Iclaprim for the Treatment of Complicated Skin and Skin Structure Infections

FDA Briefing Document for
Anti-Infective Drugs Advisory Committee Meeting
November 20, 2008

Table of Contents

I.	**BACKGROUND**	3
II.	**CLINICAL DEVELOPMENT**	3
III.	**PHARMACOLOGY-TOXICOLOGY**	4
IV.	**CLINICAL MICROBIOLOGY**	6
V.	**CLINICAL PHARMACOLOGY**	10
VI.	**EFFICACY**	11
VII.	**SAFETY**	21
VIII.	**ISSUES FOR DISCUSSION**	30

I. BACKGROUND

Arpida AG submitted New Drug Application NDA 22-269, for iclaprim on March 18, 2008. Iclaprim is a dihydrofolate reductase (DHFR) inhibitor, similar in mechanism of action to trimethoprim. The proposed indication for iclaprim is treatment of adults with complicated Skin and Skin Structure Infections (cSSSI) caused by susceptible strains of the following Gram-positive microorganisms: *Staphylococcus aureus* including methicillin-susceptible and resistant strains, *Streptococcus pyogenes*, *Enterococcus faecalis*, and *Streptococcus agalactiae*.

The drug product is a mesylate salt of the active ingredient, iclaprim. Iclaprim is manufactured in ampoules containing a 64 mg/5 mL concentrated solution for intravenous use. The concentrated solution is diluted in 250 mL of 0.9% sodium chloride, 5% dextrose, or Ringer's solution and infused over 30-45 minutes. The dose studied in clinical trials is 0.8 mg/kg of iclaprim base administered twice daily for 8-14 days.

This briefing document summarizes the information submitted in the iclaprim NDA. The last section of this document (**VIII**) highlights the expected issues for advisory committee discussion.

II. CLINICAL DEVELOPMENT

Arpida AG submitted an investigational new drug application (IND 68,663) for iclaprim in February 2005. Much of the clinical development (phase 1 and phase 2 studies) was conducted in Europe prior to submission of the IND. The first study proposed under the IND was a phase 3 trial of intravenous iclaprim for the treatment of cSSSI, the ASSIST-1 study.

The table on the following page provides a summary description of the studies conducted with iclaprim in patients with complicated skin and skin structure infections. Both of the phase 3 studies of iclaprim for the treatment of cSSSI were conducted under the IND and are multi-national studies including US centers. The design and results of these studies are discussed in detail in later sections of this briefing document.

Table 2.1: Overview of Clinical Efficacy Studies

Study	Study Dates No. of Centers Study Location	Phase/Study Design	Iclaprim Dose, Regimen Comparator	Total Pts Iclaprim IV or comparator
AR-100-SSTI-001	5/2002 – 6/2003 7 centers Germany, Latvia, Lithuania	Phase 2/ Randomized, evaluator-blind, active control	Iclaprim: 0.8 or 1.6 mg/kg BID over 30 min × 10 days Vancomycin: 1 g IV BID over 60 min ×10 days	N=92 Iclaprim N=62 0.8 mg/kg N=30 1.6 mg/kg N=32 Vancomycin N=30
ICLA-08-CSI1 ASSIST-1	6/2005-08/2006 9 centers North America and Europe	Randomized, evaluator-blind, active control	Iclaprim: 0.8 mg/kg q12h over 30 min × 10-14 days Linezolid: 600 mg q12h over 30 min × 10-14 days	N=497 (105 N.A.; 392 Europe) ITT/Safety: N=250 (iclaprim) N=247 (linezolid)
ICLA-09-CSI2 ASSIST-2	4/2006-4/2007 96 centers North America, Europe, and South Africa	Randomized, evaluator-blind, active control	Iclaprim: 0.8 mg/kg q12h over 30 min × 10-14 days Linezolid: 600 mg q12h over 30 min × 10-14 days	N=494 (290 N.A.; 204 ROW) ITT/Safety: N=250 (iclaprim) N=244 (linezolid)

III. PHARMACOLOGY-TOXICOLOGY

Safety pharmacology studies of single doses of iclaprim produced no biologically significant pharmacodynamic effects on the respiratory and nervous systems in rodents at the doses tested. *In vitro* evidence of selective and reversible inhibition of hERG channel-mediated potassium current with an IC_{50} of 0.86 μM was demonstrated, but *in vivo* effects in telemetrized dogs administered single IV doses of up to 10 mg/kg iclaprim mesylate (HED = 5 mg/kg) revealed decreases in heart rate and no alterations to ECG waveforms. In general toxicology studies of iclaprim mesylate in marmosets, decreases in heart rate and prolongation of QT interval by as much as 9-18 msec were seen at an IV dose of 50/40 mg/kg for 2 weeks (approximately 3 times clinical daily systemic exposure) and at an oral dose of 100 mg/kg/day for 13 weeks (approximately 6 times clinical daily systemic exposure).

A standard battery of genetic toxicology tests of iclaprim mesylate were conducted, including the mouse lymphoma assay, the chromosomal aberrations test in cultured human lymphocytes, and a rat micronucleus test. No evidence of genetic toxicity was detected. However, mesylate salts have the potential to degrade to form alkyl sulfonates, which are known to be genotoxic.

General toxicology studies were conducted by the IV and oral routes in rats and/or mice, and marmosets. Additional dose range-finding studies were conducted in rabbits and minipigs. These studies identified the CNS, liver, thyroid, and spleen as targets of toxicity. Signs or lesions included:

- CNS – lethargy, restlessness or hyperactivity, tremors, convulsions, ataxia, dyspnea / rapid respiration, and / or vocalization
- Liver – clinical chemistry changes suggestive of hepatic effects, increased liver weight and / or centrilobular hepatocyte hypertrophy in rats in 4 week IV and 4 and 13 week oral studies.
- Thyroid – increased organ weight and / or follicular cell hypertrophy in 4 and 13 week oral studies in rats
- Spleen – grossly mottled with increased germinal center development in 4 and 13 week oral studies in rats

Additional findings included scratching and salivation / emesis in both oral and IV studies, decreased white blood cell counts in rats in 4 week IV and oral studies, and spermatid degeneration in rats in a 4 week IV study. Vascular irritation, thrombus formation and deterioration of adjacent tissues at the site of administration limited the dose and duration of studies of intravenous iclaprim mesylate. Additionally, IV studies in rats and marmosets were complicated by some degree of apparent intravascular hemolysis due to the propylene glycol vehicle.

Systemic exposures at NOAEL doses in IV and oral toxicology studies generally ranged from one-half to two times the daily clinical exposure. Most adverse effects seen in 13 week studies were reversible.

