#)).

The combined safety results showed:

- The overall safety profiles of iclaprim and linezolid were comparable ([Section 6.2.2](#));
- The overall incidence of drug-related adverse events (AEs) was lower in the iclaprim treatment group than in the linezolid group (22.6% versus 27.9%) ([Section 6.2.1](#));

- No significant differences in safety were observed between subgroups stratified by age, ethnicity, or gender (Section 6.2.2);
- There were no cardiac serious AEs (SAEs) or non-electrocardiographic cardiac AEs directly related to the use of iclaprim. A change in QTc from baseline was evident but relatively small -- approximately 5-7 msec higher values for either QTcB or QTcF relative to linezolid (Section 6.2.6);
- The possibly/probably related AEs for >2% of the study population are shown in Figure 1-9.

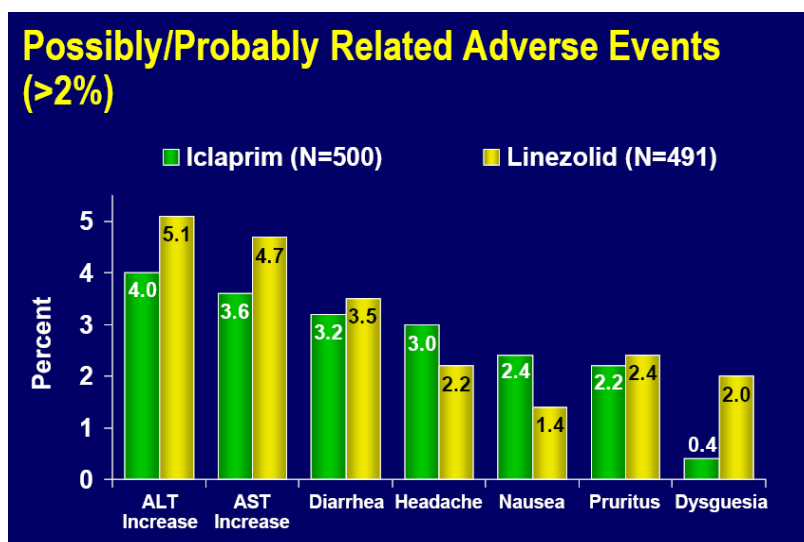


Figure 1-9: Possibly/Probably Related Adverse Events of Combined Safety Population

1.11 Conclusion

Iclaprim, a novel, second-generation DHFR inhibitor, can be considered an important advance in the treatment of cSSSI. Over four decades of clinical use of TMP and the combination TMP/SMX, the second most commonly prescribed antibacterial agent, attests to the high safety and efficacy of this class of antibiotics. The drug's high potency and low propensity for

resistance allows for its use as a single molecular entity (ie, without the need for a combination with a sulfonamide), enabling iclaprim to avoid sulfonamide-related side effects. Its potent *in vitro* activity against resistant pathogens, low propensity for resistance development, good clinical efficacy, and bacterial eradication rates (especially in MRSA-infected patients) are important attributes that address a serious medical need. Combined with a favorable safety profile, iclaprim is expected to provide a valuable alternative to treat Gram-positive infections, including those caused by MRSA. Despite the presence of recent alternatives to glycopeptides antibiotics, the prospect for emerging resistance to any antibacterial cannot be understated, and new effective and safe compounds to treat MRSA infections are required.

This Briefing Document summarizes results provided by the Sponsor in a New Drug Application (NDA 22-269) to the FDA dated March 18, 2008, for the proposed indication of cSSSI supported by data from the two Phase 3 studies ASSIST-1 and ASSIST-2.

2. MICROBIOLOGY

Numerous studies were undertaken to determine the microbiological properties of iclaprim. This section describes the mode of action and mechanisms of resistance, presents surveillance studies defining current activity of iclaprim against recent clinical isolates, compares surveillance data to sensitivity to iclaprim of baseline pathogens encountered during the Phase 3 program, and defines putative iclaprim breakpoints. Numerous large susceptibility surveillance studies were undertaken to test iclaprim and comparator compounds against recent clinical isolates from both US and European patients. For the Phase 3 clinical trials, a central reference laboratory undertook all microbiology testing for clinical trial isolates.

2.1 Mechanism of Action

The antimicrobial activity of iclaprim is mediated by competitive inhibition of bacterial DHFR; this mechanism of action is similar to that observed with TMP (Hawser S. et al., 2006).

Inhibition of DHFR and depletion of the folate pool results in the inhibition of RNA, DNA, and protein synthesis, resulting in cell death (Hawser S. et al., 2006). Biochemical and crystallographic studies have demonstrated that iclaprim binds several orders of magnitude tighter to DHFR than TMP; this increased affinity is mediated by additional hydrophobic interactions between iclaprim and DHFR. The IC_{50} against TMP-R *S. aureus* clinical isolate B71 is 0.027 μ M for iclaprim, compared with 1.2 μ M for TMP (Hartmann P.G. et al., 2002). Against *S. pyogenes* American Type Culture Collection (ATCC) 19615, the IC_{50} was 1.49 μ M for iclaprim versus 49.7 μ M for TMP. The substantially lower MICs to clinical isolates from these species compares favorably to TMP. Moreover, the increased binding affinity of iclaprim overcomes the predominant mechanism of resistance to TMP in *S. aureus*, the amino acid alteration Phe98Tyr.

2.2 Mechanism of Resistance

In contrast to the great degree of heterogeneity in Gram-negative bacteria, which often acquire resistance to TMP by horizontal transfer, the genes encoding TMP resistance in *S. aureus* and non-pneumococcal streptococci, the target species for iclaprim, are limited in number and generally result from target-site alteration (Fleming et al., 1972; Hawser S. et al., 2006; Huovinen, 2001). Resistance in *S. aureus* is predominantly determined by a single amino acid change (Phe98Tyr) within the TMP-binding site of DHFR (Huovinen, 2001). The increased binding affinity of iclaprim to the active site of *S. aureus* DHFR results in a negligible difference

in the MIC of iclaprim between TMP-susceptible (TMP-S) and Phe98Tyr TMP-resistant (TMP-R) isolates. This most predominant mutation type is not encoded on transmissible genetic elements (Dale et al., 1993; Dale et al., 1995; Dale et al., 1997; Leelaporn et al., 1994). Among β -hemolytic streptococci, resistance to TMP is extremely rare and is caused by a target site alteration at position 100 (I1100L). Despite more than 40 years of use of diaminopyrimidines in clinical practice, acquired alternative DHFR genes are very rare among *S. aureus* and are not reported among streptococcal species. A recent analysis showed that 98.4% of all *S. aureus* (N=95,381) derived specifically from skin and wound infections in the US were susceptible to TMP/SMX (Tillotson et al., 2008).

2.2.1 In Vitro Assessment of Resistance

As previously discussed, the target site alteration Phe98Tyr is the most common mechanism of resistance to TMP among *S. aureus*. Although TMP induces such mutations relatively easily in *in vitro* systems, (Huovinen, 2001) induction of mutations by iclaprim does not occur (Hawser S. et al., 2002). A series of experiments were conducted to determine the propensity for the development of *in vitro* resistance to iclaprim (Hawser S. et al., 2002). In direct-selection experiments, no iclaprim mutants were detected, irrespective of the TMP-sensitivity of the strain. Additionally, in serial passage experiments at sub-MIC concentrations against TMP-susceptible or resistant strains, iclaprim exhibited only a 3-4 dilution-step increase. The MICs returned close to those observed at baseline after removal of the antibiotic pressure and continued passage, thus indicating that no stable mutations had occurred. This finding was confirmed by molecular characterization of the *dhfr* gene loci. In contrast, MICs of TMP increased to >128 μ g/mL after 4-5 passages and did not show reversal after removal of drug

pressure and subsequent passaging. Molecular characterization showed a stable mutation (the presence of alteration Phe98Tyr). Similarly, as expected, the MIC of the control antibiotic rifampicin increased several-fold to >128 µg/mL after 3-4 passages and did not revert after serial passage in rifampicin-free media.

2.3 *In Vitro* Antibacterial Activity

2.3.1 *Susceptibility Test Methodologies and the Effect of Addition of Plasma*

Laboratories can test for susceptibility to iclaprim using standard test methodologies without variations, as defined by the Clinical and Laboratory Standards Institute (CLSI). Studies designed to investigate the effects of standard test variables, including inoculum, media pH, and cation concentration, showed no effects, with the exception of a low pH test media, which tended to raise MICs by twofold. The same effect was seen with TMP.

As iclaprim is 93% protein bound, the effect of adding human plasma was also investigated. These studies consistently showed that the addition of human plasma has little or no effect on the *in vitro* activity of iclaprim: all MIC values (with and without plasma) were within one doubling dilution. Similarly MIC/minimum bactericidal concentration (MBC) ratios were unchanged in the presence of human plasma (Laue et al., 2007).

2.3.2 *Antibacterial Spectrum*

Iclaprim demonstrated potent *in vitro* activity against Gram-positive pathogens associated with cSSSI, including *S. aureus* (MSSA and MRSA), *S. pyogenes*, *S. agalactiae*, other β-haemolytic streptococci, and *E. faecalis*. Iclaprim also exhibited *in vitro* activity against several Gram-

negative species, including *Neisseria gonorrhoeae*, *Hemophilus influenzae*, *Legionella pneumophila*, and the intracellular pathogens *Chlamydia pneumoniae* and *Chlamydia trachomatis*. Against Enterobacteriaceae, iclaprim was somewhat less potent and generally inactive against non-fermenters (eg, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*) and anaerobes.

2.3.2.1 In Vitro Activity Against Gram-Positive Pathogens from Surveillance Studies and Encountered During the Phase 3 Clinical Program

Numerous *in vitro* surveillance studies from North America and Europe, testing more than 15,000 clinical isolates from more than 100 centers worldwide, demonstrated that iclaprim had potent *in vitro* activity, particularly against Gram-positive pathogens. For the clinically relevant Gram-positive species commonly associated with cSSSI, iclaprim MIC_{90s} were 0.12 µg/mL for *S. aureus* and MRSA 0.12 µg/mL, ≤ 0.03 µg/mL for *S. pyogenes*, 0.25 µg/mL for *S. agalactiae*, and 0.5 µg/mL for other β-hemolytic streptococci. More important, iclaprim also demonstrated potent *in vitro* activity against MRSA that was not susceptible to linezolid, daptomycin, and vancomycin (hGISA, VRSA). In addition, iclaprim activity did not vary between nosocomial and community MRSA and was independent of PVL status.

A large pivotal surveillance study evaluated recent clinical isolates (2004-2006) from hospitalized patients throughout the US and Europe. Included were countries in which the iclaprim Phase 3 clinical program was carried out. All organisms were tested by a single central laboratory (JMI laboratories, North Liberty, IA). This study demonstrated the potent *in vitro* activity of iclaprim against contemporary clinical isolates and found that the *in vitro* activity of iclaprim against *S. aureus* was independent of oxacillin resistance (Figure 2-1).

	N	MIC ₉₀ (µg/mL)	
		ICL	TMP
<i>S. aureus</i>	4516	0.12	2
MRSA	3003	0.12	2
MSSA	1513	0.12	1
GAS	604	0.03	0.5
GBS	204	0.25	4

Sader H.S., et al. Presented at: 47th ICAAC 2007; Abstract E902.
Jones R.N., et al. Presented at: 47th ICAAC 2007; Abstract E911.

Figure 2-1: Activity of Iclaprim Against Recent Clinical Isolates From US and Europe

In addition, all isolates encountered from patients enrolled in the Phase 3 program were identified and tested for susceptibility in a central laboratory (Eurofins Medinet, Chantilly, VA). A comparison of the iclaprim MIC distributions for the key pathogens demonstrated that the majority of strains of each tested species fell within a relatively narrow MIC range. The iclaprim MIC distribution of clinical isolates was essentially the same as those defined for the pivotal international surveillance study, a finding confirming that organisms encountered during the Phase 3 studies were representative of the broader population.

It should be pointed out that, consistent with available *in vitro* data available, no emergent resistance to iclaprim was apparent in any of the baseline pathogens encountered during the Phase 3 program. Although uncommon, some isolates of *S. aureus* with MICs >1 µg/mL were detected during both surveillance studies and during the clinical trials. Nevertheless, of the 9 patients with such *S. aureus* strains, 8 were clinical cures. These rates were similar to that

observed in the overall population. These strains were isolates from specific hospitals and might represent the same clone.

2.3.3 Bactericidal activity

Iclaprim demonstrated bactericidal activity against cSSSI target organisms at concentrations close to the MIC for *S. aureus* (0.12 µg/mL) and *S. pyogenes* (≤ 0.03 µg/mL). Bactericidal activity was confirmed by both MBC and time-kill experiments against clinical isolates of *S. aureus* (including MRSA, VISA, and VRSA, respectively), streptococci (including penicillin- and erythromycin-resistant strains), and enterococci (including vancomycin-resistant strains). In general, the MBC₉₀ of iclaprim for MRSA was ≤ 0.5 µg/mL, which was several fold lower than that of vancomycin, and for the majority of *S. aureus* the MBC was within one doubling dilution of the MIC. MBCs measured for most *S. pyogenes* or *S. agalactiae* was 1-4 doubling dilutions higher than the MIC. Time-kill kinetic studies were determined for clinical isolates of target species, including different relevant resistant phenotypes (Hawser S. et al., 2002; Weiss L. et al., 2004). For *S. aureus*, a 99.9% ($>3 \log_{10}$) reduction was typically observed within 6-8 hours of exposure. As expected, the comparator vancomycin was slowly bactericidal against susceptible isolates at low multiples of their MICs, whereas linezolid was only bacteriostatic. For *S. agalactiae*, a 99.9% reduction in colony forming units (CFUs) was attained within 4 hours of exposure to an iclaprim concentration equivalent to twice the MIC. This finding contrasted with vancomycin, which produced slightly less killing ($<3 \log_{10}$) of these strains only after 24 hours of exposure at double the MIC. For *S. pyogenes* (including some strains with high MBC values), a 3 \log_{10} reduction was typically observed within 24 hours. Exposure to relatively low

concentrations of iclaprim (0.12-0.25 µg/mL) for 24 hours produced at least a 99.9% reduction in CFUs for both *E. faecalis* and *E. faecium* isolates. As observed with *S. aureus*, the bactericidal activity of iclaprim against β -hemolytic streptococci and enterococci was time-dependent.

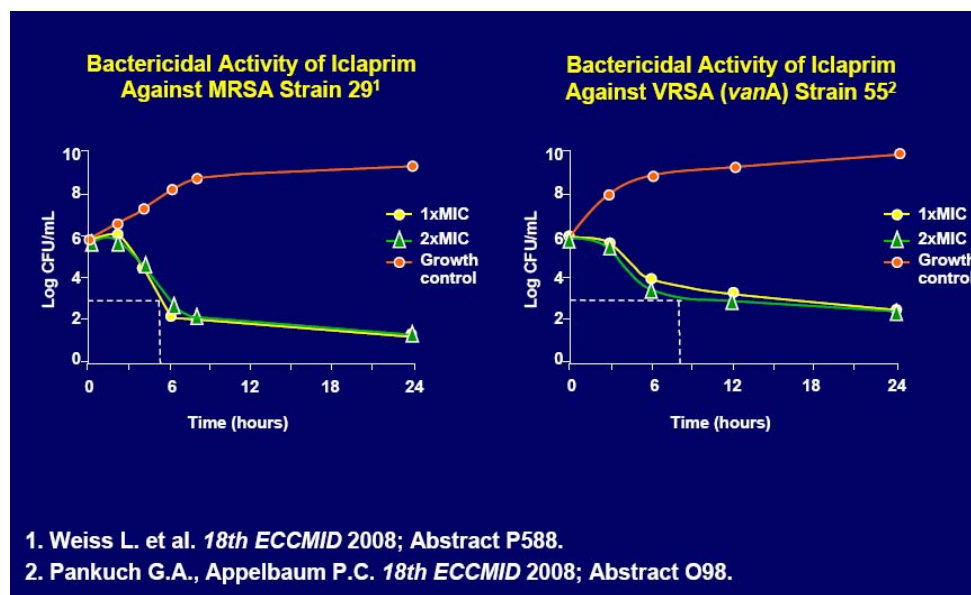


Figure 2-2: Bactericidal Activity of Iclaprim Against Clinical Isolates of MRSA

2.4 Interaction of Iclaprim with Other Antimicrobial Agents

Iclaprim was tested for synergy or antagonism using a checkerboard methodology with a large number of antibiotic agents from all commonly used drug classes. No antagonism was observed when iclaprim was tested with 29 antibiotic agents, most of which demonstrated indifference or some marginal additive effect. Consistent with its mechanism of action, synergy was observed when iclaprim was tested in combination with either sulfadiazine or SMX (Laue et al., 2007). Most important, neither synergy nor antagonism was observed for iclaprim when tested in combination with either aztreonam or metronidazole (Laue et al., 2007).