Reproductive and developmental toxicology studies included evaluation of male and female fertility and early embryonic development in rats, embryo-fetal development studies in rats and minipigs, and a pre- and postnatal development study in rats. No adverse effects on fertility in rats were seen at IV doses equivalent to 3.5 times the clinical dose in males and 2.5 times the clinical dose in females. No adverse effects on early embryonic development were seen at IV doses equivalent to 1.5 times the clinical dose. Higher dosing was limited by vascular irritation. In animals treated with higher doses, decreased male reproductive organ weights and lower sperm counts were seen, and effects on early embryonic development could not be assessed. Embryo-fetal development studies in rats by both the IV and oral routes revealed dose-related fetal and litter incidences of multiple skeletal and visceral abnormalities related to the head, lower or upper jaw, palate, lungs, cardiovascular system, liver/diaphragm, spleen, kidneys, limbs, tail, vertebral column and ribs. At the lowest doses in both studies, the incidences of anomalies were within the range of historical controls but were consistent with findings at higher doses and/or occurred as clusters of multiple malformations. Systemic exposure at the lowest doses was 60-75% of daily clinical exposure, while exposure at the next highest dose was approximately 4 times daily clinical exposure. Similar findings were observed in minipigs administered IV doses, including cleft lip/palate, cardiac anomalies, specific effects on sternum, ribs, and hyoid, and other skeletal alterations. The daily systemic exposure in human subjects fell between that at the low and mid-dose (5 and 10 mg/kg/day, respectively) in minipigs. In a pre- and post-natal developmental toxicology study in rats, malformations seen at the highest dose were consistent with the embryo-fetal alterations described above. The mid-dose, 150 mg/kg/day, was considered the NOAEL for maternal toxicity and for pre- and post-natal effects on the F1 generation, with systemic exposure approximating 4 times the daily clinical exposure.

Developmental anomalies associated with iclaprim exposure in the above reproductive and developmental toxicology studies are consistent with those seen in humans and animals following *in utero* exposure to other inhibitors of DHFR, including the antibacterial agent trimethoprim, in published reports and in epidemiological studies of clinical use. It would seem reasonable for iclaprim, like trimethoprim, to be a Pregnancy Category C drug, with similar precautions and recommendations for folic acid supplementation in pregnancy.

IV. MICROBIOLOGY

Summary of Microbiology Findings

- Iclaprim acts on bacterial cells by competitively inhibiting dihydrofolate reductase (DHFR), a key enzyme in the folate cycle; the same mode of inhibition is exerted by trimethoprim.
- Iclaprim resistance is mainly determined by point mutations in the *dfr* gene as studied in *S. aureus* and *S. pneumoniae*.
- Surveillance studies demonstrate that the spectrum of activity of iclaprim includes many organisms indicated in cSSSI including *S. aureus* and *S. pyogenes.*
- Iclaprim is bactericidal *in vitro*, generally at concentrations equal to the MIC that are maintained in human plasma for several hours after a therapeutic dose. Bactericidal activity is primarily time-dependent and concentration independent.
- Due to its structural similarity with trimethoprim, iclaprim is synergistic with sulfonamides against a broad spectrum of bacterial species. No antagonism was noted.
- The area under the concentration-time curve (AUC) is the most relevant pharmacodynamic parameter for predicting efficacy.
- While iclaprim has been tested in several animal infection models, dosages utilized were high due to the antagonistic effect of TdR and the short half-time in rodents; thus, results were difficult to interpret.
- Clinical and bacteriological success rates in patients treated with iclaprim were comparable to patients treated with linezolid when patients were infected with *S. aureus*, *S. pyogenes* and *E. faecalis*.
- There was no apparent MIC trend in clinical or bacteriological success rates among patients infected with the target pathogens for the cSSSI indication.

Spectrum of Activity

Iclaprim and comparators were evaluated in a large multinational surveillance study in 2004-2006, concentrating on pathogens likely to be found in cSSSI. MICs of iclaprim for nearly 6000 Gram-positive aerobic cocci were determined using broth microdilution methodology.

Susceptibility to iclaprim was compared among the various Gram-positive organisms responsible for cSSSIs (Table 4.1).

Table 4.1: Activity of Iclaprim and Comparator Agents against Clinical Isolates of Gram-Positive Cocci Collected in Europe, Israel and the United States (2004—2006)

	MIC (µg/mL)

Organism	Drug	N	50%	90%	Range
MSSA	Iclaprim	1,513	0.06	0.12	0.008 - 4
	Trimethoprim		1	1	0.06- > 64
MRSA	Iclaprim	3,003	0.06	0.12	≤ 0.004 - 8
	Trimethoprim		1	2	0.06- > 64
VISA/hVISA	Iclaprim	24	0.5	8	0.06 - > 8
	Trimethoprim		8	> 64	0.5- > 64
VRSA	Iclaprim	5	-	-	0.06 - > 8
	Trimethoprim		-	-	0.5- > 64
S. pyogenes	Iclaprim	604	0.015	0.03	≤ 0.004 - 0.12
	Trimethoprim		0.25	0.5	≤ 0.03 - 2
S. agalactiae	Iclaprim	204	0.12	0.25	0.015 - 0.5
	Trimethoprim		1	4	0.25 - 8
E. faecalis	Iclaprim	310	0.015	4	≤ 0.004 - > 8
	Trimethoprim		0.25	> 64	≤ 0.03 - > 64
E. faecium	Iclaprim	303	2	> 8	≤ 0.004 - > 8
	Trimethoprim		32	> 64	≤ 0.03 - > 64

MSSA: methicillin-susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*; VISA: vancomycin intermediate *Staphylococcus aureus*; hVISA: heterogeneously VISA; VRSA: vancomycin-resistant *Staphylococcus aureus*;
Source: Table 53, Microbiology Section – NDA 22-269

Against both MSSA and MRSA isolates, the MIC50 and MIC90 of iclaprim were 0.06 and 0.12 µg/mL, respectively. The potency of iclaprim was greater than that of TMP (which had MIC90s of 1 and 2 µg/mL against MSSA and MRSA, respectively). A small proportion (2.2%) of the isolates had iclaprim MICs above the proposed breakpoint of 1.0 µg/mL. Iclaprim had variable activity against VISA and VRSA strains; iclaprim MICs ranged from 0.06 to > 8 µg/mL for 6 hVISA/VISA and VRSA isolates.

Iclaprim has activity against at least 90% of isolates of the principal targeted species, *S. aureus* and ß-hemolytic streptococci. Beta-hemolytic streptococci are intrinsically poorly susceptible to TMP; however, iclaprim has activity against these organisms. Viridans streptococci are less susceptible to both TMP and iclaprim. Among enterococci, although the iclaprim MIC distribution is bimodal, a majority of strains are inhibited by very low concentrations of iclaprim.

Mechanism of Action

The antimicrobial mechanism of action of iclaprim is mediated by competitive inhibition of bacterial DHFR, the same mode of inhibition exerted by TMP. The activity of iclaprim against TMP-R mutants of *S. aureus* and *S. pneumoniae* is attributable to additional hydrophobic interaction between iclaprim and the enzyme. The same mechanism of action of iclaprim, competitive inhibition with the natural substrate DHF, is seen against both TMP-S and -R enzymes. Additional evidence that inhibition of DHFR is the only mechanism of action of iclaprim includes antagonism of its antimicrobial activity by metabolites of the tetrahydrofolate pathway (which can be reversed by mutation in TK) and synergy with sulfonamides. Although the folate pathway is similar in higher organisms and bacteria, these inhibitors can be safely used to treat infection because they are much less active against the mammalian enzyme.

Bactericidal Activity

In vitro, iclaprim is bactericidal for cSSSI target organisms at concentrations near the MIC. In general, these concentrations are attained in human plasma with the proposed dosage regimen and persist for approximately three hours. Bactericidal activity has been demonstrated against *S. aureus* (including MRSA, VISA and VRSA strains), streptococci (including penicillin- and erythromycin-resistant isolates) and enterococci (including vancomycin-resistant isolates)

In general, iclaprim is bactericidal at lower concentrations than TMP, and its action is more rapid than that of some comparators, including vancomycin. The bactericidal action of iclaprim appears to be predominantly time-dependent; i.e., increasing the concentration above the MBC does not usually affect the rapidity or extent of reduction in CFU. The *in vitro* activity of iclaprim, including its bactericidal activity, is affected by the presence of excess TdR in the medium.

Mechanisms of Resistance

Resistance to TMP has been studied in *S. aureus* and *S. pneumoniae*, and is largely determined by point mutations in the *dfr* gene of these species. Iclaprim has more activity than TMP against these organisms by virtue of its enhanced interaction with the altered DHFRs. In general, iclaprim does not have advantages over TMP against Gram-negative species with acquired or intrinsic TMP resistance or Gram-positive species with intrinsic resistance. Exceptions include some fastidious species in which intrinsic TMP resistance, or low susceptibility to TMP alone, appears to be determined by chromosomal DHFRs.

In vitro studies demonstrated that it was relatively difficult to select for stably increased iclaprim MIC in *S. aureus* strains, either by direct selection or serial passage. Consistent with this observation, emergence of resistance to iclaprim was not observed in the course of clinical trials. These results suggest a low potential for development of resistance to iclaprim in susceptible organisms.

Interactions with other Antimicrobials

As expected from its mechanisms of action, iclaprim, like TMP, shows synergistic activity with sulfonamides against a broad spectrum of bacterial species, but does not show synergy with the other antibiotic classes tested that do not affect the folate pathway. No antagonism was seen between iclaprim and other agents.

Pharmacokinetics and Pharmacodynamics

PK/PD parameters in the thigh-infection model indicate a correlation with AUC/MIC and time above MIC (T > MIC) for efficacy but not with peak/MIC ratios.

Efficacy in Animal Infection Models

Iclaprim has been tested in a variety of infection models, mainly in mice (including in immunocompromised animals). Endpoints have included survival, prevention of the development of infection, and reduction of the bacterial burden in organs and tissues. Although these studies demonstrated proof of principle of the efficacy of iclaprim against *S. aureus* (including MRSA) and *Streptococcus pneumoniae*, the dosages utilized were often high, due to the antagonistic effect of TdR and the short half-life of the compound in rodents.

Clinical and Microbiological Efficacy at TOC by MIC

Table 4.2 shows there was no apparent MIC-related trend in eradication rates among patients infected with the target pathogens for the cSSSI indication. In addition, there were relatively few isolates with iclaprim MICs > 0.5 µg/mL

Table 4.2: Iclaprim By-Pathogen Microbiological and Clinical Success Rates at TOC by MIC, Overall and by Species

	Iclaprim MIC (mcg/ml)	Microbiological Success	Clinical Success
S. aureus (all) N=251	≤ 0.008	0/1 (0)	1/1 (100)
	0.015	1/3 (33)	3/3 (100)
	0.03	7/7 (100)	7/7 (100)
	0.06	65/82 (79)	68/82 (83)
	0.12	106/135 (79)	113/135 (84)
	0.25	9/11 (82)	9/11 (82)
	0.5	2/2 (100)	2/2 (100)
	1	1/1 (100)	1/1 (100)
	8	1/1 (100)	1/1 (100)
	16	1/1 (100)	1/1 (100)
	> 16	5/5 (100)	4/5 (80)
	Unknown	0/2 (0)	0/2 (0)
S. aureus (MRSA) N=111	0.015	0/2 (0)	2/2 (100)
	0.03	7/7 (100)	7/7 (100)
	0.06	35/44 (80)	34/44 (77)
	0.12	40/49 (82)	40/49 (82)
	0.25	2/3 (67)	2/3 (67)
	0.5	1/1 (100)	1/1 (100)
	1	1/1 (100)	1/1 (100)
	8	1/1 (100)	1/1 (100)
	16	1/1 (100)	1/1 (100)
	> 16	1/2 (50)	2/2 (100)
S. pyogenes N=36	≤ 0.008	9/10 (90)	10/10 (100)
	0.015	0/6 (0)	2/6 (33)
	0.03	11/12 (92)	11/12 (92)
	0.06	2/3 (67)	3/3 (100)
	0.12	3/3 (100)	2/3 (67)
	0.25	1/1 (100)	1/1 (100)
	Unknown	0/1 (0)	1/1 (100)

Table 4.2 (Continued)

S. agalactiae N=5	0.12	2/3 (67)	2/3 (67)
	0.25	2/2 (100)	1/2 (50)
S. equisimilis N=3	0.06	½ (50)	2/2 (100)
	0.12	1/1 (100)	1/1 (100)
Streptococcus, Viridans Group N=10	≤ 0.008	3/3 (100)	3/3 (100)
	0.015	2/2 (100)	2/2 (100)
	Unknown	5/5 (100)	5/5 (100)
E. faecalis	≤ 0.008	4/4 (100)	4/4 (100)

N=15	0.015	1/3 (33)	2/3 (67)
	0.03	2/2 (100)	2/2 (100)
	0.5	2/2 (100)	1/1 (100)
	4	1/1 (100)	1/1 (100)
	> 16	1/3 (33)	2/3 (67)

MIC50 values are shaded in yellow, MIC90 values are shaded in red;
Source: Tables 113 and 124, Microbiology section, NDA 22-269

Proposed Susceptibility Breakpoints
The Sponsor proposes the following susceptibility breakpoints for iclaprim based on a number of factors as outlined in the CLSI M23 guideline.

Table 4.3: Proposed Iclaprim Susceptibility Breakpoints

	MIC (µg/ml)				Zone Diameter (mm)			
Pathogen	**S**	**NS**	**I**	**R**	**S**	**NS**	**I**	**R**
Staphylococcus aureus	≤ 1.0	2	-	-	≥ 21	≤ 20	-	-
Streptococcus pyogenes	≤ 0.5	1	-	-	NR[a]	NR[a]	-	-
Enterococcus faecalis	≤ 0.5	-	1	≥ 2	≥ 20	-	17-19	≤

[a] Disk method not recommended.
S, susceptible; NS, not susceptible, I, intermediate, R, resistant.
Source: Table 134, Microbiology section, NDA 22-269

V. CLINICAL PHARMACOLOGY

When administered intravenously at the proposed dose of 0.8 mg/kg over 30 minutes, iclaprim reaches a mean Cmax value of 0.85 µg/mL at the end of infusion. Its elimination half-life is approximately 2.5 hours, and there is no accumulation with repeat dosing. Iclaprim exposure (Cmax and AUC) increases linearly with increasing dose (given the same infusion duration), from 0.4 to 3.2 mg/kg. In general, inter-patient variability in iclaprim exposure is limited (%CV <50%). It is ~93% protein bound in humans.

Metabolism and Elimination
Iclaprim undergoes nearly complete biotransformation prior to excretion, with only 2% of the parent drug excreted unchanged in the urine. CYP450 enzymes CYP3A4 and CYP2C19 are primarily responsible for most of the Phase 1 metabolism, with CYP2C9 and CYP2D6 providing marginal contributions. Most of the Phase 1 metabolites are subsequently conjugated to glucuronide metabolites. Over 30 distinct metabolites have been detected in urine, plasma and feces, though 3 glucuronide metabolites make up the majority of eliminated drug. Approximately 70% of the metabolites are eliminated in urine and 20% in feces. None of the metabolites have antibacterial activity.