2.5 Metabolite Activity

The metabolism of iclaprim in humans produces 3 main metabolites, M6/7, M13, and M10; of these metabolites, M6/7 and M13 are glucuronates. Glucuronated metabolites demonstrated no *in vitro* activity, while the activity of the non-glucuronated metabolites was several fold lower than iclaprim and unlikely to exert an antibacterial effect *in vivo*.

2.6 Animal Infection Models

Iclaprim was tested in a variety of well-established mouse and rat models of infection. These included lethal and non-lethal infection systems, infecting pathogens and resistant phenotypes, and routes of administration. It consistently demonstrated efficacy and proof-of-principle in clearing infection or significantly reducing bacterial load. However, compared to humans, rodents have high plasma levels of thymidine, which is well known to antagonize the activity of DHFR inhibitors. Furthermore, high thymidine levels can significantly affect several different pharmacodynamic (PD) parameters, including *in vitro* activity and cidal activity (Entenza J.M. et al., 2004). The antagonistic effect of thymidine on the PD properties of iclaprim, combined with the short half life of the drug in mice, suggests that such models underestimate the *in vivo* potency of iclaprim. Experiments with thymidine kinase mutant (TK-) and isogenic wild-type strains of *S. aureus* showed that the potency of iclaprim was greatly underestimated in rodents (Haldimann A. et al., 2006). Studies designed to investigate which PK/PD parameter most closely correlated with efficacy showed that the AUC/MIC was the best measure (Murphy T. et al., 2007). On the other hand, a reliable PK/PD factor for extrapolation to humans could not be determined, due to the antagonistic effects of high levels of thymidine in most animal models.

2.7 Tentative Susceptibility Breakpoint

Iclaprim is 93% protein bound. However, the absence of a human plasma effect on the *in vitro* activity of iclaprim, along with the Phase 2 and Phase 3 clinical trial results, supports the use of total drug concentration to establish susceptibility breakpoints. Overall, data from MIC distributions, animal tissue distribution studies, human population pharmacokinetics, and clinical efficacy supported a proposed susceptibility breakpoint of ≤ 2 µg/mL for Gram-positive pathogens. No intermediate or resistant breakpoint was derived from these results. Disk testing correlated well with MIC testing; therefore, defining zone-size breakpoints based on defined MIC breakpoints will be possible.

3. NONCLINICAL SAFETY STUDIES

Iclaprim was evaluated in *in vitro* and *in vivo* safety pharmacology and toxicology studies conducted according to ICH guidelines. Safety pharmacology tests for central nervous and respiratory system effects were performed in standard rodent models. Effects on the cardiovascular system were evaluated in instrumented conscious dogs and *in vitro* tests for inhibition of human cardiac ion channels. These results indicate that iclaprim would not be expected to have major adverse effects on central nervous and respiratory system functions. Although, no effects on the cardiovascular system were noted in dogs, a potential for prolongation of the QT interval was identified, based on selective inhibition of the hERG channel activity.

Toxicology studies included IV (up to 4 weeks in duration) and oral studies (13 weeks in duration) in rats and marmosets. The results of these studies showed that iclaprim was well

tolerated except for injection site reactions, which necessitated the use of oral administration for the 13-week toxicity studies. These studies were supported by toxicokinetic data demonstrating that exposure to iclaprim at the no-observed-adverse-effect level (NOAEL) for both rat and marmoset was several-fold higher relative to that in humans at the therapeutic dose.

A complete battery of genetic toxicology studies was conducted with iclaprim. Results from these studies indicated that iclaprim was neither mutagenic nor clastogenic. In addition, a complete set of reproductive toxicology studies including fertility, teratology, and pre-/post-natal studies were also conducted. There was no effect of iclaprim on fertility with skeletal and visceral findings seen in the teratology and pre-/post-natal studies. These latter findings were expected based on the results of similar studies with the folate antagonist TMP (Sullivan GE and Tacacs E, 1971), although their relevance in humans is unknown.

4. CLINICAL PHARMACOLOGY

4.1 Pharmacokinetics

Single ascending doses demonstrated that the kinetic profile was linear from 0.2 mg/kg to 3.2 mg/kg. Repeated twice-daily dosing over a 10-day period in healthy volunteers demonstrated that the maximum plasma concentration (C_{\max}) and AUC were similar on study days 1 and 10, indicating there was no accumulation of iclaprim during this period (Table 4-1; Figure 4-1).

Dose Infusion Time	0.8 mg/kg, 30-minute infusion
No. of Subjects	N = 22
C_{\max} (ng/mL)	831.1 (245.1)*
AUC_{0-t} (ng.h/mL)	2058 (691.7)*
AUC_{0-∞} (ng.h/mL)	2082 (709.7)*
$t_{1/2}$ (h)	2.52 (1.23)*
V_{ss} (mL/kg)	1392 (324.4)*

* Standard deviation in parentheses

Table 4-1: PK Mean Parameters – 0.8 mg/kg Dose

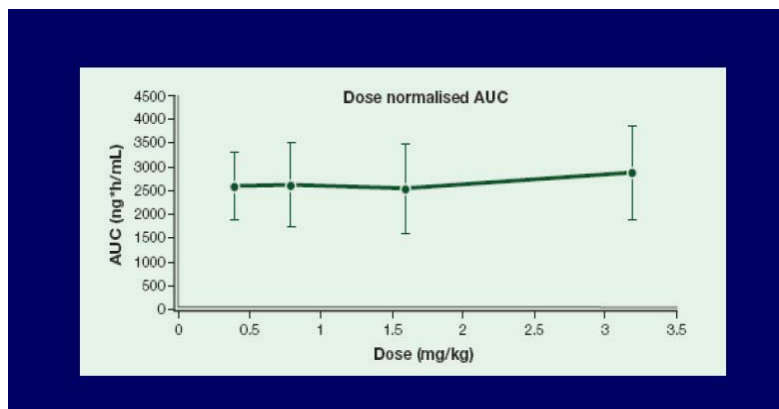


Figure 4-1: Linear PK - AUC Normalized to 0.8 mg/kg Therapeutic Dose

4.2 Protein Binding, Distribution, Metabolism, and Excretion Data

In human plasma, about 93% of iclaprim is bound to protein, with albumin being the major binding protein followed by α -1 acid glycoprotein. A study with ^{14}C -labeled iclaprim was performed to determine the ADME properties of iclaprim. After IV administration of radiolabeled iclaprim, the highest drug and total radioactivity concentrations were observed at the end of infusion. The mean terminal half-life of radioactivity in plasma was 4.9 hours, and the mean terminal elimination half-life of the iclaprim parent substance was 2.2 hours. The entire ^{14}C -labeled dose was almost completely excreted within 168 hours post-dose. The primary route of iclaprim excretion in humans was via the urine, and biotransformation was observed prior to excretion. All major metabolites were identified.

4.3 Influence of Intrinsic Factors

The PK profile of iclaprim in certain special populations (ie, renal impairment, hepatic impairment, obesity) was examined in a Phase 1 clinical study. In renally-impaired subjects, there were no relevant changes in the PK profile or evidence of a relationship between AUC, C_{max} , and disease state. These results suggest that no dose adjustment of iclaprim is needed in this population. PK studies in hepatically-impaired subjects show that no dose adjustment is required for subjects with mild liver disease; however, a dose adjustment of approximately 50% is recommended in patients with moderate hepatic impairment. No data are available on subjects with severe liver dysfunction. In obese subjects, the body-weight-based dosing regimen for iclaprim produced a higher level of drug exposure, which may be explained by the fact that iclaprim does not distribute well in fatty tissue. Therefore, a dose limit of 100 mg is recommended in this special population. Lastly, based on population PK data from the Phase 3

clinical studies, no differences were observed in PK parameters in subgroups stratified by age, gender, or race.

4.4 Role of Extrinsic Factors

4.4.1 Cytochrome P450 Interaction Potential

In human liver microsomes, iclaprim was shown to have only a slight inhibitory effect on CYP 3A4 activity *in vitro* at concentrations that might be reached after the therapeutic dose in humans; other CYP isozymes are unlikely to be inhibited. Iclaprim and its metabolites showed no potential for induction or inhibition of hepatic microsomal CYP P450 isoforms *in vivo* in marmosets. Therefore, the potential for PK interactions due to either inhibition or induction of CYP P450 isozymes by iclaprim is low. Metabolism studies revealed that the human hepatic I metabolism of ¹⁴C -labeled iclaprim is principally catalyzed by CYP 2C19 and CYP 3A4.

4.4.2 Potential for Drug-Drug Interaction

As iclaprim is metabolized mainly by CYP 3A4/5 and CYP 2C19, other drugs that induce, inhibit, or are metabolized by these isozymes might influence the PK of iclaprim. Studies with the CYP 3A4/5 inhibitor ketoconazole and the CYP 2C19 inhibitor omeprazole demonstrated that concomitant administration of these drugs did not cause clinically relevant changes in the PK parameters of iclaprim.

Additional interaction studies were conducted with digoxin and warfarin, two frequently used medications with narrow therapeutic windows. Data from these studies indicated that iclaprim had no clinically relevant effect on the systemic exposure to these drugs. Alternatively, the rate

and extent of iclaprim exposure was not influenced by concomitant administration of either warfarin or digoxin under steady-state conditions.

5. OVERVIEW OF CLINICAL EFFICACY

5.1 Phase 2 Study AR-100-SSTI-001

5.1.1 Overview of Study Design

The Phase 2 study, AR-100-SSTI-001, initiated in May 2002, was an evaluator-blinded, randomized, multicenter study designed to assess the efficacy and safety of 2 doses of iclaprim (0.8 and 1.6 mg/kg IV) administered twice daily as a 30-minute infusion, compared with vancomycin 1 g administered twice daily in the treatment of patients with cSSSI known or suspected to be caused by susceptible pathogens. The primary endpoint was the investigator assessment of clinical cure at the TOC visit. An independent Data Safety and Monitoring Board (DSMB) was established and assessed the safety throughout the course of the trial. This study was not powered to show statistical significance, and there was no adjustment for multiple comparisons or early stopping rules.

In this supportive Phase 2 study, the duration of study drug treatment was 10 days. Patients were evaluated daily through Day 10 or to the last day of therapy (EOT); the TOC visit was conducted on Day 20 ± 5 days after the end of treatment.

5.1.2 Study Population

The following populations were defined for analysis of efficacy in the Phase 2 study:

Table 5-1: Study Populations for Phase 2 Study AR-100-SSTI-001

Population	Definition
ITT:	All patients who had a post-randomization primary efficacy measurement.
Clinical Eligible:	All patients in the safety population who met the disease definition.
Clinical Evaluable (CE):	All clinically eligible patients who met the criteria for evaluability, ie, who completed the treatment and the study.
Microbiologically Evaluable (ME):	All clinically evaluable patients who had a recognized pretreatment bacterial pathogen.

5.1.3 Key Results

The primary endpoint was the assessment of the clinical efficacy of iclaprim as compared to vancomycin in the treatment of cSSSI, measured by the proportion of patients achieving clinical cure at the TOC visit (ie Day 20 \pm 5 days after the EOT). Clinical cure rates of 92.9% in the iclaprim 0.8 mg/kg group, 90.3% in the iclaprim 1.6 mg/kg group and 92.9% in the vancomycin group were observed at the TOC visit. The clinical cure rates for all three treatment groups were higher than planned in the protocol (ie, 80%). Eradication of Gram-positive pathogens were 89.7% [0.8 mg/kg iclaprim], 80.0% [1.6 mg/kg iclaprim] and 72.0% [1 g vancomycin]. *S. aureus* was the most frequently isolated baseline pathogen and the eradication rates were 80% [0.8 mg/kg iclaprim], 72.2% [1.6 mg/kg iclaprim] and 58.8% [1 g vancomycin]. Five cases with BL MRSA were documented, four in the 0.8 mg/kg iclaprim group and one in the vancomycin group; all patients were both clinically and microbiologically cured.

Although, this study was not powered to show statistical significance, the clinical cure rates were comparable between the three treatment groups. The treatment difference based on comparison

of the iclaprim 0.8 mg/kg and vancomycin treatment arms was 0.8 (97.5% CI: -14.9), while comparison of the iclaprim 1.6 mg/kg and vancomycin treatment groups yielded a treatment difference of -0.6% (97.5 % CI: -14.7). In summary, the results show a trend towards non-inferiority of iclaprim compared to vancomycin.

5.2 Phase 3 Studies ASSIST-1 and ASSIST-2

5.2.1 Overview of Study Design

The two pivotal, double-blind, Phase 3 studies, ASSIST-1 and ASSIST-2, were conducted under congruent protocols. The ASSIST-1 study began in June 2005, while the ASSIST-2 study commenced in April 2006. Both were evaluator-blinded, randomized, multi-center studies designed to compare the efficacy and safety of 0.8 mg/kg iclaprim and 600 mg linezolid (both IV administered twice daily) in the treatment of patients with cSSSI known or suspected to be caused by susceptible pathogens.

Patients were evaluated daily for the first four days and then every other day thereafter during the 10-14 day treatment period, at the end of therapy (EOT), the TOC visit (7–14 days post treatment), and at a Late Follow-Up (F/U) visit 7–14 days after the TOC visit. The primary endpoint was the investigator's assessment of clinical cure at the TOC visit. Central patient randomization (1:1) and stratification by country were performed for these clinical studies.

The first study, ASSIST-1 was conducted in five countries: Latvia, Romania, Russia, Canada and the US, with the largest proportion of patients being recruited in Russia, whereas 10 countries were involved in ASSIST-2: Latvia, Lithuania, Poland, France, Germany, Italy, the UK, South Africa, Canada, and the US, with most subjects coming from the US. Both studies were

monitored for safety by the same unblinded Data Monitoring Committee (DMC). The studies were planned to follow two stages, with the safety data from both studies pooled and evaluated.

ASSIST-1 and ASSIST-2 had two stages:

- Stage A included the first 200 patients and had an exclusion criterion for a baseline QTc >470 ms. The study progressed to Stage B if no significant iclaprim-related cardiovascular AEs or significant changes from baseline in electrocardiogram (ECG) results relative to the linezolid group were observed.
- In Stage B, patients with baseline QTc of >470 msec were eligible to enter the study. This stage was implemented following a positive recommendation by the Data Monitoring Committee (DMC)

5.2.2 Critical Aspects of Study Design

5.2.2.1 Study Population

As defined in the stringent inclusion criteria listed for the Phase 3 studies, only patients with proven cSSSI requiring hospitalization were enrolled and over 90% of patients in Phase 3 studies had a severe infection. In addition, 46.4% of patients were diagnosed with Systemic Inflammatory Response Syndrome (SIRS). More than 70% of enrolled patients had a Gram-positive pathogen isolated at baseline.

The causative pathogen distribution in this population was well balanced between treatment groups; *S. aureus* was the predominant pathogen isolated (70%), of which 40% were MRSA. Demographics, disease state, and microbiological findings also were well balanced between both arms and studies. Certain patient-types were excluded: those with infected diabetic foot or

decubitus ulcers; patients <18 years of age; immunocompromised patients; pregnant or lactating women; severely obese patients (BMI index >40 or body weight >150 Kg); individuals with severe renal impairment, hepatic disease or cardiovascular disease; and patients requiring high dose steroids.

5.2.2.2 Diagnosis of cSSSI

Special attention was taken to select patients with severe cSSSI. Purulent or seropurulent drainage, or at least three of the following five signs and symptoms, were necessary for inclusion: (1) drainage and/or discharge; (2) erythema (extending at least 1cm beyond a wound edge); (3) swelling and/or induration; (4) heat and/or localized warmth; and (5) pain and/or tenderness to palpation. In addition, at least one of the following pathogen-related conditions must be present: (1) fever >38°C; (2) elevated total peripheral white blood cells >10,000/mm³; or (3) > 15% immature neutrophils (bands), regardless of total peripheral WBC count.