Drug Interactions
Given that iclaprim is primarily metabolized by two CYP enzymes (CYP2C19 and CYP3A4), and partially metabolized by other minor routes, inhibition of either CYP2C19 or CYP3A4 individually is not expected to result in clinically significant increases in iclaprim exposure. This was demonstrated in a drug interaction study with the potent CYP3A4 inhibitor ketoconazole, in

which co-administration of the two drugs resulted in a 20% and 66% increase in iclaprim Cmax and $AUC_{0-\infty}$, respectively. Concomitant use of a CYP3A4 inhibitor with iclaprim is not expected to pose a safety concern at the proposed dose of 0.8 mg/kg. A drug interaction study with omeprazole (CYP2C19 inhibitor) is currently being conducted by the Sponsor. Based on *in vitro* study results, iclaprim may be a clinically relevant inhibitor of CYP3A4, while inhibition of CYP2C9 and 2C19 is less likely. A drug interaction study with a CYP3A4 probe substrate (e.g. midazolam) has not been conducted. A drug interaction study conducted with iclaprim 1.6 mg/kg BID and warfarin (substrate of CYP2C9, 2C19 and 3A4) indicated iclaprim has no effect on warfarin PK or INR. Iclaprim may also potentially inhibit P-glycoprotein (P-gp) based on *in vitro* study findings; a drug interaction study with P-gp substrate digoxin is currently ongoing.

Specific Populations
Renal impairment (mild to ESRD) does not significantly impact iclaprim exposure, though accumulation of certain inactive metabolites might be expected. In subjects with mild and moderate hepatic impairment, iclaprim clearance (CL) was reduced by <7% and 50%, respectively, relative to normal subjects. Administration of half the proposed dose (0.4 mg/kg over 30 min.) to subjects with moderate hepatic impairment results in a comparable AUC to that observed in healthy subjects administered 0.8 mg/kg. The Sponsor's proposed dosage adjustment of 0.4 mg/kg Q12 hours in patients with moderate hepatic impairment is appropriate. Iclaprim PK has not been assessed in individuals with severe hepatic impairment.

Iclaprim CL and volume of distribution (Vd) are unrelated to body weight. As a result, weight-based dosing results in a linear increase in iclaprim exposure with increasing weight. Iclaprim Cmax and AUC in severely obese subjects (BMI $\geq$ 40 kg/m^2) are 1.5- and 2-fold higher than those of subjects with normal body weight, respectively. Due to safety concerns related to an increased risk of QTc prolongation with increasing iclaprim exposure, particularly Cmax, the Sponsor has proposed a maximum dose of 100 mg (corresponding to 125 kg body weight). The clinical pharmacology reviewer is evaluating the appropriateness of this dose ceiling.

Exposure/Response
Sparse PK sampling was performed in all patients enrolled in ASSIST-1 and ASSIST-2, and a population-PK analysis conducted. Estimates of iclaprim exposure and elimination in patients were similar to those values observed in Phase 1 healthy volunteer studies. Exposure/response analyses were conducted to evaluate the PK/PD parameters of interest, AUC/MIC and time above MIC (T>MIC), and clinical and microbiological outcomes in Phase 3. There was no relationship observed between either AUC/MIC or T>MIC and outcome. However, it is noted that there were few "failures" in the final PK/PD dataset (<9%), and MIC values were generally low. Exposure/response analyses for safety revealed a significant association between iclaprim AUC_{0-12} and QTc increases > 30 ms in Phase 3.

VI. EFFICACY

Study Overview
Study Design: There were two pivotal Phase 3, randomized, investigator-blind, multi-center, active-control clinical studies, namely, ASSIST-1 and ASSIST-2, conducted to evaluate the

efficacy and safety of IV iclaprim versus IV linezolid in cSSSI. These studies were designed to enroll hospitalized patients with clinical evidence of cSSSI. At entry, adult patients (≥18 years of age) were randomized centrally in a 1:1 ratio, and stratified by country, to receive either iclaprim or linezolid for 10 to 14 days. They were evaluated daily for the first four days and then every other day thereafter during the treatment period, at the end of therapy (EOT), the test-of-cure (TOC) visit (7 to 14 days post treatment), and at a Late Follow-Up (F/U) visit 7-14 days after the TOC visit. Concomitant aztreonam and metronidazole use was permitted for suspected or proven Gram-negative and anaerobic pathogens, respectively.

The two studies were designed to demonstrate efficacy using the same primary clinical endpoint, i.e., clinical cure rates at the TOC visit in the co-primary intent-to-treat (ITT) and per protocol (PP) populations. The PP population is a prospectively defined subset of the ITT population and includes patients who received at least 4 days of treatment, received at least 7 doses of treatment, had no major protocol violations, and had adequate clinical evaluations performed. Secondary clinical endpoints were also evaluated, including clinical response at end of treatment (EOT), time to resolution of signs and symptoms of infection, microbiological outcomes, and *in vitro* susceptibility of isolated pathogens. Furthermore, these studies were also intended to provide an adequate database for the evaluation of safety and population pharmacokinetics in cSSSI patients. Analyses were also conducted in the modified ITT (MITT), clinically evaluable (CE), and microbiologically evaluable (ME) populations.

Efficacy Assessment: The primary objective of these studies was to compare the clinical cure rates of IV iclaprim and IV linezolid at the TOC visit (7 to 14 days after the end of treatment). The clinical response was based on the Investigator's assessment of signs and symptoms, based on the following criteria:

(i) *Cure*: all signs and symptoms of the cSSSI present at baseline have resolved; the patient did not receive new systemic or any topical antibacterial treatment up to and including the EOT or TOC visit (as applicable for the assessment); 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; patient did not receive new systemic or any topical antibacterial treatment up to and including the EOT or TOC (as applicable for the assessment); and received at least four days of treatment and at least seven doses;

(ii) *Failure*: conditions for "Cure" are not fulfilled and after >2 days and ≥4 doses of treatment, at least one of the following criteria regarding symptoms and therapies is fulfilled: persistence or progression of signs and symptoms relevant to the pre-treatment infection site; development of new clinical signs and symptoms relevant to the pre-treatment infection site; additional antibacterial therapy (except aztreonam or metronidazole) required for the treatment of the pre-treatment infection site; a surgical procedure is 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;

(iii) *Indeterminate*: conditions for "Cure" and conditions for "Failure" were not met and for EOT: patients who had <4 days or <7 doses of treatment but did not fulfill all other

criteria for "Cure;" For TOC: patients who had <4 days or <7 doses of treatment but did not fulfill all other criteria for "Cure" or patients with "Cure" at EOT but no TOC visit;

(iv) *Missing*: all other cases.