5.2.2.3 Study Treatments

Iclaprim

Iclaprim was administered at a dose of 0.8 mg/kg body weight as an iclaprim mesylate IV solution in 300 mL N-saline. This solution was infused over 30 minutes every 12 hours (±2 hours) for 10-14 days. The duration of infusion was typically 30 minutes but could be extended to 45 minutes at the discretion of the investigator.

Linezolid

The comparator linezolid was chosen for use in Phase 3 clinical trials for the following reasons:

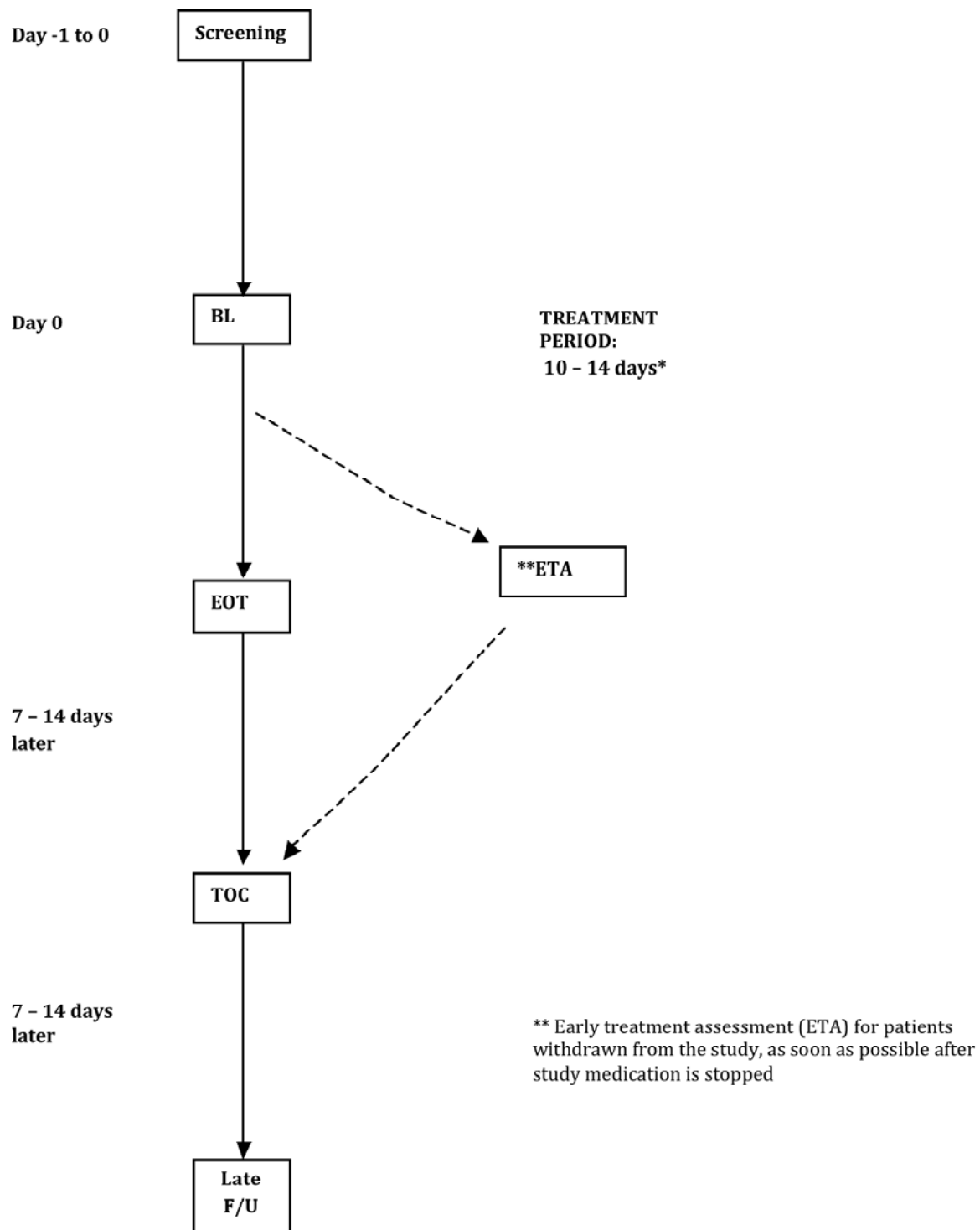
- It is an approved treatment for cSSSI, including infections due to MRSA, with a treatment duration of 10-14 days;
- It can be infused over a 30-minute period as is the case for iclaprim
- A study comparing linezolid with vancomycin in the treatment of adults with MRSA infections found slightly higher cure rates with linezolid (79% with linezolid and 73% with vancomycin); (Stevens et al., 2002; Wiegelt et al., 2005)
- MSSA and MRSA are susceptible to both linezolid and iclaprim; and
- Based on results from Phase 1 clinical studies, linezolid and iclaprim did not require dose adjustments for the degree of renal or hepatic impairment allowed by the study entry criteria.

Linezolid was infused at a dose of 600 mg in 300 mL of IV solution over 30-minute every 12 hours (± 2 hours) for 10–14 days. As with iclaprim, the infusion duration was not shorter than 30 minutes but could be prolonged to 45 minutes at the investigator's discretion.

5.2.2.4 Patient Monitoring

A schematic depicting the overall design of the Phase 3 studies is shown in Figure 5-1.

Figure 5-1: Study Schematic for the Phase 3 Clinical Trials ASSIST-1 and ASSIST-2



5.2.2.5 Randomization

For each study, a total of 500 patients were to be randomized in a 1:1 ratio to either iclaprim or linezolid. Outpatient parenteral antimicrobial therapy (OPAT) was possible under certain circumstances. In eligible patients, after initial hospital treatment, study medication could be continued in an outpatient setting.

5.2.2.6 Data Monitoring Committee

An independent, unblinded, external DMC pooled and evaluated efficacy and safety data in both Phase 3 clinical studies. The DMC evaluated safety parameters on a regular basis, in particular any AEs, serious adverse events (SAEs), or cardiovascular/laboratory parameters.

5.2.2.7 Assessments

Microbiology Assessment

The local microbiology laboratories cultured specimens from the infection site and evaluated them via Gram stain, aerobic and anaerobic culture (as clinically indicated), blood culture, and antimicrobial sensitivity testing. All recovered isolates (aerobic and anaerobic bacteria) were sub-cultured and sent to the central microbiology laboratory. The study site's local microbiology laboratory retained a duplicate of each isolate until the central laboratory reported the results.

Acceptable causative pathogens were *S. aureus*, *S. pyogenes*, *S. agalactiae*, *E. faecium*, or *E. faecalis*. The medical monitor determined the clinical relevance of other isolates, based on the site of the cSSSI and the laboratory culture results. A review board blinded to treatment allocation analyzed and confirmed all other organisms classified by the study site or laboratory microbiologist as a valid pathogen of cSSSI for the purposes of microbiological outcome analysis.

5.2.2.8 Outcomes

Clinical Outcomes

All clinical outcomes were defined as shown in Table 5-2.

Table 5-2: Criteria for Evaluating Clinical Response

Clinical response	Criteria
Cure:	All cSSSI signs and symptoms present at baseline had resolved and the patient did not receive new systemic or any topical antibacterial treatment up to and including that visit (EOT or TOC, as appropriate);
	Or
	Clinically relevant improvement of the local and systemic signs and symptoms of cSSSI present at baseline such that the patient would not meet study entry criteria, and the patient did not receive new systemic or any topical antibacterial treatment up to and including that visit (EOT or TOC, as appropriate);
And	
	Received at least four days of treatment and at least seven doses.
Failure:	Conditions for “Cure” are not fulfilled
And	
	After >2 days and ≥4 doses of treatment, at least one of the following criteria must be met:
	<ul style="list-style-type: none"> • Persistence or progression of signs and symptoms relevant to the pretreatment infection site; • Development of new clinical signs and symptoms relevant to the pretreatment infection site; • Additional antibacterial therapy (except aztreonam or metronidazole) required for the treatment of the pre-treatment infection site; and/or • A surgical procedure was required as adjunct or F/U therapy due to failure of the study medication
And	
	Received at least two days of treatment and at least four doses.
	Note: any patient classified as “Failure” at EOT was also classified as “Failure” at the TOC visit (carry-forward of failure)
Indeterminate:	Conditions for “Cure” or “Failure” are not fulfilled
And	
	<ul style="list-style-type: none"> • For EOT: patients who did fulfill all other criteria for “Cure” but had <4 days and/or <7 doses of treatment; or • For TOC: patients who did fulfill all other criteria for “Cure” but had <4 days and/or <7 doses of treatment or patients with “Cure” at EOT but with no TOC visit

Clinical response	Criteria
<i>Missing:</i>	All other cases.

Note: for patients who withdrew before the EOT visit, the clinical response was determined at the time of withdrawal.

Microbiological Outcomes

Bacteriological response for each causative organism identified at baseline was determined separately for EOT and TOC. The definitions used are shown in Table 5-3.

Table 5-3: Criteria for Evaluating Bacteriological Response by Pathogen

Bacteriological Response	Criteria
<i>Eradication</i>	Baseline causative organism could not be isolated from any culture(s) at the EOT/TOC assessment.
<i>Presumed Eradication</i>	The patient was a clinical cure at the EOT/TOC assessment, and there was no appropriate material for culture from the original site of infection.
<i>Persistence</i>	The baseline causative pathogen (based on susceptibility profile or molecular typing) was isolated at the EOT/TOC assessment. Note: Persistence at EOT was carried forward to TOC if no appropriate material for culture was available at TOC.
<i>Presumed Persistence</i>	The patient was a clinical failure at the EOT/TOC assessment, and no appropriate material was available for culture from the original site of cSSSI. Note: Presumed Persistence at EOT was carried forward to TOC.
<i>Indeterminate</i>	Clinical response was Indeterminate at the EOT/TOC assessment, and no appropriate material was available for culture from the original site of cSSSI.
<i>Colonization</i>	The patient was a clinical cure at the EOT/TOC assessment, and a causative pathogen was isolated during therapy that was different from the baseline causative pathogen.
<i>Superinfection</i>	The patient was a clinical failure at the EOT/TOC assessment, and a causative pathogen was isolated during therapy that was different from the baseline causative pathogen.
<i>Reinfection</i>	The patient was a clinical failure at the TOC assessment, and a causative pathogen that had been eradicated at the EOT visit was isolated at the TOC visit
<i>Missing</i>	The clinical response was Missing at the EOT/TOC visit, and there was no appropriate material for culture.

Only patients with at least one Gram-positive baseline pathogen were considered for the evaluation of the by-patient bacteriological response, and only Gram-positive pathogens were considered for the determination of the response categories.

Safety assessments

Safety assessments consisted of monitoring and recording:

- All AEs and SAEs;
- Hematology, clinical chemistry and urinalysis results; and

- Vital sign measurements, physical examination and ECG test results.

All patients who received at least one dose of study medication were included in the safety analysis.

All AEs were reported, and changes in physical examinations, vital signs, and laboratory test results from pre- to post-treatment were summarized. The investigator continued to follow all SAEs and non-SAEs until they resolved or were confirmed to be chronic or stable. This follow-up may have extended beyond the study's end.

5.2.3 Statistical Considerations

5.2.3.1 Analysis Populations

The following definitions of analysis populations of patients were used:

- **Intent-to-Treat (ITT) Population** - included all enrolled patients who received at least one dose of study medication;
- **Modified Intent-to-Treat (MITT) Population** - included all patients in the ITT population who had an infecting Gram-positive pathogen isolated at baseline;
- **Per Protocol (PP) Population** - patients included in the PP population met all of the following conditions:
 - Clinical criteria for study infection;
 - Were treated for a minimum of four calendar days and received at least seven doses of study medication, except for patients with documented clinical failure (who had to have been treated for a minimum of two calendar days and received at least four doses of study medication);

- Must not have received any another systemic antibacterial therapy (except for aztreonam or metronidazole) before the TOC assessment, unless the indication for the new antibiotic was lack of efficacy;
- Had the necessary clinical evaluations performed (EOT and TOC evaluations) and were classified as cure or failure;

Patients with mixed Gram-positive and Gram-negative pathogens or mixed Gram-positive and anaerobic pathogens who were classified as clinical failures at the EOT or TOC visit must have received effective therapy against the Gram-negative organism or anaerobic pathogens, respectively.

- **Microbiologically Evaluable Per Protocol (ME_{PP}) Population** - a subgroup of patients from the PP population, with an infecting Gram-positive pathogen at baseline.

Subsequent to the release of the protocol and statistical analysis plan (SAP) for the ASSIST-2 clinical study report (CSR), an additional two analysis populations were defined:

- **Modified Clinically Evaluable (MCE) Population** – included all patients who had no other protocol violation than treatment with prohibited antibacterials or high-dose steroids;
- **Microbiologically Evaluable MCE Population (ME_{MCE})** - A subgroup of patients from the MCE population with an infecting Gram-positive pathogen at baseline.

Efficacy was analyzed in each of the above populations, while safety was analyzed in the ITT population only. Demographic and background variables and efficacy variables were analyzed for the populations specified above.

5.2.3.2 Efficacy Endpoints

Primary Endpoint

The primary endpoint of the Phase 3 trials was the comparative clinical cure rates of IV iclaprim and IV linezolid at the TOC visit (7–14 days after the end of treatment) in the ITT and PP populations. The MCE population was defined as an additional sensitivity analysis population (ICH E9), based on the observation of a strong imbalance in the use of prohibited antibiotics and as a consequence an imbalance in the exclusion of these patients from the PP population in ASSIST-2, the results provide supporting evidence for the primary outcome.

Secondary Endpoints

- Clinical efficacy at EOT;
- Time to resolution of systemic and local cSSSI signs and symptoms;
- Clinical and bacteriological outcomes in the MCE and MITT populations;
- Bacteriological eradication rates of baseline pathogen;
- Clinical efficacy at TOC, stratified by MIC analysis;
- Baseline *in vitro* susceptibility of isolated pathogens in the MCE population

5.2.4 Efficacy Analysis

5.2.4.1 Primary Efficacy Endpoint Evaluation

Both ASSIST-1 and ASSIST-2 were judged individually according to their respective protocols. A statistical comparison was performed using a chi-square test on a 2 x 2 table in which all patients were classed simply as Cure or Failure; Indeterminate responses were classed as Failures. The counts and percentages of Cure, Indeterminate (ITT population only), and Failure for both study populations were tabulated, and the 95% CIs calculated for the percentage cure. For those patients in the ITT population who received prohibited antibacterials during the study but were recorded as

“Cure” by the investigator, the clinical response was corrected to “Indeterminate” according to the SAP.

5.2.4.2 Secondary Efficacy Evaluation

Analyses for the secondary efficacy endpoints included:

- Clinical response;
- Area and volume of infection;
- Severity of infection;
- Time to symptom resolution;
- Time to defervescence;
- By-patient bacteriological outcome;
- By-pathogen bacteriological outcome; and
- Overall therapeutic response

No alpha adjustment was made for the secondary analyses, and results of these analyses were not part of the confirmatory analysis.

5.2.5 *Determination of Sample Size*

Using Blackwelder’s method for non-inferiority testing with a one-sided alpha of 0.025, 85% clinical cure rate, and a 12.5% margin, statisticians calculated that a sample size of 172 evaluable patients per treatment group would be required for 90% power. Assuming that 20% of patients would be non-evaluable, the study design therefore required 430 patients for randomization (215 per treatment arm). The target sample size was determined separately for the 2 studies; each study was calculated to recruit a total of 500 patients (250 in each treatment arm).

5.2.6 Justification for Non-Inferiority (NI) Margin

The two pivotal non-inferiority studies were designed using essentially identical protocols, and the pre-defined non-inferiority margin against linezolid for each of the studies was set at -12.5%.