The secondary objectives of these studies were to compare iclaprim and linezolid with respect to: (i) clinical efficacy at the end of study and EOT for all study populations; (ii) time to resolution of systemic and local signs and symptoms of cSSSI; (iii) clinical outcome in the microbiologically evaluable (ME) population; (iv) bacteriologic outcome in the modified intent-to-treat (MITT) and ME population; (v) bacteriologic eradication rates of baseline (BL) pathogens; (vi) clinical outcome in the MITT population; (vii) BL *in vitro* susceptibility of isolated pathogens in the ME populations; (viii) clinical efficacy at TOC by minimum inhibitory concentration (MIC) analysis; (ix) safety and tolerability of iclaprim treatment; and (x) obtain population pharmacokinetic (PK) data for patients who received iclaprim.

Statistics: The Sponsor calculated projected sample size to provide sufficient power for the demonstration of non-inferiority of iclaprim compared to linezolid in terms of clinical cure rate. The non-inferiority margin for the cure rate was prospectively set to 12.5%. The Sponsor assumed that if the actual cure rate was 85% in both treatment groups, 172 patients would be needed in each group to give 90% power for the proof of non-inferiority. This was based on Blackwelder's method for non-inferiority testing with a 1-sided alpha of 0.025, which is equivalent to requiring that the lower bound for the 95% confidence interval for the difference "iclaprim – linezolid" is ≥ -12.5%. Furthermore, assuming 20% of patients were non-evaluable for the PP population, the Sponsor projected that a total of 430 patients were required for randomization (215 per treatment group). For purposes of collecting additional safety and other information, the Sponsor asked to increase sample size and enroll a total of 500 patients (250 per treatment group).

Study Results

Patient Disposition: ASSIST-1 had a total of 499 randomized patients, including 250 randomized to iclaprim and 249 randomized to linezolid. Two randomized patients, 1 in each group, did not receive treatment; therefore, a total of 497 patients were included in the ITT population for analysis of efficacy, including 249 and 248 patients in the iclaprim and linezolid groups, respectively. One patient who was randomized to the linezolid group was dosed with iclaprim; therefore, the ITT/safety population includes 250 patients in the iclaprim arm and 247 in the linezolid arm.

A total of 510 patients were randomized to treatment in ASSIST-2, including 257 randomized to iclaprim and 253 randomized to linezolid. There were sixteen randomized patients, including 6 in the iclaprim group and 10 in the linezolid group, who did not receive treatment; therefore, a total of 494 patients were included in the ITT population for the analysis of efficacy, including 251 and 243 patients in the iclaprim and linezolid groups, respectively. One patient who was randomized to the iclaprim group was dosed with linezolid; therefore, the ITT safety population includes 250 patients in the iclaprim group and 244 in the linezolid group. The sizes of the rest of the analysis populations are given in the Table 6.1.

Table 6.1: Patient Disposition and Populations for Analysis – All Patients Screened

	ASSIST-1		ASSIST-2	
Disposition/Population	**Iclaprim N (%)**	**Linezolid N (%)**	**Iclaprim N (%)**	**Linezolid N (%)**
Patients Randomized	250 (100)	249 (100)	257 (100)	253 (100)
ITT (for efficacy)	249 (99.6)	248 (99.6)	251 (97.7)	243 (96)
ITT (for safety)	250 (100)	247 (99.2)	250 (97.3)	244 (96.4)
PP	206 (82.4)	213 (85.5)	209 (81.3)	195 (77.1)
MITT	183 (73.2)	191 (76.7)	192 (74.7)	184 (72.7)
ME and PP (MEPP)	150 (60)	167 (67.1)	165 (64.2)	149 (58.9)
Patients completing the study	223 (89.2)	228 (91.6)	228 (88.7)	213 (84.2)
Patients withdrawn prematurely	27 (10.8)	21 (8.4)	23 (8.9)	30 (11.9)

Partially recreated from Sponsor's Table 10-1 found in both icla-09-csi1 and icla-09-csi2.

Baseline Characteristics: In general, patient demographics were similar in both studies (particularly in the ITT and PP populations). In ASSIST-1, the mean age for the iclaprim arm was 50 and 47.2 in the linezolid arm. In ASSIST-2, the mean age for the iclaprim arm is 47.1 and 46.8 in the linezolid arm. However, there were more patients over 75 years old recruited under the iclaprim arm in ASSIST-1. On the other hand, there were more males recruited in both studies accounting for more than two-thirds of the study population. Furthermore, majority of the patients are Caucasians: 91.3% and 74.5% in ASSIST-1 and ASSIST-2, respectively. Both treatment arms have similar profiles with regards to age, sex, race, weight, height and BMI across studies.

Table 6.2: Demographic Characteristics – ITT/Efficacy Population

	ASSIST-1				ASSIST-2			
	Iclaprim N = 249		Linezolid N = 248		Iclaprim N = 251		Linezolid N = 243	
Age, n (%)								
< 65	203	(81.5)	217	(87.5)	222	(88.4)	216	(88.9)
65 – 75	32	(12.9)	24	(9.7)	19	(7.6)	16	(6.6)
≥ 75	14	(5.6)	7	(2.8)	10	(4.0)	11	(4.5)
Sex, n (%)								
Male	163	(65.5)	175	(70.6)	159	(63.3)	154	(63.4)
Female	86	(34.5)	73	(29.4)	92	(36.7)	89	(36.6)
Race, n (%)								
Caucasian	228	(91.6)	226	(91.1)	178	(70.9)	190	(78.2)
Black	8	(3.2)	5	(2.0)	21	(8.4)	13	(5.3)
Hispanic	12	(4.8)	13	(5.2)	42	(16.7)	34	(14.0)
Asian	0		1	(0.4)	**0**		**0**	
Other	1	(0.4)	3	(1.2)	10	(4.0)	6	(2.5)
Diabetic Patients								
Diabetic	34	(13.7)	25	(10.1)	29	(11.6)	30	(12.3)
BMI (kg/m2) n (%)								
Underweight < 18.5	3	(1.2)	5	(2.0)	1	(0.4)	3	(1.2)
Normal Wt 18.5 – 25	103	(41.4)	114	(46.0)	96	(38.2)	104	(42.8)
Overweight 25 – 30	78	(31.3)	71	(28.6)	89	(35.5)	78	(32.1)
Obese 30 – 40	61	(24.5)	54	(21.8)	61	(24.3)	54	(22.2)
Morbidly Obese ≥ 40	4	(1.6)	4	(1.6)	4	(1.6)	4	(1.6)
Type of Infection[1] n (%)								
Infected ulcers	37	(14.9)	36	(14.5)	22	(8.8)	18	(7.4)
First or second degree burns	34	(13.7)	31	(12.5)	15	(6.0)	22	(9.1)
Major abscess	53	(21.3)	53	(21.4)	76	(30.3)	71	(29.2)
Deep or extensive cellulitis	121	(48.6)	117	(47.2)	71	(28.3)	69	(28.4)
Wound infections	29	(11.6)	43	(17.3)	112	(44.6)	111	(45.7)

Primary Efficacy Outcomes: The Sponsor designed these trials to demonstrate the non-inferiority in the clinical cure rate of iclaprim to that of an approved comparator antibiotic, linezolid, in patients with complicated skin and skin structure infections. The pre-specified co-primary populations are the ITT and PP.

In the FDA analysis, iclaprim-treated patients in the ITT and PP populations achieved cure rates of 80.7% and 92.2%, while linezolid-treated patients achieved cure rates of 88.7% and 99.1%, respectively in ASSIST-1. In ASSIST-2, iclaprim-treated patients in the ITT and PP populations achieved cure rates of 80.1% and 88.5%, while linezolid treated patients achieved cure rates of 80.7% and 94.9%, respectively as given in table 6.3 below.