Historically, cSSSI studies have been conducted using a non-inferiority design, with an active comparator, and no placebo-controlled trials have been reported. The non-inferiority margin was conservatively based on an estimated placebo effect and followed the ICH E9 and E10 guidelines. For example, data from a recent, randomized, Phase 2 cSSSI dose-finding study for dalbavancin demonstrates that two doses of dalbavancin was 30% more effective than one dose of dalbavancin, both for the intent-to-treat and clinically evaluable population ([Jauregui 2005](#)). It is likely that one dose of dalbavancin was still superior to placebo, although a placebo was not tested in the study. Therefore, the minimal magnitude of efficacy of an effective antibiotic relative to placebo for cSSSI is 30%. To preserve 50% of that antibiotic efficacy, a non-inferiority margin of -15% is a reasonable margin for a non-inferiority clinical trial of antibiotics for cSSSI. The two independent pivotal trials of iclaprim for cSSSI each had a pre-defined NI margin of -12.5%, which was chosen to add an additional, conservative “buffer zone” and to ensure that the margin for each study was well below the expected antibiotic efficacy versus placebo for cSSSI. Furthermore, the identical design of the two trials allowed for the additional powering of the pooled data from these studies; a highly conservative non-inferiority margin of -10% was defined for the pooled analysis.

5.2.7 Results

5.2.7.1 Study Patients

Patient Disposition

Of the 1161 patients screened, 151 were not randomized, most frequently because they did not meet the eligibility criteria. Of those who were randomized, 18 did not receive study drug

treatment, mainly because of withdrawal of informed consent. The numbers of patients who were entered, received study drug, and completed the two studies are shown in Table 5-4.

Table 5-4: Patient Disposition – All Patients

	ASSIST-1		ASSIST-2		Integrated		
	Iclaprim N (%)	Linezolid N (%)	Iclaprim N (%)	Linezolid N (%)	Iclaprim N (%)	Linezolid N (%)	Total
Patients screened		538		623		1161	
Patients randomized	250 (100%)	249 (100%)	257 (100%)	253 (100%)	508 ^b (100%)	502 (100%)	1010 (100%)
Patients randomized and treated							
ITT (for efficacy)	249 (99.6%)	248 (99.6%)	251 (97.7%)	243 (96.0%)	500 (98.4%)	491 (97.8%)	991 (98.1%)
ITT (for safety)	250 (100%)	247 (99.2%)	250 (97.3%)	244 (96.4%)	500 (98.4%)	491 (97.8%)	991 (98.1%)
Patients treated and withdrawn prematurely	27 (10.8%)	21 (8.4%)	23 (9.2%)	30 (12.3%)	49 (9.6%)	50 (10.0%)	99 (9.8%)
Patients completed	223 (89.2%)	228 (91.6%)	228 (90.8%)	213 (87.7%)	451 (88.8%)	441 (87.8%)	892 (88.3%)

All efficacy analysis populations are shown in Table 5-5.

Table 5-5: Assignment of Randomized Patients to Evaluation Populations

Patient population	ASSIST-1		ASSIST-2		Combined	
	Iclaprim	Linezolid	Iclaprim	Linezolid	Iclaprim	Linezolid
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Number of patients randomized	250 (100%)	249 (100%)	257 (100%)	253 (100%)	508 ^a (100%)	502 (100%)
ITT (for efficacy evaluation)	249 (99.6%)	248 (99.6%)	251 (97.7%)	243 (96.0%)	500 (98.4%)	491 (97.8%)
ITT (for safety evaluation)	250 (100%)	247 (99.2%)	250 (99.6%)	244 (96.4%)	500 (98.4%)	491 (97.8%)
PP	206 (82.4%)	213 (85.5%)	209 (81.3%)	195 (77.1%)	415 (81.7%)	408 (81.3%)
MCE	218 (87.2%)	228 (91.6%)	222 (86.4%)	217 (85.8%)	440 (86.6%)	445 (88.6%)
MITT	183 (73.2%)	191 (76.7%)	192 (74.7%)	184 (72.7%)	375 (73.8%)	375 (74.7%)
ME _{PP}	150 (60.0%)	167 (67.1%)	165 (64.2%)	149 (58.9%)	315 (62.0%)	316 (62.9%)
ME _{MCE}	156 (62.4%)	176 (70.7%)	172 (66.9%)	164 (64.8%)	328 (64.6%)	340 (67.7%)

The studies, treatment groups, and different analysis populations were comparable with respect to patient numbers, and no differences were seen between geographical regions.

Reasons for Withdrawal

Similar numbers of patients withdrew prematurely from the study treatment in both treatment groups (Table 5-6). Overall, the two treatment groups were balanced with respect to the reasons for withdrawal in both studies and between studies.

Table 5-6: Reasons for Premature Study Termination – ITT Population*

	ASSIST-1		ASSIST-2		Combined	
	Iclaprim N=249	Linezolid N=248	Iclaprim N=251	Linezolid N=243	Iclaprim N=500	Linezolid N=491
Treatment Prematurely Terminated (any reason)	19 (7.6%)	12 (4.8%)	19 (7.6%)	22 (9.1%)	37 (7.4%)	33 (6.7%)
Consent withdrawn	8 (3.2%)	4 (1.6%)	2 (0.8%)	5 (2.1%)	9 (1.8%)	8 (1.6%)
Infection-related reasons	2 (0.8%)	2 (0.8%)	0	4 (1.7%)	2 (0.4%)	6 (1.2%)
Treatment-emergent cardiovascular abnormalities	0	1 (0.4%)	0	1 (0.4%)	0	2 (0.4%)
Treatment failure	3 (1.2%)	0	1 (0.4%)	1 (0.4%)	4 (0.8%)	1 (0.2%)
Lost to follow-up	0	0	1 (0.4%)	1 (0.4%)	1 (0.2%)	1 (0.2%)
AE	3 (1.2%)	3 (1.2%)	3 (1.2%)	1 (0.4%)	6 (1.2%)	4 (0.8%)
Death	1 (0.4%)	0	0	0	1 (0.2%)	0
Patient's condition changed/non-compliance/Sponsor or Investigator request	1 (0.4%)	2 (0.8%)	8 (3.2%)	5 (2.1%)	9 (1.8%)	7 (1.4%)
Other	1 (0.4%)	0	4 (1.6%)	4 (1.7%)	5 (1.0%)	4 (0.8%)
Missing data	8 (3.2%)	9 (3.6%)	7 (2.8%)	10 (4.1%)	15 (3.0%)	19 (3.9%)

*Baseline Characteristics***Demographics**

The two treatment groups were similar with respect to gender, age, race, body weight, height, and BMI. In ASSIST-2, there were more Hispanics due to the higher percentage of US patients and Blacks due to the higher percentage of US patients, as well as those from South Africa.

Type of Infection

Overall, deep or extensive cellulitis was the most common infection type, occurring in over one-third of patients in each treatment group, followed by wounds and major abscesses (Table 5-7). Whereas deep or extensive cellulitis was by far the most frequent type of cSSSI (47.8%) in ASSIST-1, major abscess and deep or extensive cellulitis each occurred in about 30% of cases in ASSIST-2. Wound infections were the most common infection type in ASSIST-2 (in 45% of the patients), whereas in ASSIST-1, this infection type was much less frequent (14.5%). Overall, the distribution of infection types was similar for both treatment groups and for all study populations.

Table 5-7: Type of Infection Treated – ITT Population

	ASSIST-1				ASSIST-2				Combined			
	Iclaprim (N=249)		Linezolid (N=248)		Iclaprim (N=251)		Linezolid (N=243)		Iclaprim (N=500)		Linezolid (N=491)	
Infected ulcers, n (%)	37	(14.9%)	36	(14.5%)	22	(8.8%)	18	(7.4%)	59	(11.8%)	54	(11.0%)
First or second degree burns, n (%)	34	(13.7%)	31	(12.5%)	15	(6.0%)	22	(9.1%)	49	(9.8%)	53	(10.8%)
Major abscess, n (%)	53	(21.3%)	53	(21.4%)	76	(30.3%)	71	(29.2%)	129	(25.8%)	124	(25.3%)
Deep or extensive cellulitis, n (%)	121	(48.6%)	117	(47.2%)	71	(28.3%)	69	(28.4%)	192	(38.4%)	186	(37.9%)
Wound infections, n (%)	29	(11.6%)	43	(17.3%)	112	(44.6%)	111	(45.7%)	141	(28.2%)	154	(31.4%)

n=number of patients in the respective category; percentage based on the total number of patients in this group.

Note: Patients may have been included in more than one category.

Clinical Signs and Symptoms of cSSSI at Baseline

There was no apparent difference between the two treatment groups with respect to the severity of each sign or symptom. There was a tendency for more severe infections in ASSIST-1, compared with ASSIST-2. Overall, results were similar for the MITT, MCE, PP, ME_{MCE}, and ME_{PP} populations.

Severe Infections at Baseline

No apparent differences between the two randomized treatment groups were reported. Overall, a high percentage (92.6%) of patients in each treatment group had a severe infection at baseline. As was previously observed, a tendency for more severe infections in ASSIST-1 was documented: in this study, essentially all patients (98.8%) had a severe infection, whereas in ASSIST-2, the number was 86.4%.

Baseline Pathogens

At baseline, 845 Gram-positive isolates (iclaprim=418, linezolid=427) were cultured from specimens of the 750 patients comprising the MITT population; 87.9% of these patients had only one pathogen. A further 11.7% of patients had 2 pathogens. Only 2 patients had 3 pathogens, and a single patient had 4. Gram-positive pathogens occurring in at least 10 patients at baseline are shown in [Table 5-8](#). The most common Gram-positive isolates were *S. aureus*, approximately 40% of which were identified as MRSA. The abundance of MRSA was different in the two studies, with 28.7% in ASSIST-1 and 50.8% in ASSIST-2, which had a higher percentage of US patients.

Table 5-8: Gram-positive Pathogens Occurring in at Least 10 Patients at baseline –MITT Population

	ASSIST-1				ASSIST-2				Combined	
	Iclaprim (N=183)		Linezolid (N=191)		Iclaprim (N=192)		Linezolid (N=184)		Iclaprim (N=375)	Linezolid (N=375)
<i>E. faecalis</i>	14	(7.7%)	13	(6.8%)	15	(7.8%)	15	(8.2%)	(7.7%)	28 (7.5%)
<i>S. aureus</i> , total*	138	(75.4%)	144	(75.4%)	149	(77.6%)	160	(87.0%)	(76.5%)	304 (81.1%)
MRSA	45	(24.6%)	36	(18.8%)	74	(38.5%)	81	(44.0%)	(41.9%)	117 (38.7%)
MSSA	93	(50.8%)	108	(56.5%)	73	(38.0%)	77	(41.8%)	(58.1%)	185 (49.3%)
<i>S. agalactiae</i>	3	(1.6%)	7	(3.7%)	5		4		(2.1%)	11 (2.9%)
<i>S. pyogenes</i>	30	(16.4%)	34	(17.8%)	28	(14.6%)	22	(12.0%)	(15.5%)	56 (14.9%)

Includes isolates of unknown methicillin susceptibility identified by local laboratories which failed to grow in the central laboratory.

^a For this combined analysis, the presence of the mecA gene and/or oxacillin resistance was used to identify MRSA. In ASSIST-1, both mecA and oxacillin susceptibility were used to determine MRSA with the mecA result taking precedence in the event of a discrepancy. In the ASSIST-2 CSR, oxacillin susceptibility was used to identify MRSA.

Antimicrobial Sensitivity

The MIC values for iclaprim against *S. aureus* overall (MRSA and MSSA, N=584) ranged from 0.008 to more than 16 µg/mL (Table 5-9). However, the MIC₉₀ values were low: 0.25 µg/mL for *S. aureus* overall and the MSSA strains. More important, the combined MIC₉₀ value for MRSA was 0.12 µg/mL. In contrast, linezolid MIC values for *S. aureus* overall ranged from 0.5–4 µg/mL, with both MIC₅₀ and MIC₉₀ values of 2.0 µg/mL. For *S. pyogenes* (N=112), the MIC range for iclaprim was 0.008 to 0.25 µg/mL, and the MIC₅₀ and MIC₉₀ values were 0.015 and 0.12 µg/mL, respectively. Against *S. agalactiae* (N=19), the MIC range for iclaprim was 0.03 to 0.25 µg/mL, with MIC₅₀ and MIC₉₀ values of 0.12 and 0.25 µg/mL, respectively. The MIC range for iclaprim against *E. faecalis* (N = 57) was 0.008 to >16 µg/mL, with MIC₅₀ and MIC₉₀ values of 0.015 and >0.16 µg/mL. In comparison, the MIC values for linezolid for *S. pyogenes* ranged from 0.25 to 1 µg/mL, and the MIC₅₀ and MIC₉₀ values were both 1.0 µg/mL. For all 19 isolates of *S. agalactiae*, the linezolid MIC was 1 µg/mL. For *E. faecalis* and linezolid, the MIC range was 0.5–2 µg/mL and the MIC₉₀ value was 2 µg/mL.

Table 5-9: Iclaprim MIC₅₀ and MIC₉₀ Values for Gram-positive Pathogens Isolated at Baseline – MITT population

	N	ASSIST-1			n	ASSIST-2			n	Combined		
		MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	MIC Range (µg/mL)		MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	MIC Range (µg/mL)		MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	MIC Range µg/mL)
<i>S. aureus</i> , total	279	0.12	0.25	0.008–16	305	0.12	0.25	0.03–>16	584	0.12	0.25	0.008–>16
MRSA	80	0.12	0.5	0.008–16	154	0.12	0.12	0.03–>16	235 ^a	0.12	0.12	0.008–>16
MSSA	199	0.12	0.25	0.015–16	151	0.12	0.25	0.03–>16	349 ^a	0.12	0.25	0.015–>16
<i>S. pyogenes</i>	63	0.015	0.06	0.008–0.12	49	0.03	0.12	0.008–0.25	112	0.015	0.12	0.008–0.25
<i>S. agalactiae</i> ^b	10	0.12	0.25	0.03–0.25	9	-	-	-	19	0.12	0.25	0.03–0.25
<i>E. faecalis</i>	27	0.015	16	0.008–16	30	0.015	8	0.008–>16	57	0.015	>16	0.008–>16

* In the source tables a value of 32 is given for all MICs >16 µg/mL, the highest concentration tested^a For this combined analysis the presence of the *mecA* gene was used to identify MRSA. In ASSIST-1 both the presence of *mecA* and oxacillin susceptibility were used to determine MRSA with the *mecA* result taking precedence in the event of a discrepancy. In ASSIST-2, oxacillin susceptibility was used to identify MRSA.

^b Data not presented for *Streptococcus agalactiae* in ASSIST-2 as fewer than 10 isolates collected.

Size of Primary Infection at Screening

In all study populations, the mean volume of the infection site appeared to be markedly greater in the iclaprim group than in the linezolid group. The median volume of the infection site in both studies was about 50% higher in the iclaprim group. In ASSIST-1, the median volumes were about 70% greater than in ASSIST-2 for both treatment groups. The mean area of the infection site was similar when comparing the 2 treatment groups.

5.2.7.2 Analysis of Efficacy

Clinical Efficacy

Clinical Cure Rate at TOC

Overall, both iclaprim and linezolid exhibited high clinical cure rates at TOC in the co-primary populations ITT and PP, as well as in the supporting MCE populations (Table 5-10). The protocol-defined non-inferiority margin was met in all these populations and in both studies. This result confirms that iclaprim was non-inferior to linezolid.

For both co-primary populations (ITT and PP) in ASSIST-1 and ASSIST-2, the protocol-defined primary endpoint was achieved. In both individual studies, one of the two co-primary populations had a lower bound of the CI for the treatment difference below 10%. For the combined pooled analysis the lower bound of the CI was below 10% for both co-primary populations. In both ASSIST-1 and ASSIST-2 the sensitivity analysis of the MCE population showed that the 95% CI for the treatment difference was below 10% in both studies. For the combined ITT, PP, and MCE populations, the lower bound of the CI for the treatment difference was always below 10%.

Table 5-10: Clinical Cure at TOC – Primary Efficacy Populations ITT and PP and Supporting Population MCE

	ASSIST-1		ASSIST-2		Combined	
	Iclaprim	Linezolid	Iclaprim	Linezolid	Iclaprim	Linezolid
ITT	N = 249	N = 248	N = 251	N = 243	N = 500	N = 491
Clinical cure, n (%)	207 (83.1%)	220 (88.7%)	204 (81.3%)	199 (81.9%)	411 (82.2%)	419 (85.3%)
95% CI	78.0% – 87.3%	84.2% – 92.1%	76.0% – 85.6%	76.6% – 86.2%	78.6% – 85.3%	81.9% – 88.2%
Treatment difference (iclaprim - linezolid) and 95% CI	-5.6% [-11.7% to 0.6%]		-0.6% [-7.5% to 6.3%]		-3.1% [-7.7% to 1.5%]	
PP	N = 206	N = 213	N = 209	N = 195	N = 415	N = 408
Clinical cure, n (%)	195 (94.7%)	211 (99.1%)	188 (90.0%)	188 (96.4%)	383 (92.3%)	399 (97.8%)
95% CI	90.7% – 97.0%	96.6% – 99.7%	85.1% – 93.3%	92.8% – 98.3%	89.3% – 94.5%	95.9% – 98.8%
Treatment difference (iclaprim - linezolid) and 95% CI	-4.4% [-8.4% to -1.0%]		-6.5% [-11.6% to -1.5%]		-5.5% [-8.7% to -2.6%]	
MCE	N = 218	N = 228	N = 222	N = 217	N = 440	N = 445
Clinical cure, n (%)	195 (89.4%)	211 (92.5%)	188 (84.7%)	188 (86.6%)	383 (87.0%)	399 (89.7%)
95% CI	84.7% – 92.9%	88.4% – 95.3%	79.4% – 88.8%	81.5% – 90.5%	83.6% – 89.9%	86.5% – 92.2%
Treatment difference (iclaprim - linezolid) and 95% CI	-3.1% [-8.6% to 2.3%]		-2.0% [-8.5% to 4.7%]		-2.6% [-6.9% to 1.6%]	

Clinical Cure Rate at TOC – All Non-Primary Populations

The clinical outcome for all non-primary populations was similar to the outcomes of the primary efficacy variables, and there were no obvious differences between the two studies. As was the case for the primary efficacy populations, the overall iclaprim clinical cure rate at TOC for all secondary populations was high (Table 5-11). With regard to the clinical cure rate, the lower bound of the 95% CI for the treatment difference (iclaprim — linezolid) was within -10% for all combined patient populations.

Table 5-11: Clinical Cure at TOC Visit – MITT, ME_{PP} and ME_{MCE} Populations

	ASSIST-1		ASSIST-2		Combined	
	Iclaprim	Linezolid	Iclaprim	Linezolid	Iclaprim	Linezolid
MITT	N = 183	N = 191	N = 192	N = 184	N = 375	N = 375
Clinical cure, n (%)	152 (83.1%)	170 (89.0%)	156 (81.3%)	150 (81.5%)	308 (82.1%)	320 (85.3%)
95% CI	77.0% – 87.8%	83.8% – 92.7%	75.0% – 86.5%	75.2% – 86.9%	77.9% – 85.9%	81.3% – 88.8%
Treatment difference (iclaprim-linezolid) and 95% CI	-5.9% [-13.1% to 1.1%]		-0.3% [-8.5% to 8.0%]		-3.2% [-8.7% to 2.3%]	
ME _{PP}	N = 150	N = 167	N = 165	N = 149	N = 315	N = 316
Clinical cure, n (%)	142 (94.7%)	165 (98.8%)	146 (88.5%)	143 (96.0%)	288 (91.4%)	308 (97.5%)
95% CI	89.8% – 97.3%	95.7% – 99.7%	82.6% – 92.9%	91.4% – 98.5%	87.8% – 94.3%	95.1% – 98.9%
Treatment difference (iclaprim-linezolid) and 95% CI	-4.1% [-9.2% to -0.2%]		-7.5% [-13.9% to -1.2%]		-6.0% [-10.0% to -2.3%]	
ME _{MCE}	N = 156	N = 176	N = 172	N = 164	N = 328	N = 340
Clinical cure, n (%)	142 (91.0%)	165 (93.8%)	146 (84.9%)	143 (87.2%)	288 (87.8%)	308 (90.6%)
95% CI	85.4 – 95.0%	89.1 – 96.8%	78.6% – 89.9%	81.1% – 91.9%	83.8% – 91.1%	87.0% – 93.5%
Treatment difference (iclaprim-linezolid) and 95% CI	-2.7% [-9.1 to 3.4%]		-2.3% [-10.1% to 5.6%]		-2.8% [-7.8% to 2.1%]	

By-Patient Bacteriological Response at TOC

The by-patient bacteriological cure rates against Gram-positive pathogens at TOC were high for both iclaprim and linezolid (Table 5-12). Overall eradication/presumed eradication rates of baseline pathogens by iclaprim at TOC were 76.0%, 84.1% and 81.1% for the MITT, ME_{PP}, and ME_{MCE} populations, respectively, and those for linezolid were, 81.1%, 91.8%, and 86.2%, respectively. Similar results were seen in both ASSIST-1 and ASSIST-2 studies. Bacteriological cure was mainly attributed to a response of “presumed eradication” rather than “eradication”.

Table 5-12: By-Patient Bacteriological Response at TOC Visit – MITT and ME Populations

	ASSIST-1		ASSIST-2		Combined	
	Iclaprim	Linezolid	Iclaprim	Linezolid	Iclaprim	Linezolid
MITT	N = 183	N = 191	N = 192	N = 184	N = 375	N = 375
Eradication/Presumed Eradication, n (%)	137 (74.9%)	160 (83.8%)	148 (77.1%)	144 (78.3%)	285 (76.0%)	304 (81.1%)
95% CI	67.9% – 81.0%	77.8% – 88.7%	70.5% – 82.8%	71.6% – 84.0%	71.4% – 80.2%	76.7% – 84.9%
Treatment difference (iclaprim-linezolid) and 95% CI	-8.9% [-17.4% to -0.3%]		-1.2% [-9.9% to 7.6%]		-5.1% [-11.1% to 1.0%]	
ME _{PP}	N = 150	N = 167	N = 165	N = 149	N = 315	N = 316
Eradication/Presumed Eradication, n (%)	127 (84.7%)	154 (92.2%)	138 (83.6%)	136 (91.3%)	265 (84.1%)	290 (91.8%)
95% CI	77.9% – 90.0%	87.1% – 95.8%	77.1% – 88.9%	85.5% – 95.3%	79.6% – 88.0%	88.2% – 94.6%
Treatment difference (iclaprim-linezolid) and 95% CI	-7.6% [-15.2% to -0.1%]		-7.6% [-15.3% to 0.2%]		-7.7% [-13.0% to -2.4%]	
ME _{MCE}	N = 156	N = 176	N = 172	N = 164	N = 328	N = 340
Eradication/Presumed Eradication, n (%)	127 (81.4%)	155 (88.1%)	139 (80.8%)	138 (84.1%)	266 (81.1%)	293 (86.2%)
95% CI	74.4% – 87.2%	82.3% – 92.5%	74.1% – 86.4%	77.6% – 89.4%	76.4% – 85.2%	82.0% – 89.7%
Treatment difference (iclaprim-linezolid) and 95% CI	-6.7% [-14.9% to 1.5%]		-3.3% [-11.8% to 5.3%]		-5.1% [-10.9% to 0.7%]	

By-Pathogen Bacteriological Response at TOC – MITT Population

The by-pathogen response categories at the TOC visit for all patients with Gram-positive baseline pathogens (MITT population) are shown in Table 5-13. Overall, 23 different Gram-positive pathogens in the iclaprim group and 18 different Gram-positive pathogens in the linezolid group were reported at baseline in the combined data set.

At the TOC visit, a high eradication/presumed eradication rate of 76.6% for all baseline Gram-positive pathogens were reported in the combined iclaprim group and 82.7% in the combined linezolid group (82.7%). Overall, the results from ASSIST-1 and ASSIST-2 were similar: 76.4% and 76.7% for iclaprim, respectively, and 84.6% and 80.8% for linezolid, respectively.

Table 5-13: By-Pathogen Bacteriological Response at TOC – All Gram-positive Pathogens in MITT Population

	ASSIST-1		ASSIST-2		Combined	
	Iclaprim (N=183)	Linezolid (N=191)	Iclaprim (N=192)	Linezolid (N=184)	Iclaprim (N=375)	Linezolid (N=375)
Number of patients with Gram-positive pathogen response assessment at TOC	169	183	192	184	361	367
Total number of Gram-positive pathogens	195	213	223	214	418	427
Total number of different Gram-positive pathogens	13	12	19	13	23	18
Eradication	6 (3.1%)	8 (3.8%)	14 (6.3%)	15 (7.0%)	20 (4.8%)	23 (5.4%)
Presumed Eradication	143 (73.3%)	172 (80.8%)	157 (70.4%)	158 (73.8%)	300 (71.8%)	330 (77.3%)
Persistence	20 (10.3%)	13 (6.1%)	15 (6.7%)	8 (3.7%)	35 (8.4%)	21 (4.9%)
Presumed Persistence	6 (3.1%)	1 (0.5%)	19 (8.5%)	6 (2.8%)	25 (6.0%)	7 (1.6%)
Colonization	0	0	0	1 (0.5%)	0	1 (0.2%)
Indeterminate	4 (2.1%)	11 (5.2%)	8 (3.6%)	13 (6.1%)	12 (2.9%)	24 (5.6%)

Percentages calculated using total number of Gram-positive baseline pathogens as denominator.

By-pathogen response categories for Gram-positive pathogens with more than 10 baseline isolates are shown for the MITT population in Table 5-14.

S. aureus was the most frequent baseline pathogen, isolated in about 60% of the ITT population in the combined and both individual studies. MRSA was isolated in 23.5% of the combined ITT population and was more abundant in ASSIST-2 compared with ASSIST-1.

The two treatments were comparable in their efficacy against *S. aureus*, with eradication/presumed eradication rates of 77.7% in the iclaprim arm and 81.0% in the linezolid arm for the combined data set. Furthermore, eradication/presumed eradication rates for MRSA were 76.4% and 78.7% in the iclaprim and linezolid treatment arms, respectively. These responses were similar in both ASSIST-1 and ASSIST-2. Similar trends were observed in the two treatment groups in the ME_{PP} and ME_{MCE} populations.

Table 5-14: By-Pathogen Bacteriological Response Categories at TOC Visit: Gram-Positive Pathogens with 10 or More Total Isolates – MITT Population

	ASSIST-1		ASSIST-2		Combined	
	Iclaprim (N = 183)	Linezolid (N = 191)	Iclaprim (N = 192)	Linezolid (N = 184)	Iclaprim (N = 375)	Linezolid (N = 375)
ITT Population	249	248	251	243	500	491
<i>S. aureus</i>, total, n (%)	138 (55.4%)	144 (58.1%)	149 (59.4%)	160 (65.8%)	287 (57.4%)	304 (61.9%)
Eradication	4 (2.9%)	1 (0.7%)	6 (4.0%)	8 (5.0%)	10 (3.5%)	9 (3.0%)
Pres. Eradication	104 (75.4%)	119 (82.6%)	109 (73.2%)	118 (73.8%)	213 (74.2%)	237 (78.0%)
Persistence	14 (10.1%)	12 (8.3%)	8 (5.4%)	7 (4.4%)	22 (7.6%)	19 (6.3%)
Pres. Persistence	5 (3.6%)	1 (0.7%)	13 (8.7%)	5 (3.1%)	18 (6.3%)	6 (2.0%)
Colonization	0	0	0	1 (0.6%)	0	1 (0.3%)
Indeterminate	2 (1.5%)	7 (4.9%)	6 (4.0%)	9 (5.6%)	8 (2.8%)	16 (5.3%)
Missing	9 (6.5%)	4 (2.8%)	7 (4.7%)	12 (7.5%)	16 (5.6%)	16 (5.3%)
MRSA, n (%)	45 (18.1%)	36 (14.5%)	74 (29.5%)	81 (33.3%)	119 (23.8%)	117 (23.8%)
Eradication	1 (2.2%)	0	0	1 (1.2%)	1 (0.8%)	1 (0.9%)
Pres. Eradication	35 (77.8%)	31 (86.1%)	55 (74.3%)	60 (74.1%)	90 (75.6%)	91 (77.8%)
Persistence	4 (8.9%)	3 (8.3%)	3 (4.1%)	4 (4.9%)	7 (5.9%)	7 (6.0%)
Pres. Persistence	2 (4.4%)	1 (2.8%)	7 (9.5%)	4 (4.9%)	9 (7.6%)	5 (4.3%)
Indeterminate	1 (2.2%)	1 (2.8%)	5 (6.8%)	7 (8.6%)	6 (5.0%)	8 (6.8%)
Missing	2 (4.4%)	0	4 (5.4%)	5 (6.2%)	6 (5.0%)	5 (4.3%)
MSSA, n (%)	93 (37.3%)	108 (43.5%)	73 (29.1%)	77 (31.7%)	166 (33.2%)	185 (37.7%)
Eradication	3 (3.2%)	1 (0.9%)	6 (8.2%)	7 (9.1%)	9 (5.4%)	8 (4.3%)
Pres. Eradication	69 (74.2%)	88 (81.5%)	54 (74.0%)	57 (74.0%)	123 (74.1%)	145 (78.4%)
Persistence	10 (10.8%)	9 (8.3%)	5 (6.9%)	3 (3.9%)	15 (9.0%)	12 (6.5%)
Pres. Persistence	3 (3.2%)	0	5 (6.9%)	1 (1.3%)	8 (4.8%)	1 (0.5%)
Colonization	0	0	0	1 (1.3%)	0	1 (0.5%)

	ASSIST-1		ASSIST-2		Combined	
	Iclaprim (N = 183)	Linezolid (N = 191)	Iclaprim (N = 192)	Linezolid (N = 184)	Iclaprim (N = 375)	Linezolid (N = 375)
Indeterminate	1 (1.1%)	6 (5.6%)	1 (1.4%)	2 (2.6%)	2 (1.2%)	8 (4.3%)
Missing	7 (7.5%)	4 (3.7%)	2 (2.7%)	6 (7.8%)	9 (5.4%)	10 (5.4%)
<i>S. pyogenes</i>, total, n (%)	30 (12.0%)	34 (13.7%)	28 (11.2%)	22 (9.1%)	58 (11.6%)	56 (11.4%)
Eradication	0	2 (5.9%)	2 (7.14%)	1 (4.6%)	2 (3.5%)	3 (5.36%)
Pres. Eradication	21 (70.0%)	28 (82.4%)	18 (64.3%)	17 (77.3%)	39 (67.2%)	45 (80.4%)
Persistence	4 (13.3%)	0	4 (14.3%)	1 (4.6%)	8 (13.8%)	1 (1.8%)
Pres. Persistence	1 (3.3%)	0	3 (10.7%)	1 (4.6%)	4 (6.9%)	1 (1.8%)
Indeterminate	2 (6.7%)	1 (2.9%)	1 (3.57%)	2 (9.1%)	3 (5.2%)	3 (5.4%)
Missing	2 (6.7%)	3 (8.8%)	0	0	2 (3.5%)	3 (5.4%)
<i>S. agalactiae</i>, total, n (%)	3 (1.2%)	7 (2.8%)	5 (2.0%)	4 (1.7%)	8 (1.6%)	11 (2.2%)
Eradication	0	2 (28.6%)	1 (20.0%)	1 (25.0%)	1 (12.5%)	3 (27.3%)
Pres. Eradication	2 (66.7%)	3 (42.9%)	2 (40.0%)	3 (75.0%)	4 (50.0%)	6 (54.5%)
Persistence	1 (33.3%)	0	1 (20.0%)	0	2 (25.0%)	0
Pres. Persistence	0	0	1 (20.0%)	0	1 (12.5%)	0
Indeterminate	0	1 (14.3%)	0	0	0	1 (9.1%)
Missing	0	1 (14.3%)	0	0	0	1 (9.1%)
<i>S. equisimilis</i>, total, n (%)	1 (0.4%)	2 (0.8%)	6 (2.4%)	4 (1.7%)	7 (1.4%)	6 (1.2%)
Eradication	1 (100%)	1 (50.0%)	0	0	1 (14.3%)	1 (16.7%)
Pres. Eradication	0	1 (50.0%)	4 (66.7%)	4 (100%)	4 (57.1%)	5 (83.3%)
Persistence	0	0	1 (16.7%)	0	1 (14.3%)	0
Pres. Persistence	0	0	1 (16.7%)	0	1 (14.3%)	0
<i>E. faecalis</i>, total, n (%)	14 (5.62%)	13 (5.2%)	15 (6.0%)	15 (6.2%)	29 (5.8%)	28 (5.7%)

	ASSIST-1		ASSIST-2		Combined	
	Iclaprim (N = 183)	Linezolid (N = 191)	Iclaprim (N = 192)	Linezolid (N = 184)	Iclaprim (N = 375)	Linezolid (N = 375)
Eradication	0	1 (7.7%)	4 (26.7%)	5 (33.3%)	4 (13.8%)	6 (21.4%)
Pres. Eradication	10 (71.4%)	9 (69.2%)	8 (53.3%)	9 (60.0%)	18 (62.1%)	18 (64.3%)
Persistence	1 (7.1%)	1 (7.7%)	1 (6.7%)	0	2 (6.9%)	1 (3.6%)
Pres. Persistence	0	0	1 (6.7%)	0	1 (3.45%)	0
Indeterminate	0	2 (15.4%)	0	1 (6.7%)	0	3 (10.7%)
Missing	3 (21.4%)	0	1 (6.7%)	0	4 (13.8%)	0

The combined data set for iclaprim showed that eradication/presumed eradication rates for *S. aureus* increased from 71.1% at EOT to 77.7% at TOC. For MRSA the eradication/presumed eradication were high at 76.5% and 76.4% at the EOT and TOC visit, respectively. In contrast, eradication/presumed eradication rates for *S. aureus* decreased from 88.2% at EOT to 81.0% at TOC and for MRSA from 84.2% at EOT to 78.7% at TOC for linezolid. Similar differences were seen in the individual studies, with the trend being somewhat more pronounced in ASSIST-1 relative to ASSIST-2. Overall, similar trends also were reported in the two treatment groups in the ME_{PP} and ME_{MCE} populations.