[1] Some patients have multiple infection types.

Table 6.3: Clinical Cure at TOC – Primary Efficacy Populations

	ASSIST-1		ASSIST-2	
	Iclaprim	**Linezolid**	**Iclaprim**	**Linezolid**
ITT	N = 249	N = 248	N = 251	N = 243
Clinical cure, n (%)	201 (80.7%)	220 (88.7%)	199 (80.1%)	193 (80.7%)
Treatment difference (iclaprim – linezolid) and [95% CI]	-8.0% [-14.3%, -1.7%]		-0.1% [-7.3%, 7.0%]	
PP	N = 206	N = 213	N = 209	N = 195
Clinical cure, n (%)	190 (92.2%)	211 (99.1%)	183 (88.5%)	182 (94.9%)
Treatment difference (iclaprim – linezolid) and [95% CI]	-6.8% [-11.4%, - 3.0%]		-5.8% [-11.6%, 0.5%]	

FDA Analyses

The Sponsor employed a pre-defined algorithm to re-classify the clinical response for the patients who had protocol violation due to use of prohibited antibiotics in both studies ASSIST-1 and ASSIST-2. The algorithm classified the outcomes for these patients as indeterminate. Thirty-four patients from the ITT population have been excluded from the analysis by the sponsor due to co-medication with prohibited antibiotics and/or steroids, 22 on linezolid and 12 on iclaprim. However, the algorithm failed to identify all of the patients who had received concomitant prohibited antibiotics. There were 6 patients in ASSIST-1, all in the iclaprim arm and there were 11 patients in ASSIST-2, including 5 patients in the iclaprim arm and 6 patients in the linezolid arm. The Agency determined that the responses for these patients should be changed from "cure" to "indeterminate" to be consistent with the protocol. This change accounts for the differences between the results in the above table and the outcomes reported by the Sponsor. Agency review of individual cases that received concomitant antibiotics is on-going.

In the table above, the lower bound of the 95% CI for the treatment difference of the clinical cure at TOC between iclaprim and linezolid exceeded the Agency's determination of the NI margin of 10% in most of the ITT and PP co-primary analyses (see the briefing document for the Justification of Non-Inferiority Margin for the Treatment of Complicated Skin and Skin Structure Infections). Therefore, the non-inferiority of iclaprim to linezolid has not been established. In addition, the upper limit of the 95% CI for the treatment difference failed to cross zero in ASSIST-1 raising concerns on the potential inferior efficacy of iclaprim compared to linezolid.

Subgroups: Noticeable difference were observed in the clinical cure rate for the ITT and PP population when analyzed by region with higher rates of clinical cure noted in Eastern Europe than in North America for both treatments, particularly in ASSIST-1. In North American sites, the treatment difference in cure rates between iclaprim and linezolid was -10.1% with a 95% CI of [-26.4%, 7.0%], in the ITT population. In Eastern European sites, the treatment difference in cure rates between iclaprim and linezolid was -4.5% with a 95% CI of [-10.7%, 1.7%, in the ITT

population. Similar results were observed in the PP population as given in table 6.4 below. The Sponsor explains that one reason why there is marked difference between cure rates in North America and Eastern Europe is the extent of outpatient antibacterial therapy (OPAT) difference in the two regions. Most patients who received OPAT were enrolled at North American investigative sites (44 of 52, 84.6%). This group of patients had a lower cure rate than patients who received their full course of antibiotics in the hospital and this differential effect was more noticeable in the iclaprim-treated patients.

Table 6.4: Clinical Cure at TOC Visit in ASSIST-1– All Primary Efficacy Populations by Geographic Region

	North America		**Eastern Europe**	
	Iclaprim	**Linezolid**	**Iclaprim**	**Linezolid**
ITT	N = 52	N = 53	N = 197	N = 195
Clinical cure, n (%)	33 (63.5%)	41 (77.4%)	168 (85.3%)	179 (91.8%)
Treatment difference (iclaprim – linezolid) and [95% CI]	-13.9% [-30.3%, 3.5%]		-6.5% [-12.9%, -0.2%]	
PP	N = 36	N = 38	N = 170	N = 175
Clinical cure, n (%)	28 (77.8%)	36 (94.7%)	162 (95.3%)	175 (100%)
Treatment difference (iclaprim – linezolid) and [95% CI]	-17.0% [-33.3%, -0.1%]		-4.7% [-9.0%, -0.2%]	

The results by region for the ASSIST-2 study are given in table 6.5.

Table 6.5: Clinical Cure at TOC Visit in ASSIST-2– All Primary Efficacy Populations by Geographic Region[2]

	North America		Rest of the World	
	Iclaprim	**Linezolid**	**Iclaprim**	**Linezolid**
ITT	N = 148	N = 142	N = 103	N = 101
Clinical cure, n (%)	114 (77.0%)	103 (72.5%)	85 (82.5%)	90 (89.1%)
Treatment difference (iclaprim – linezolid) and [95% CI]	4.5% [-5.5%, 14.4%]		-6.6% [-16.3%, 3.2%][3]	
PP	N = 123	N = 108	N = 86	N = 87
Clinical cure, n (%)	106 (86.2%)	98 (90.7%)	77(89.5%)	84 (96.6%)
Treatment difference (iclaprim – linezolid) and [95% CI]	-4.6% [-12.9%, 4.0%]		-7.0% [-15.5%, 0.9%][8]	

The occurrence of relatively higher cure rates in Eastern Europe/Rest of the World is counterintuitive with the severity of the disease affecting patients in these regions. The Sponsor stated that infections in Eastern Europe/Rest of the World are more severe than in North America. In ASSIST-1, 99 out of 105 patients in North America had severe infections compared to 392 out of 392 in Eastern Europe. In ASSIST-2, 229 out of 290 patients in North America had severe infections compared to 198 out of 204 in the rest of the world.

Table 6.6: Clinical Cure at TOC Visit– ITT Population by Type of Infection[4]

	ASSIST-1						ASSIST-2					
	Iclaprim			**Linezolid**			**Iclaprim**			**Linezolid**		
	Cured	**Total**	**Rate**	**Cured**	**Total**	**Rate**	**Cured**	**Total**	**Rate**	**Cured**	**Total**	**Rate**
Infected ulcers,	34	37	91.9	33	36	91.7	17	22	77.3	14	18	77.8
First or second degree burns	26	34	76.5	25	31	80.7	12	15	80.0	17	22	77.3
Major abscess	39	53	73.6	47	53	88.7	59	76	77.6	54	71	76.1
Deep or extensive cellulitis	95	121	78.5	104	117	88.9	50	71	70.4	53	69	76.8
Wound infections	20	29	69.0	36	43	83.7	94	112	83.9	91	111	82.0

The most frequent infection type in ASSIST-1 was 'deep or extensive cellulitis' (47.9%), followed by 'major abscess' (21.3%) while in ASSIST-2 wound infections were the most common infection type, occurring in almost half of the patients (45.1%), followed by major abscesses (29.8%) and deep or extensive cellulitis (28.3%). Linezolid appeared to have higher cure rates in treating deep or extensive cellulitis than iclaprim. Cure rates in cellulitis patients

[2] Confidence interval uses Newcomb-Altman method illustrated in the previous section.
[3] Confidence interval slightly differs from Sponsor calculations.

were 88.9% for linezolid vs. 78.5% for iclaprim in ASSIST-1. Cure rates in cellulitis patients were 76.8% for linezolid vs. 70.4% for iclaprim in ASSIST-2.