Efficacy at TOC by MIC Value

Of the 500 patients randomized to iclaprim, 288 (284 with a MIC value) had a baseline isolate of *S. aureus*; of these 119 were MRSA. In the combined iclaprim group, 58 (56 with a MIC) had an infection with *S. pyogenes* and 31 (29 with a MIC) with *E. faecalis*. All other 44 causative baseline Gram-positive pathogens were found in an abundance of less than 10 per species. As a result, no meaningful analysis could be performed. There was no apparent correlation between the iclaprim MIC values and the clinical success rates for infections caused by the specified baseline pathogens, but the number of baseline isolates with higher MIC values was low (Table 5-15 and Table 5-16). From the pattern of response against these pathogens, no MIC value could be deduced above which the failure rate was high (of 8 patients with *S. aureus* isolates with a MIC ≥ 16 $\mu\text{g/mL}$ 7 were cures).

Table 5-15: Clinical Efficacy at TOC by Iclaprim MIC Value – *S. aureus* (total and MRSA) – Iclaprim Patients, MITT Population

MIC (µg/mL)	<i>S. aureus</i> (total), N = 284			<i>S. aureus</i> (MRSA), N = 119		
	Cure N (%)	Failure N (%)	Indeterminate N (%)	Cure N (%)	Failure N (%)	Indeterminate N (%)
0.015	3 (100%)	0	0	2 (100%)	0	0
0.03	7 (87.5%)	1 (12.5%)	0	7 (100%)	0	0
0.06	76 (81.7%)	9 (9.7%)	8 (8.6%)	36 (75.0%)	7 (14.6%)	5 (10.4%)
0.12	123 (82.6%)	13 (8.7%)	13 (8.7%)	42 (80.8%)	3 (5.8%)	7 (13.5%)
0.25	13 (76.5%)	2 (11.8%)	2 (11.8%)	2 (66.7%)	1 (33.3%)	0
0.5	4 (100%)	0	0	1 (100%)	0	0
1	1 (100%)	0	0	1 (100%)	0	0
8	1 (100%)	0	0	1 (100%)	0	0
≥16	7 (87.5%)	1 (12.5%)	0	3 (75.0%)	1 (25.0%)	0
Total	235	26	23	95	12	12

Table 5-16: Clinical Efficacy at TOC by Iclaprim MIC Value – *S. pyogenes* and *E. faecalis* – Iclaprim Patients, MITT Population

MIC (µg/mL)	<i>S. pyogenes</i> , N = 56			<i>E. faecalis</i> , N = 29		
	Cure N (%)	Failure N (%)	Indeterminate N (%)	Cure N (%)	Failure N (%)	Indeterminate N (%)
0.008	11 (91.7%)	0	1 (8.3%)	9 (81.8%)	1 (9.1%)	1 (9.1%)
0.015	10 (62.5%)	3 (18.8%)	3 (18.8%)	5 (71.4%)	0	2 (28.6%)
0.03	12 (92.3%)	0	1 (7.7%)	2 (100%)	0	0
0.06	7 (87.5%)	1 (12.5%)	0	1 (100%)	0	0
0.12	3 (60.0%)	2 (40.0%)	0	0	0	0
0.25	1 (50.0%)	1 (50.0%)	0	0	0	0
0.5	0	0	0	1 (100%)	0	0
4	0	0	0	1 (100%)	0	0
8	0	0	0	1 (100%)	0	0
≥16	0	0	0	4 (80.0%)	1 (20.0%)	0
Total	44	7	5	24	2	3

For both tables, the percentages are calculated as % of total isolates at each MIC value

Indeterminate includes indeterminate and missing. In ASSIST-1 failure and indeterminate were reported together. In ASSIST-2 indeterminate and missing were reported together.

Comparative Efficacy in Sub-Groups

The efficacy results of the combined Phase 3 program in specific subpopulations are summarized below. In general, these analyses demonstrate that the treatment effects were observed consistently across relevant sub-populations.

Ethnicity

Among the primary efficacy populations, there were no notable differences in clinical cure rates at TOC between the different ethnicities (Table 5-17).

Table 5-17: Clinical Cure at TOC Visit Stratified by Ethnicity, Combined ASSIST-1 and ASSIST-2 Studies

Ethnicity	ITT Population		PP Population	
	Iclaprim	Linezolid	Iclaprim	Linezolid
ALL	N = 500	N = 491	N = 415	N = 408
Cure, n (%)	411 (82.2%)	419 (85.3%)	383 (87.0%)	399 (97.8%)
Blacks	N = 29	N = 18	N = 23	N = 16
Cure, n (%)	24 (82.8%)	16 (88.9%)	22 (95.7%)	15 (93.8%)
Caucasian	N = 406	N = 416	N = 339	N = 348
Cure, n (%)	338 (83.3%)	357 (85.8%)	316 (93.2%)	341 (98.0%)
Hispanic	N = 54	N = 47	N = 45	N = 37
Cure, n (%)	40 (74.1%)	38 (80.9%)	39 (86.7%)	37 (100%)
Other	N = 11	N = 10	NA	NA
Cure, n (%)	9 (81.8%)	8 (80.0%)	NA	NA

The slightly lower cure rates seen in Hispanics is most likely due to the geographic difference: all Hispanics were in the North American subgroup, and the cure rate was overall slightly lower in North America than in the rest of the world (ROW). The same tendencies were seen in the linezolid treatment group.

Age

Among the primary efficacy populations, there were no notable differences between the treatment groups in clinical cure rates at TOC of patients below 65 years and those aged ≥ 65 years, as shown in Table 5-18.

Table 5-18: Clinical Cure at TOC Visit Stratified by Age, Combined ASSIST-1 and ASSIST-2 Studies

Age	ITT Population		PP Population	
	Iclaprim	Linezolid	Iclaprim	Linezolid
< 65 years	N = 422	N = 430	N = 355	N = 356
Cure, n (%)	349 (82.7%)	365 (84.9%)	327 (92.1%)	350 (98.3%)
≥ 65 years	N = 78	N = 61	N = 60	N = 52
Cure, n (%)	62 (79.5%)	54 (88.5%)	56 (93.3%)	49 (94.2%)

Gender

Among the primary efficacy populations, there were no notable differences between the 2 treatment groups in clinical cure rates at TOC of male and female patients, but slightly lower cure rates were observed in females, compared with males, in both treatment arms, as shown in Table 5-19.

Table 5-19: Clinical Cure at TOC Visit Stratified by Gender, Combined ASSIST-1 and ASSIST-2 Studies

Gender	ITT Population		PP Population	
	Iclaprim	Linezolid	Iclaprim	Linezolid
Male	N = 322	N = 329	N = 270	N = 278
Cure, n (%)	269 (83.5%)	285 (86.6%)	252 (93.3%)	273 (98.2%)
Females	N = 178	N = 61	N = 60	N = 52
Cure, n (%)	142 (79.8%)	134 (82.7%)	131 (90.3%)	126 (96.9%)

Geographical Region

Clinical cure was analyzed by geographic region, which were defined as the European Union (EU) (France, Germany, Latvia, Lithuania, Poland, Romania, United Kingdom,), US, and the ROW (Canada, Russia, and South Africa). Cure rates by region are shown in Table 5-20.

Table 5-20: Clinical Cure at TOC Visit Stratified by Geographic Region, Combined ASSIST-1 and ASSIST-2 Studies

Region	ITT Population		PP Population	
	Iclaprim	Linezolid	Iclaprim	Linezolid
European Union	N = 172	N = 170	N = 148	N = 150
Cure, n (%)	149 (86.6%)	153 (90.0%)	141 (95.3%)	149 (99.3%)
US	N = 195	N=190	N = 157	N=144
Cure, n (%)	151 (77.4%)	146 (76.8%)	139 (88.5%)	136 (94.4%)
Rest of World	N = 133	N = 131	N = 110	N = 114
Cure, n (%)	111 (83.5%)	120 (91.6%)	103 (93.6%)	114 (100%)

Markedly higher cure rates for both treatments were noted in the ITT and PP populations in patients from the EU and the ROW relative to the US. The reason for this finding is not clear, as the severity of infection according to clinical signs and symptoms was higher in the EU and the ROW, compared with the US, but geographical differences in the treatment of cSSSI could have contributed to this difference. Interestingly, for the ITT population in the US, the cure rate was higher in the iclaprim arm.

In all geographic regions and treatment arms, *S. aureus* was the most common organism, having been isolated from specimen in 49.6% to 66.8% of ITT patients. The proportion of *S. aureus* was comparable between treatment groups in each region. Bacteriological response rates against *S. aureus* in both treatment arms were similar within each region. For iclaprim and linezolid, the eradication/presumed eradication rates in the EU were 71.8% and 74.1%, respectively. In the US, these rates were 76.0% and 78.0%, and in the ROW, the percentages were 89.4% and 97.1%.

Against MRSA, the eradication/presumed eradication rates in the US were 75.6% and 80.5% for iclaprim and linezolid, respectively, whereas in the EU, the percentages were 72.2% and 65.2%. In the ROW population, the rates were 90.9% and 100%. It should be noted that in this region, the number of MRSA isolates was very low in both treatment arms. The

bacteriological response rates by pathogen analyzed by geographic region are shown in Table 5-21 for the combined ASSIST-1 and ASSIST-2 data set.

Table 5-21: By-Pathogen Bacteriological Response at TOC Visit – MITT Population by Geographic Region, Combined ASSIST-1 and ASSIST-2 Dataset only

	Europe		USA		Rest of World	
	Iclaprim	Linezolid	Iclaprim	Linezolid	Iclaprim	Linezolid
ITT Population	172	170	133	131	195	190
<i>S. aureus</i> , total ¹ , n (%)	92 (53.5%)	108 (63.5%)	129 (66.2%)	127 (66.8%)	66 (49.6%)	69 (52.7%)
Eradication	9 (9.8%)	8 (7.4%)	0 (0%)	1 (0.8%)	1 (1.5%)	0
Pres. Eradication	57 (62.0%)	72 (66.7%)	98 (76%)	98 (77.2%)	58 (87.9%)	67 (97.1%)
Persistence	19 (20.7%)	18 (16.7%)	3 (2.3%)	1 (0.8%)	0 (0%)	0 (0%)
Pres. Persistence	3 (3.3%)	0 (0%)	13 (10.1%)	6 (4.7%)	2 (3.0%)	0 (0%)
Colonization ²	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Indeterminate	1 (1.1%)	4 (3.7%)	7 (5.4%)	11 (8.7%)	0 (0%)	1 (1.4%)
Missing	3 (3.3%)	5 (4.6%)	8 (6.2%)	10 (7.9%)	5 (7.6%)	1 (1.4%)
MRSA, n (%)	18 (10.5%)	23 (13.5%)	90 (46.2%)	87 (45.8%)	11 (8.3%)	7 (5.3%)
Eradication	0 (0%)	1 (4.3%)	0 (0%)	0 (0%)	1(9.1%)	0 (0%)
Pres. Eradication	13 (72.2%)	14 (60.9%)	68 (75.6%)	70 (80.5%)	9 (81.8%)	7 (100%)
Persistence	5 (27.8%)	7 (30.4%)	2 (2.2%)	0 (0%)	0 (0%)	0 (0%)
Pres. Persistence	0 (0%)	0 (0%)	9 (10%)	5 (5.7%)	0 (0%)	0 (0%)
Colonization	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Indeterminate	0 (0%)	1 (4.3%)	6(6.7%)	7 (8.0%)	0 (0%)	0 (0%)
Missing	0 (0%)	0 (0%)	5 (5.6%)	5 (5.7%)	1 (9.1%)	0 (0%)
MSSA, n (%)	74 (43.0%)	85(50.0%)	37 (19%)	38 (20.0%)	55 (41.4%)	62 (47.3%)
Eradication	9 (12.2%)	7 (8.2%)	0 (0%)	1 (2.6%)	0(0%)	0 (0%)
Pres. Eradication	44 (59.5%)	58 (68.2%)	30 (81.1%)	27 (71.1%)	49 (89.1%)	60 (96.8%)
Persistence	14 (18.9%)	11 (12.9%)	1 (2.7%)	1 (2.6%)	0 (0%)	0 (0%)

	Europe		USA		Rest of World	
	Iclaprim	Linezolid	Iclaprim	Linezolid	Iclaprim	Linezolid
Pres. Persistence	3 (4.1%)	0 (0%)	3 (8.1%)	1 (2.6%)	2 (3.6%)	0 (0%)
Colonization ²	0 (0%)	1 (1.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Indeterminate	1 (1.4%)	3 (3.5%)	1 (2.7%)	4 (10.5%)	0 (0%)	1 (1.6%)
Missing	3 (4.1%)	5 (5.9%)	2 (5.4%)	4 (10.5%)	4 (7.3%)	1 (1.6%)
<i>S. pyogenes, total, n (%)</i>	33 (19.2%)	28 (16.5%)	3 (1.5%)	4 (2.1%)	22 (16.5%)	24 (18.3%)
Eradication	2 (6.1%)	3 (10.7%)	0 (0%)	0 (0%)	0(0%)	0 (0%)
Pres. Eradication	22 (66.7%)	23 (82.1%)	1 (33.3%)	1 (25.0%)	16 (72.7%)	21 (87.5%)
Persistence	8 (24.2%)	1 (3.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pres. Persistence	1 (3.0%)	0 (0%)	1 (33.3%)	1 (25.0%)	2 (9.1%)	0 (0%)
Colonization	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Indeterminate	0 (0%)	1 (3.6%)	1 (33.3%)	2 (50.0%)	2 (9.1%)	0 (0%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (9.1%)	3 (12.5%)
<i>S. agalactiae, total, n (%)</i>	4 (2.3%)	5 (2.9%)	2 (1.0%)	3 (1.6%)	2 (1.5%)	3 (2.3%)
Eradication	1 (25.0%)	3 (60.0%)	0 (0%)	0 (0%)	0(0%)	0 (0%)
Pres. Eradication	1 (25.0%)	2 (40.0%)	1 (50.0%)	3 (100.0%)	2 (100.0%)	1 (33.3%)
Persistence	1 (25.0%)	0 (0%)	1 (50.0%)	0 (0%)	0 (0%)	0 (0%)
Pres. Persistence	1 (25.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Colonization	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Indeterminate	0 (0%)	0 (0%)	0 (0%)	2 (0%)	0 (0%)	1 (33.3%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (33.3%)
<i>S. dysgalactiae subsp. equisimilis,</i>	6 (3.5%)	3 (1.8%)	0 (0%)	0 (0%)	1 (0.8%)	3 (2.3%)

	Europe		USA		Rest of World	
	Iclaprim	Linezolid	Iclaprim	Linezolid	Iclaprim	Linezolid
<i>total, n (%)</i>						
Eradication	0 (0%)	1 (33.3%)	0 (0%)	0 (0%)	1(100%)	0 (0%)
Pres. Eradication	4 (66.7%)	2 (66.7%)	0 (0%)	0 (0%)	0 (0%)	3 (100%)
Persistence	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pres. Persistence	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Colonization	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Indeterminate	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<i>E. faecalis,</i>						
<i>total, n (%)</i>	15 (8.7%)	13 (7.6%)	3 (1.5%)	3 (1.6%)	11 (8.3%)	12 (9.2%)
Eradication	4 (26.7%)	6 (46.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pres. Eradication	8 (53.3%)	5 (38.5%)	1 (33.3%)	1 (33.3%)	9 (81.8%)	12 (100%)
Persistence	2 (13.3%)	1 (7.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pres. Persistence	0 (0%)	0 (0%)	1 (33.3%)	0 (0%)	0 (0%)	0 (0%)
Colonization	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Indeterminate	0 (0%)	1 (7.7%)	0 (0%)	2 (66.7%)	0 (0%)	0 (0%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (18.2%)	0 (0%)
Pres.=presumed.						
Includes 5 isolates of unknown methicillin susceptibility identified by local laboratories but failed to grow in the central laboratory.						
Patient 554-01 had a BL S. aureus isolated which was eradicated at EOT. At TOC, a S. aureus was isolated; therefore, this case is shown as a colonization at TOC.						
Total pathogen percentages are calculated using the ITT population as the denominator.						
Outcome percentages are calculated using all outcomes for the BL pathogen as the denominator.						