Exploratory analysis was also done for patients with history of diabetes mellitus and baseline renal impairment. No statistically meaningful conclusions can be drawn because of small sample size.

Microbiology: Clinical outcomes in patients with baseline bacterial isolates were evaluated. The microbiological Intent-to-Treat (MITT) population included all ITT patients with a baseline Gram-positive pathogen. Similarly, the microbiologically evaluable per protocol (MEPP) population included PP patients with a baseline Gram-positive pathogen. Table 6.7 provides clinical outcomes for patients in the MITT and MEPP populations. In ASSIST-1, clinical cure rates were lower for iclaprim than linezolid in the MITT and MEPP populations. In ASSIST-2, the clinical cure rates were similar for iclaprim (78.7%) and linezolid (79.4%) in the MITT population. However, the cure rates were lower for iclaprim (85.5%) than for linezolid (93.3%) in the MEPP population for this study.

Table 6.7: Clinical Cure at TOC – MITT and MEPP Populations

	ASSIST-1		**ASSIST-2**	
	Iclaprim	**Linezolid**	**Iclaprim**	**Linezolid**
MITT	N = 183	N = 191	N = 192	N = 184
Clinical cure, n (%)	146 (79.8%)	170 (89%)	151 (78.7%)	146 (79.4%)
Treatment difference (iclaprim – linezolid) and [95% CI]	-9.2% [-16.6%, -1.9%]		-0.7% [-8.9%, 7.6%]	
MEPP	N = 150	N = 167	N = 165	N = 149
Clinical cure, n (%)	137 (91.3%)	165 (98.8%)	141 (85.5%)	139 (93.3%)
Treatment difference (iclaprim – linezolid) and [95% CI]	-7.5% [-13.1%, -2.8%]		-7.8% [-14.7%, -0.9%]	

Table 6.8 shows the clinical cure rates by baseline pathogen for MITT patients in the two clinical trials. For patients with *S. aureus*, clinical outcomes are shown separately for patients with methicillin susceptible (MSSA) and methicillin-resistant (MRSA) strains. Clinical cure rates by pathogen are higher for linezolid than iclaprim, particularly with *Streptococcus pyogenes*. The numbers of patients with *Enterococcus faecalis* and *Streptococcus agalactiae* are small.

Table 6.8: Clinical Cure at TOC visit by Pathogen - MITT Population

Baseline Gram-positive Pathogen	ASSIST-1						ASSIST-2					
	Iclaprim (N = 183)			Linezolid (N = 191)			Iclaprim (N = 192)			Linezolid (N = 184)		
	Cure	Tot	Rate	Cure	Tot	Rate	Cure	Tot	Rate	Cure	Tot	Rate
Staphylococcus aureus, total	113	138	81.9	131	144	91.0	115	149	77.2	127	160	79.4
S. aureus, MRSA	35	45	77.8	34	36	94.4	55	74	74.3	60	80	75.0
S. aureus, MSSA	78	93	83.9	97	108	89.8	60	73	82.2	66	78	84.6
Streptococcus pyogenes	24	30	80.0	30	34	88.2	20	28	71.4	19	22	86.4
Enterococcus faecalis	11	14	78.6	11	13	84.6	13	15	86.7	14	15	93.3
Streptococcus agalactiae	1	3	33.3	4	7	57.1	3	5	60.0	4	4	100

Efficacy Considerations

Comparison with Linezolid: The results suggest that there is a statistically significant difference between linezolid and iclaprim in some of primary analysis populations. The non-inferiority margin and comparative results with linezolid are issues to be discussed at the advisory committee meeting.

Concomitant Antibacterial Therapy: The Sponsor reported that use of pre-study antibacterial therapy was recorded in 39.8% in the iclaprim group and 36.7% in the linezolid group in ASSIST-1 and 12.7% in the iclaprim group and 20.2% in the linezolid group in ASSIST-2. The use of pre-study antibacterial therapy was allowed if administered for less than 24 hours prior to enrollment or if the patient did not respond to the previous administration of antibacterial therapy or the bacterial pathogen was resistant to the previously-administered antibacterial treatment. In addition, use of antibacterial therapy concomitant with study drug treatment was also high, i.e., 37.8% for iclaprim and 28.2% for linezolid in ASSIST-1 and 39.8% of iclaprim and 35.0% for linezolid in ASSIST-2, which primarily reflects the allowed use of aztreonam and metronidazole for suspected or proven concomitant Gram-negative and anaerobic pathogens, respectively.

The extensive use of these antibacterial drugs prior and concomitant treatment was not properly accounted for when the Sponsor reported clinical efficacy. This level of prohibited concomitant antibacterial drug use has the potential to artificially make the treatments look similar in a non-inferiority trial, when in fact they are not.

Microbiology Subgroups: Lower clinical cure rates with iclaprim for patients with *Streptococcus pyogenes* were noted in both trials. Clinical cure rates for patients with *S. aureus* appeared to follow a similar pattern to the primary clinical outcome results.

VII. SAFETY

Three clinical studies were reviewed to assess the safety and tolerability of intravenous iclaprim. The Phase 2 study, under protocol AR-100-SSTI-001, compared iclaprim with vancomycin. Two subsequent Phase 3 studies: ASSIST-1 and ASSIST-2 compared iclaprim with linezolid.

Table 7.1: Safety Population for cSSSI Studies of Iclaprim

	Number of Subjects Exposed	
Study Group	**Iclaprim**	**Comparator**
Phase 2 Study		
AR-100-SSTI-001	62	30
Phase 3 Studies		
ASSIST-1 (ICLA-08-CSI1)	250	247
ASSIST-2 (ICLA-09-CSI2)	250	244
Total Phase 3	500	491
Total Safety and Efficacy Studies	**562**	**521**

For the purposes of the safety review, data from the Phase 2 (AR-100-SSTI-001) and Phase 3 (ASSIST-1 and ASSIST-2) studies were analyzed separately and combined. For statistical comparison, pooled data was assessed from only ASSIST-1 and ASSIST-2, in which iclaprim was dosed at 0.8mg/kg. All of the safety data were based on the ITT population, which was defined as all subjects who were randomized and received at least one dose of study medication.

	Combined Phase 3 Data	
	Study Group	
	Iclaprim (n = 500)	**Linezolid** (n = 491)
	Number (%) of Patients Experiencing:	
Any TEAE	249 (49.8%)	257 (52.3%)
Any SAE	20 (4.0%)	16 (3.3%)
Any severe TEAE	34 (6.8%)	34 (6.9%)
Any TEAE causing discontinuation	11 (2.2%)	6 (1.2%)
Deaths	6 (1.2%)	1 (0.2%)

Deaths

There were nine deaths reported in the Phase 2 and 3 studies. One death occurred in a patient treated with iclaprim mesylate, 1.0 mg/kg, in the phase 2 trial. In phase 3, six deaths occurred in patients treated with iclaprim 0.8 mg/kg, and two deaths occurred in patients treated with the comparator, linezolid. These nine deaths are summarized in the table 7.2.