Severity of Infection

Similar results were seen in patients stratified by severity of infection and SIRS, with clinical cure rates comparable to those reported in the primary efficacy analysis.

Patients with Mixed Infections

The Phase 3 combined study data set was analyzed to assess whether the clinical response at TOC varied among patient subgroups according to baseline infection type. The majority (about 50%) of patients had a single Gram-positive pathogen isolated at baseline. For this group, cure rates were identical in the iclaprim and linezolid arms (approximately 83%) as shown in Table 5-22. When two or more Gram-positive pathogens were identified at baseline, cure rates in patients from the linezolid arm were apparently higher than in those in the iclaprim arm (97.0% vs 63.0%), but the number of cases was low. Cure rates were also indistinguishable between treatment arms in mixed infections with Gram-negative pathogens involvement.

Table 5-22: Clinical Cure at TOC Stratified by Infection Type, Combined ASSIST-1 and ASSIST-2 Studies (MITT)

BL Microbiology	MITT Population	
	Iclaprim	Linezolid
Single Gram-positive	N=275	N=264
Cure, n (%)	230 (83.6%)	220 (83.3%)
Several Gram-positives	N=27	N=33
Cure, n (%)	17 (63.0%)	32 (97.0%)
Gram-positive plus at least 1 Gram negative	N=72	N=78
Cure, n (%)	61 (84.7%)	68 (87.2%)
Gram-positive plus at least 1 anaerobe	N=1	N=0
Cure, n (%)	1(100%)	0

6. OVERVIEW OF CLINICAL SAFETY

6.1 Critical Aspects of Safety Population and the Extent of Exposure

All safety tabulations and listings are based on the Safety (ITT) population of the two Phase 3 cSSSI studies, which was defined as all subjects who received at least one dose of study medication. Overall, 500 patients received iclaprim, while 491 received linezolid. One patient in ASSIST-1 (100-11) was randomized to linezolid but received iclaprim. As per the SAP, this patient was included in the linezolid population for efficacy but in the iclaprim group for safety. Conversely, in ASSIST-2, one patient was randomly assigned to the iclaprim group but actually received linezolid; therefore, this patient was included in the iclaprim group for efficacy and in the linezolid group for safety.

In both studies, exposure to study drug was comparable between treatment groups in the ITT population (Table 6-1). Fewer than 10% of the patients received study medication for less than the protocol-defined 10 to 14 days. Treatment for 10 days was reported for 68.2% of the patients in ASSIST-1 and 55.3% in ASSIST-2. There was a tendency for a higher percentage of patients to receive treatment for more than 10 days in the second study (25.4% in ASSIST-1 vs. 37.2% in ASSIST-2).

Table 6-1: Summary of Extent of Exposure: Number of Treatment Days – ITT (Safety) Population

Number of Treatment Days	ASSIST-1		ASSIST-2	
	Iclaprim	Linezolid	Iclaprim	Linezolid
	(N = 250)	(N = 247)	(N = 250)	(N = 244)
	n (%)	n (%)	n (%)	n (%)
1	0	0	5 (2.0%)	0
2	4 (1.6%)	2 (0.8)	2 (0.8%)	2 (0.8%)
3	4 (1.6%)	0	0	1 (0.4%)
4	2 (0.8)	1 (0.4%)	1 (0.4%)	5 (2.1%)
5	0	0	3 (1.2%)	3 (1.2%)
6	1 (0.4%)	1 (0.4%)	2 (0.8%)	4 (1.6%)
7	5 (2.0%)	1 (0.4%)	3 (1.2%)	0
8	3 (1.2%)	4 (1.6%)	1 (0.4%)	3 (1.2%)
9	1 (0.4%)	3 (1.2%)	2 (0.8%)	0
10	164 (65.6%)	175 (70.9%)	134 (53.6%)	139 (57.0%)
11	7 (2.8%)	9 (3.6%)	20 (8.0%)	28 (11.5%)
12	7 (2.8%)	10 (4.0%)	17 (6.8%)	13 (5.3%)
13	7 (2.8%)	1 (0.4%)	5 (2.0%)	4 (1.6%)
14	41 (16.4%)	38 (15.4%)	52 (20.8%)	41 (16.8%)
15	4 (1.6%)	2 (0.8)	3 (1.2%)	1 (0.4%)

6.2 Adverse Events

6.2.1 Overview

The percentage of patients experiencing any category of treatment-related AEs was comparable between treatment groups (Table 6-2). Half of the patients in either treatment group reported AEs, whereas the proportion of patients with study-drug related AEs was slightly lower in the iclaprim group (22.6%), compared with the linezolid group (27.9%). Approximately 10% more patients in ASSIST-2 reported treatment-emergent AE (TEAEs) and drug-related AEs, compared with ASSIST-1; this finding might be a consequence of regional differences in reporting practice and the higher proportion of US patients in ASSIST-2. There were no apparent differences between the studies in the number of patients with SAEs, severe AEs, or AEs leading to discontinuation.

Table 6-2: Overview of Treatment-Emergent AEs – ITT Population

Number (%) of Patients Experiencing	Combined Phase III Data							
	Iclaprim (N = 500)				Linezolid (N = 491)			
	All AEs		Related		All AEs		Related	
Any TEAE	245	(49.0%)	113	(22.6%)	249	(50.7%)	137	(27.9%)
Any SAE	20	(4.0%)	1	(0.2%)	16	(3.3%)	0	--
Any severe TEAE	34	(6.8%)	7	(1.4%)	34	(6.9%)	9	(1.8%)
Any TEAE causing permanent discontinuation ^a	11	(2.2%)	6	(1.2%)	6	(1.2%)	6	(1.2%)
Deaths	6	(1.2%)	0	--	1	(0.2%)	0	--

^a In ASSIST-1 patient 311-04 (consent withdrawn) was also included in Any AE causing permanent discontinuation

A higher proportion of patients from North American sites reported an AE than did those from the ROW (North America: 132/200 [66.0%] for iclaprim and 140/195 [71.8%] for linezolid; ROW: 113/300 [37.7%] for iclaprim and 109/296 [36.8%] for linezolid). A similar regional difference for study-drug related AEs was apparent (North America: 83/200 [41.5%] for iclaprim and 99/195 [50.8%] for linezolid; ROW: 30/300 [10.0%] for iclaprim and 38/296 [12.8%] for linezolid).

6.2.2 Overall AEs

Table 6-3 shows all AEs reported for at least 2% of patients in either treatment group. Generally the frequency of reported AEs was similar in both treatment groups. More patients in either treatment group experienced AEs associated with the gastrointestinal system and laboratory investigations (both approximately 18%) than other categories. The four most frequently reported AEs in the iclaprim group were increased ALT (6.6%), increased AST (6.4%), headache (6.0%), and nausea (6.0%). The same four AEs most frequently reported for the linezolid cohort were nausea (7.9%), followed by increased ALT (6.3%), headache (5.7%), and

increased AST (5.3%). Treatment differences in the incidence of individual events were most marked for dysgeusia (11 patients in the linezolid group, compared with only 2 patients in the iclaprim group) and body temperature increase (10 patients in the iclaprim group and only 3 in the linezolid group).

Table 6-3: AEs Reported for At Least 2% of Patients in Either Treatment Group – ITT Population

System Organ Class and Preferred Term	Combined Phase III Data	
	Iclaprim N = 500	Linezolid N = 491
Patients with at least one AE, n (%)	245 (49.0%)	249 (50.7%)
Blood and lymphatic system disorders	29 (5.8%)	35 (7.1%)
Anemia	17 (3.4%)	17 (3.5%)
Gastrointestinal disorders	87 (17.4%)	91 (18.5%)
Constipation	27 (5.4%)	19 (3.9%)
Diarrhea	29 (5.8%)	22 (4.5%)
Nausea	30 (6.0%)	39 (7.9%)
Vomiting	12 (2.4%)	12 (2.4%)
General disorders and administration site conditions	77 (15.4%)	56 (11.4%)
Pyrexia	26 (5.2%)	10 (2.0%)
Investigations	92 (18.4%)	86 (17.5%)
ALT increased	33 (6.6%)	31 (6.3%)
AST increased	32 (6.4%)	26 (5.3%)
Body temperature increased	10 (2.0%)	3 (0.6%)
C-reactive protein increased	11 (2.2%)	6 (1.2%)
Platelet count increased	5 (1.0%)	10 (2.0%)
Musculoskeletal and connective tissue disorders	27 (5.4%)	19 (3.9%)
Pain in extremity	11 (2.2%)	8 (1.6%)
Nervous system disorders	55 (11.0%)	51 (10.4%)
Dizziness	16 (3.2%)	10 (2.0%)
Dysgeusia	2 (0.4%)	11 (2.2%)
Headache	30 (6.0%)	28 (5.7%)
Psychiatric disorders	32 (6.4%)	27 (5.5%)
Anxiety	11 (2.2%)	5 (1.0%)
Insomnia	15 (3.0%)	17 (3.5%)
Skin and subcutaneous tissue disorders	55 (11.0%)	46 (9.4%)
Pruritus	20 (4.0%)	18 (3.7%)
Rash	14 (2.8%)	17 (3.5%)
Vascular disorders	21 (4.2%)	26 (5.3%)
Hypertension	12 (2.4%)	10 (2.0%)
Total number of patient events	872	816

Data relate to numbers of patient events and percentages of patients.

These findings demonstrate that iclaprim at the therapeutic dose of 0.8 mg/kg administered as an IV infusion over 30 minutes, is safe and well tolerated in patients with cSSSI.

6.2.2.1 AEs Possibly or Probably Related to Study Treatment

Overall, more patients in the linezolid group (27.9%) than the iclaprim group (22.6%) experienced study drug-related AEs. This trend toward higher drug-related AEs in the linezolid group, compared with the iclaprim group, was apparent in both ASSIST-1 and ASSIST-2. The different types of study-drug related AEs occurred at similar frequencies in the two treatment groups and were more commonly (>7%) associated with the gastrointestinal system and laboratory investigations. Table 6-4 shows the study drug-related AEs that were reported in greater than 1% of patients in either treatment group.

Table 6-4: AEs Reported as Possibly or Probably Related to Study Drug in At Least 1% of Patients in Either Treatment Group – ITT Population

System Organ Class	Combined Phase 3 Data	
	Iclaprim	Linezolid
Preferred Term	N = 500	N = 491
Gastrointestinal disorders	37 (7.4%)	51 (10.4%)
Constipation	9 (1.8%)	4 (0.8%)
Diarrhoea	16 (3.2%)	17 (3.5%)
Dry mouth	1 (0.2%)	5 (1.0%)
Nausea	12 (2.4%)	27 (5.5%)
Vomiting	4 (0.8%)	5 (1.0%)
General disorders and administration site conditions	21 (4.2%)	19 (3.9%)
Pyrexia	7 (1.4%)	3 (0.6%)
Investigations	42 (8.4%)	48 (9.8%)
ALT increased	20 (4.0%)	25 (5.1%)
AST increased	18 (3.6%)	23 (4.7%)
Hepatic enzyme increased	5 (1.0%)	4 (0.8%)
Liver function test abnormal	5 (1.0%)	0
Nervous system disorders	24 (4.8%)	32 (6.5%)
Dizziness	6 (1.2%)	5 (1.0%)
Dysgeusia	2 (0.4%)	10 (2.0%)
Headache	15 (3.0%)	11 (2.2%)
Somnolence	1 (0.2%)	6 (1.2%)
Skin and subcutaneous tissue disorders	21 (4.2%)	22 (4.5%)
Pruritus	11 (2.2%)	12 (2.4%)
Rash	6 (1.2%)	6 (1.2%)
Number of patient events possibly or probably related to study medication	252	315

Data relate to numbers of patient events and percentages of patients.

6.2.2.2 Comparative Safety in Sub-Groups

Subgroup analyses were performed for the overall frequency of AEs and individual AEs. Generally, no significant differences were seen between the treatment groups and in the rates of TEAEs, drug-related AEs, serious AEs, severe AEs,, or AE-related treatment discontinuations.

Ethnicity

More TEAEs and drug-related AEs were observed in Hispanics as compared to Caucasians. This difference was probably due to geography: all Hispanics were from the North American subgroup, in which the AE rate was numerically higher relative to ROW. The same trend occurred in the linezolid treatment group. A similar, although less obvious, pattern appeared in African-Americans, about 2/3 of whom were recruited in the US. The numbers in the “Others” group were too small to enable any conclusions.

Age

An increase in the rate of serious AEs and, severe AEs as well as in discontinuations due to AEs, was observed in patients with increasing age. For patients at or above 75 years, an increase in the rate of all AE categories was noted but the rate of drug-related AE's did not increase.

Analysis of individual AEs by preferred term did not reveal any major differences between the treatment arms for the different age groups. In addition, this analysis did not reveal any major differences in the different age groups, except for diarrhea, which seemed to occur slightly more often in the 50 – 64 year age group. In the 75-year-and-above age group, some AEs seemed to occur with a slightly higher frequency, but again, the total number of events was low. Overall, none of the AEs occurred more frequently in any specific age group.

Gender

The frequency of all AEs was slightly higher in females than in males. In the iclaprim treatment group, a higher rate of AE-related discontinuations was seen in females as well, although the total number of events was too low to draw any meaningful conclusions. Analysis of individual AEs by preferred term did not reveal any major differences for the different gender groups with the exception of a higher

frequency of such side effects as nausea, gastrointestinal AEs, pruritus, anemia, dizziness, and anxiety in females relative to males.

Geographic Distribution

Both ASSIST-1 and ASSIST-2 included an international population of patients with cSSSI. In ASSIST-1, about 80% and 20% of patients were from Eastern Europe and North America, respectively, whereas the 59% and 41% of patients participating in ASSIST-2 were from North America and ROW (33%=Eastern Europe, 5.6%=South Africa and 2.4% from the European Union).

Overall, there was a greater frequency of AEs in ASSIST-2. However, analysis of AE occurrence by system organ class revealed no differences between the iclaprim and linezolid groups within each study.

Despite the disparities in the overall state of health in the subpopulations of cSSSI patients, iclaprim exhibited a safety profile comparable to that of linezolid in both studies. The frequency of AEs for each system organ class, although different in the two studies, was consistent for both study drugs, and the incidence rates were similar. Taken together, these results demonstrate that iclaprim compares favorably with linezolid with respect to both efficacy and safety.

6.2.3 SAEs

In ASSIST-1, SAEs (other than death) were reported for six patients in the iclaprim group and four patients in the linezolid group. The investigator determined that all SAEs were unrelated to the study drug, and all patients recovered. In ASSIST-2, eight and ten patients in the iclaprim and linezolid groups, respectively, reported SAEs other than death. All but one SAE, which was considered to be

possibly treatment related (elevated ALT in one iclaprim-treated patient), were determined to be unrelated to study medication.

Each SAE was reported in one patient only, with the exception of pneumonia (three patients treated with iclaprim, one patient treated with linezolid), abdominal abscess (one patient in each treatment group), and deep vein thrombosis (one patient in each treatment group).

6.2.4 AEs Leading to Permanent Discontinuation of Study Drug

The frequency of AEs leading to permanent discontinuation of the study drug did not differ between the two treatments, (11 [2.2%] patients in the iclaprim group of which 3/11 patients died; and 6 [1.2%] patients in the linezolid group). Most of the AEs that led to the discontinuation of study drug were reported in a single patient. Only sepsis and cardiac failure were reported for two patients in the iclaprim group, and a prolonged QTc interval was reported for two patients in each treatment group.

Six patients (1.2%) in the iclaprim group were reported to have a total of 7 AEs that were judged to be treatment-related, leading to discontinuation of the study drug. The investigator considered 3 AEs (1 case of infusion-related reaction, two cases of prolonged QTc interval) likely to be related to study drug, and 4 events (one each of nausea, infusion-related reaction, rash, and face swelling) to be possibly related. Six patients (1.2%) in the linezolid group were reported to have a total of 11 treatment-related AEs leading to discontinuation of study drug, with a single patient experiencing 6 of the events. Most of the AEs in this treatment group (10/11) were possibly related to the study drug; the investigator judged the remaining AE (prolonged QTc interval) as severe and probably related to the study drug.

6.2.5 Deaths

Six deaths were reported during the ASSIST-1 study: five in the iclaprim group and one in the linezolid group. Two deaths were recorded in ASSIST-2: one in the iclaprim group and one in the linezolid group (Table 2.7.4-61). The investigators judged all deaths to be unrelated to study drug.

The investigator, the Sponsor, and the external safety officer concluded that all deaths in ASSIST-1 and ASSIST-2 were related to serious underlying diseases rather than to the study drugs. All deaths occurred in Eastern European centers and had different causes. There was no indication that these deaths were concomitant with cardiovascular system-related AEs; each event was thoroughly assessed by the DMC, and no concerns were raised. A review of the available ECGs for these patients did not reveal any prior abnormal ECG morphology or significant change in QTc that could have been attributable to iclaprim. Additionally, four deaths occurred well beyond 5 half-lives of the drug (3-12 days after the last dose of iclaprim). The causes of the 6 (1.2%) deaths in the iclaprim group were sepsis or septic shock (2 patients), alcoholic cardiomyopathy (1 patient), acute cardiac failure (1 patient), acute renal failure (1 patient), and colon cancer (1 patient).

6.2.6 Clinical Laboratory Values

In the Phase 3 studies, there were no obvious differences between the study treatments in the hematologic parameters, except for an increase in platelet count, which was somewhat more pronounced in the iclaprim arm. This change is linked to the body's inflammatory response to infection. Leukocyte counts were elevated in both treatment groups at baseline, which is consistent with the presence of an infectious disease.

6.2.6.1 Hepatic Parameters

The pooled results for the patients from ASSIST-1 and ASSIST-2 suggest that twice-daily IV administration of iclaprim caused an elevation in ALT or AST from normal baseline levels to more than 3x ULN in 21 individuals (4.2% of the population and 5.5% of patients with normal baseline values), with the majority of these elevations occurring after completion of treatment. For 23/108 (21%) individuals with an elevated ALT or AST at baseline, a value above 3x ULN was observed during the course of the study. Of these 23 individuals, 19 had a further increase of at least one grade that occurred during treatment or at follow-up, and 4 had no appreciable change from their baseline values. No instances of liver failure were observed among any patients with normal or elevated baseline values.

An independent hepatologist reviewed all available clinical data and concluded that iclaprim has a favorable hepatic safety profile and is well tolerated. The overall results obtained from IV studies indicated that iclaprim exhibits a dose-dependent, reversible effect on ALT/AST levels. In this respect, iclaprim was similar to vancomycin and linezolid in the treatment of hospitalized patients with severe skin infection. In the case of IV iclaprim, the incidence of elevations greater 3x ULN in a large group of patients with serious skin infections was low, with no cases of hepatic failure as defined by Hy Zimmerman's Law or the modified Hy's Law (ie, with concomitant rise in serum bilirubin). Most of the ALT/AST elevations occurred after the course of treatment was completed, and there was no evidence that patients with baseline LFT abnormalities developed any signs of hepatic impairment.

6.2.7 *QT Prolongation Analysis*

Iclaprim exhibits a potential to cause a dose-dependent, transient, and rapidly reversible, prolongation of the QT interval. A comprehensive review of the cardiac safety of iclaprim was performed using data from all sources that assessed QTc prolongation following single or multiple doses. Furthermore, an

independent cardiologist analyzed the cardiac AEs and effects on QTc in all studies. The report concluded that there were no cardiac SAEs or non-ECG cardiac AEs that were directly related to the acute use of iclaprim in the cSSSI population for up to 14 days at a dosage of 0.8 mg/kg b.i.d. However, there is a relationship between increased QTc and use of iclaprim relative to linezolid. In pooled data from the Phase 3 trials, the mean increase in QTcF in the iclaprim group on Day 1 was about 9 msec compared to a mean increase in the linezolid group of about 3 msec. At Day 4 \pm 1, the iclaprim group showed a mean QTcF increase of about 11 msec, compared with the linezolid group of approximately 6 msec.

Patients with traditional risk factors such as gender, age, and BMI showed a pattern similar to the population as a whole. The QT prolongation was similar in patients irrespective of previous cardiac history. The iclaprim group had a consistently higher mean QTcF and a slightly higher number of outliers, compared with linezolid. The pooled data do not indicate that there are any major subgroups that might be particularly susceptible to this increased risk. However, caution is recommended when using iclaprim with other QT prolonging medications or in patients with on-going proarrhythmias or long QT syndrome.

7. BENEFITS AND RISKS

7.1 Dosing Recommendations

The efficacy of iclaprim as an antibacterial agent appears to be exposure dependent, according to animal PK/PD models, which showed that AUC/MIC is the best predictor of response. In humans, exposure is related linearly to the dose. The Phase 2 study in cSSSI demonstrated that the 0.8 mg/kg provides comparable efficacy to vancomycin. The double dose of 1.6 mg/kg did not further increase the clinical cure rate of about 90%. Therefore, 0.8 mg/kg twice a day appears to be a reasonable therapeutic

dose in cSSSI with at least a 2-fold safety margin. This proven safety margin provides the rationale for dose-adjustments only in cases in which exposure can exceed a factor of 2 as compared to the recommended dose.

As was seen in Phase 1 clinical studies, the prolongations observed in the QTc intervals in ECGs appear to be dependent on dose and concentration. Maximal QTc prolongations were observed around T_{\max} ; however, the effects were transient (1-4 hours) and fully reversible, as would be expected. The first indications of QTc prolongation were detected with the 0.8 mg/kg dose. The placebo-corrected mean maximal prolongation around C_{\max} was 10 msec on average. Such QTc effects are not considered to be clinically meaningful so long as no additional signs of arrhythmia occur (eg, increased frequency of ventricular polymorph extra beats).

There was a correlation between the occurrence of AEs and iclaprim dose. In general, iclaprim-treated healthy subjects reported approximately 30% more AEs, compared with placebo-treated controls.

Above the 1.6 mg/kg dose, there was an increase in the rate and severity of AEs. Up to and including the 1.6 mg/kg dose, the distribution and intensity of AEs was comparable across all studies and all iclaprim doses used (ie., 0.4 mg/kg, 0.8 mg/kg and 1.6 mg/kg). Repeated twice-daily administration of 1.6 mg/kg iclaprim for more than 10 days resulted in occasional increases of $>3\times$ ULN in liver transaminases.

Taken together, these results suggest that the recommended dose and dosing regimen for IV iclaprim of 0.8 mg/kg *q12h*, (at an infusion concentration of ≤ 1 mg/ml), provides the optimal balance between safety and efficacy. In severely obese patients, the dose should be limited to 100 mg per treatment. Patients with a moderate degree of liver impairment (classified as Child-Pugh Grade B) should receive

half of the recommended body weight-adjusted iclaprim dose. Renal impairment does not require any dose adjustment. The duration of iclaprim treatment depends on the clinical course of the basic infection but should not exceed 14 consecutive days. Using this treatment and dosing scheme, iclaprim appears to be a safe and efficacious alternative for the treatment of cSSSI.

7.2 Benefit-Risk Ratio

Results from the Phase 3 studies showed that IV treatment of iclaprim in cSSSI may confer the following advantages:

- Iclaprim has a focused Gram-positive spectrum with potent *in vitro* activity against most Gram-positive causative pathogens of cSSSI. In multinational surveillance and clinical studies, the MIC₉₀ for *S. aureus* was 0.12 µg/ml; for MRSA, it was 0.12 µg/ml (includes HA- and CA-MRSA); for *S. pyogenes*, it was ≤ 0.03 µg/ml, for *S. agalactiae*, it was 0.25 µg/ml, and the MIC distribution for *E. faecalis* was bimodal, with a MIC₅₀ of 0.06 µg/ml;
- Against *S. aureus*/MRSA and β-hemolytic streptococci, iclaprim was rapidly bactericidal and showed a post-antibiotic effect at sub-MIC concentrations;
- The product of a rational optimization program, iclaprim belongs to the class of selective DHFR inhibitors, which has proven to be efficacious and safe in over 4 decades of clinical use. The mechanism of action of DHFR inhibitors resulting in a shutdown of RNA, DNA and protein synthesis would be expected to lead to a decrease in toxin production. If approved, iclaprim would be the first DHFR inhibitor indicated for the treatment of cSSSI infections caused by MRSA, offering physicians the option of a new class of antibacterial agent;

- Iclaprim has a low propensity for resistance development and shows evidence of activity against organisms resistant to other drugs used to treat MRSA, including vancomycin, linezolid, and daptomycin;
- Iclaprim has a favorable PK profile, low propensity for interactions, and high and rapid tissue penetration;
- Iclaprim shows dose-linear pharmacokinetics, with no accumulation upon repeated administration. No clinically relevant differences are observed based on age, race, or gender;
- No dose adjustment is necessary for renal and mild hepatic impaired patients, and no monitoring of plasma levels is needed. Dose adjustments are necessary only in patients with moderate hepatic impairment (Child-Pugh Class B, 0.5 x dose) and high BMI, for whom a single dose should not exceed 100 mg;
- Iclaprim shows a low potential for drug-drug interactions;
- Iclaprim demonstrates non-inferiority to linezolid in the ITT, PP and MCE populations;
- Iclaprim demonstrates high bacterial eradication/presumed eradication rates and associated clinical efficacy against both *S. aureus* and MRSA that were similar to linezolid;
- In the two Phase 3 trials, the overall safety profile of iclaprim was comparable to that of linezolid. Most AEs were mild or moderate and unrelated to the study drug. The overall incidence of drug-related AEs was lower in the iclaprim cohort than in the linezolid group (22.6% vs. 27.9%).

The aforementioned benefits must be weighed against the following risks that may be associated with iclaprim therapy:

- Iclaprim infusion was associated with dose-dependent, T_{\max} -related, transient, and reversible QTc prolongation. However, an independent cardiac safety assessment of data from both Phase 3 studies concluded that there were no severe cardiac AEs or non-electrocardiographic cardiac AEs directly related to the use of iclaprim. Nevertheless, there was a relationship between increased QTc and iclaprim therapy, compared with the use of linezolid. The mean prolongation of QTc from baseline was 6-8 msec and 4-6 msec higher with iclaprim than with linezolid (QTcB and QTcF). QTc prolongations of >30 msec were more frequent with iclaprim, but the number of patients with prolongations of >60 msec was small and similar in both treatment groups. No differences between subgroups (ie, age, gender, BMI, cardiovascular history, baseline QTc, study day) were apparent, and the effect of concomitant medications was small and comparable between iclaprim and linezolid. QT interval prolongations are not uncommon in other classes of antibacterials, most notably the macrolides and quinolone classes. The cardiac safety report concluded that QTc increases seen with iclaprim at the therapeutic dose compare favorably to these classes.
- LFT increases were observed with iclaprim treatment in the Phase 3 studies at about the same frequency as with the comparator linezolid. No cases of hepatic failure or concomitant increase in bilirubin were observed.

In summary, the favorable benefit-to-risk ratio confirms iclaprim's profile as a safe, potent antibiotic that could be useful for the treatment of cSSSI.

8. CONCLUSION

Iclaprim is a new antibacterial agent with an anti-Gram-positive spectrum covering the clinically relevant cSSSI pathogens, particularly MRSA. It represents the second generation of the well-established DHFR inhibitor class represented for over 4 decades by trimethoprim. Using structural information of the target enzyme, the design of iclaprim resulted in a superior level of potency, thus allowing the use of iclaprim without combining its administration with a sulfonamide as well as overcoming the resistance conferred by a DHFR mutation induced by TMP. The clinical cure rates observed with iclaprim, supported by its activity against multi-resistant strains of *S. aureus*, indicate that iclaprim will meet an important therapeutic need. The safety profile of iclaprim is similar to other antibiotics. Therefore, iclaprim appears to offer a clinically well-balanced benefit/risk ratio. Furthermore, it represents a differentiated class of safe, well-established, antibacterials and provides a focused Gram-positive spectrum with a low propensity for resistance development.

In a time when the epidemiology of multi-resistant Gram-positive pathogens is becoming a serious medical problem, MIC creep is increasing, and vancomycin resistance of MRSA strains is burgeoning, iclaprim offers an alternative treatment option with a mechanism unlike that of other anti-MRSA drugs. Moreover, resistance to these newer antibiotics is already emerging, and safety problems are becoming more obvious. For instance, although linezolid is restricted to refractory patients or those who have failed first-line therapy, an increasing proportion of MRSA pathogens are now resistant to linezolid (Weigelt et al., 2005). Indeed, iclaprim is active on vancomycin-, linezolid-, and daptomycin-resistant strains *in vitro*. Thus, iclaprim addresses an important and mounting public health need and has the potential to complement the limited remaining therapeutic options at a time of increasing prevalence of multi-resistant pathogens that can no longer be treated with first- and second-line cSSSI therapy.

Another issue is the growing prevalence of community-acquired MRSA (CA-MRSA)-associated cSSSI. The USA300 clone is a cause of community-acquired infections and has now been found to induce nosocomial infections as well (Al Rawahi et al., 2008). Although CA-MRSA strains demonstrate high *in vitro* susceptibility to TMP-SMX, a drug with related mode of action to iclaprim, there are concerns that the sulfamethoxazole component is unable to achieve the required proportional tissue penetration to be synergistically effective with the TMP component in cSSSI. This absence of proportionality may explain the much lower than expected clinical efficacy of this compound. Finally, iclaprim is active against Group A streptococci (GAS), a common cause of skin infections and abscesses, for which TMP-SMX is ineffective.

A high incidence of AEs, as well as some severe AEs, is a problematic factor for most antibiotics active against MRSA and used for the treatment of cSSSI. For example, linezolid has caused such events as myelosuppression and neuropathy; interactions with other drugs, such as selective serotonin reuptake inhibitors, also have been described. (Narita et al., 2007; Hachem et al., 2003)

The antibiotic daptomycin has the potential to cause musculoskeletal disorders (Patel et al., 2007).

Iclaprim's safety profile compares favorably with some currently marketed systemic antibiotics that treat cSSSI. The drug is safe and well-tolerated, and it exhibits a low propensity for drug-drug interactions. In contrast to the currently marketed drugs, no patient monitoring is required. Moreover, no dose-adjustments are required for patients with renal dysfunction.

In summary, iclaprim has the potential to be a valuable new option in the treatment of cSSSI. Its preclinical and clinical development programs have demonstrated:

- Non-inferior efficacy in cSSSI, compared with linezolid;

- A spectrum of activity that is at least equivalent to the best currently available antibiotics – including linezolid – against Gram-positive pathogens relevant for cSSSI;
- *In vitro* activity against multiresistant pathogens, including pathogens resistant to co-trimoxazole, linezolid, daptomycin and vancomycin (as well as such antibiotics as the quinolones);
- Comparable safety and tolerability to currently marketed systemic antibiotics;
- Bactericidal activity and good tissue penetration;
- Low propensity for resistance development.

Therefore, iclaprim can be considered an important advance in the treatment of cSSSI. More than 4 decades of clinical use of TMP and TMP/SMX (the second most common antibacterial prescribed, with millions of safe exposures) confirm the safety and efficacy of this class of antibiotics.

Iclaprim has a focused spectrum, a low propensity for resistance development, and due to its differentiated mechanism of action, the impact on resistance of other agents can be expected to be low. Inhibition of protein synthesis, combined with cidal activity, may be important in some infections by MRSA and Group A Streptococci. Iclaprim is also orally bioavailable, and development of an oral formulation is ongoing. In conclusion, these features mark iclaprim as a potentially powerful alternative for the treatment of Gram-positive infections, including those caused by MRSA.

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