Table 7.2: Deaths in cSSSI Studies

Drug/Dose Patient ID	Age/ Sex	Adverse Event with Outcome of Death	Time of AE Relative to Study Treatment	FDA: Related to Study Medication?
Iclaprim 1mg/kg				
202-003	22/M	Staphylococcal pneumonia Acute respiratory distress syndrome Sepsis with multiple organ failure Cavernous sinus thrombosis	During During During During	Not related
Iclaprim 0.8mg/kg				
303-005	70/F	Sepsis (*Klebsiella* bacteremia) Septic shock	During During	Not related
306-027	63/M	Anemia Sudden death	During 7 days post	Possibly
306-033	31/F	Anemia Hypoalbuminemia Peripheral edema Swelling of the face Cardiac failure, acute	During During During During During	Possibly
306-034	70/M	Erysipelas Septic arthritis Acute renal failure	3 days post 4 days post 12 days post	Possibly
504-020	51/M	Staphylococcal pneumonia Septic shock	During During	Not related
455-001	77/F	Colon cancer (liver metastasis)	7 days post	Not related
Linezolid				
304-038	48/M	Kidney infection Acute renal failure Pulmonary thromboembolism	10 days post 10 days post 10 days post	Possibly
456-004	57/F	Adenocarcinoma	14 days post	Not related

There were seven deaths among the iclaprim-treated patients (one in AR-100-SSTI-001, five in ASSIST-1, and one in ASSIST-2). Three of the deaths in the patients treated with iclaprim were assessed as possibly related to study medication by the FDA:

Patient 306-027 (ASSIST-1) was treated with iclaprim for right leg cellulitis. He had a complicated medical history including anemia, chronic obstructive bronchitis, and alcohol abuse manifested by alcoholic cardiomyopathy and peripheral neuropathy. The patient was found dead in his hospital bed seven days after his last dose of iclaprim. Anemia was reported as a TEAE, and the autopsy revealed bilateral pneumonia as well as findings consistent with the medical history of alcohol abuse including cardiomyopathy, hepatitis and chronic pancreatitis, adrenal cortical atrophy.

Patient 306-033 (ASSIST-1) was treated with iclaprim for cellulitis of the right buttock, which required extensive surgical debridement. She had a prior medical history of multiple prior traumatic head injuries, encephalopathy, epilepsy, meningitis, alcoholic cardiomyopathy, alcoholic polyneuropathy, anemia and hypoproteinemia. She had completed 11 of 14 days of therapy on the day she was found unconscious in her hospital bed. Attempts to resuscitate her were unsuccessful, and an autopsy was not performed. TEAEs reported were swelling of the face and peripheral edema due to hypoproteinemia and anemia. On Days 1 and 4, ΔQTcF's were +33.7 ms and +16 ms, respectively.

Patient 306-034 (ASSIST-1) was treated with iclaprim for cellulitis of the left knee. He reportedly responded well to treatment without any adverse effects; however, the patient was noted to have recurrent infection of his left leg, described as erysipelas, three days after EOT. Septic arthritis of the left knee was diagnosed the next day. He was treated with alternate antibiotics, but 12 days after his last dose of iclaprim, the patient had an acutely elevated serum creatinine level and was found unconscious in his hospital bed. Attempts to resuscitate him were unsuccessful. No autopsy was performed.

Serious Adverse Events (SAEs)

In the combined Phase 3 studies, there were 36 SAEs. Of the patients treated with iclaprim, there were 22 SAEs experienced by 20 (4.0%) of the patients. Of the patients treated with the comparator, linezolid, 16 (3.3%) patients experienced a total of 21 SAEs. The following table summarizes these events by system organ class:

Table 7.3: SAE by System Organ Class

	Combined Phase 3 Data	
	Study Group	
	Iclaprim (n = 500)	**Linezolid** (n = 491)
MedDRA System Organ Class	**Number (%) of Patients Experiencing:**	
Blood and Lymphatic System	0	0
Cardiac	3 (0.6%)	1 (0.2%)
Gastrointestinal	0	2 (0.4%)
General Disorders and Administration Site Conditions	1 (0.2%)	1 (0.2%)
Infections and Infestations	11 (2.2%)	8 (1.6%)
Injury, Poisoning or Procedural	1 (0.2%)	0
Investigations	1 (0.2%)	0
Metabolism and Nutrition	0	1 (0.2%)
Musculoskeletal and Connective Tissue	0	0
Neoplasms	1 (0.2%)	1 (0.2%)
Nervous System	1 (0.2%)	0
Psychiatric	0	0
Renal and Urinary	2 (0.4%)	1 (0.2%)
Respiratory, Thoracic and Mediastinal	0	1 (0.2%)
Skin and Subcutaneous Tissue	0	0
Surgical and Medical Procedures	0	1 (0.2%)
Vascular	1 (0.2%)	4 (0.8%)
Total SAEs	**20 (4.0%)**	**16 (3.3%)**

Overall, the balance between both arms was even with regard to all SAEs reported. There were no SAEs in either group belonging to the blood and lymphatic, musculoskeletal and connective tissue, or skin and subcutaneous tissue organ systems. SAEs other than death were reported for 14 patients in each treatment group.

The most common SAE by system organ class in both study arms was infection. The majority of these events were secondary complications such as pneumonia, septic arthritis, osteomyelitis or the development of an abscess, most of which appear to have been related to underlying conditions or prolonged hospitalizations.

With the exception of pneumonia (three patients in the iclaprim group), no specific SAE preferred term was reported in a patient more than once per group. These three patients who developed pneumonia had prolonged hospital courses that were related to comorbid conditions. One patient (302-029) was a 28-year old male with a history of intravenous drug use who developed *Staphylococcus haemolyticus* bacteremia, bilateral pneumonia, and subsequent abscesses of the left arm and leg. The other two patients (303-15 and 304-37) were both greater than 60 years of age and had past medical histories including diabetes mellitus, hypertension, ischemic stroke and cardiovascular disease. None of these observations of secondary infection could be directly attributed to the use of iclaprim.

Study Treatment Discontinuations

Treatment-emergent AEs (TEAEs) resulting in early discontinuation of study medication in both Phase 3 studies occurred in 12 (2.4%) of the iclaprim-treated patients and 6 (1.2%) of the linezolid-treated patients. Death was the outcome in 3 patients in the iclaprim group, and none associated with premature discontinuation in the linezolid group.

Table 7.4: Reasons for patients not completing the study

	Iclaprim n (%)	Linezolid n (%)
Patients randomized	508	503
Excluded from all evaluations[1]	1	0
Randomized but never treated	7	12
ITT safety population	500	491
Completed study therapy[2]	451	441
Treated but withdrawn prematurely	46	39
Consent withdrawn	10	8
Infection-related reasons	3	6
Treatment-emergent cardiovascular abnormality	2	2
Treatment failure	5	1
Lost to follow-up	6	7
Adverse event	4	5
Death	3	0
Other[3]	13	10

[1] Patient 103-01 was excluded from all evaluations due to non-compliance of the study site with GCP.
[2] Patient 616-37, who completed the study, was randomized to receive iclaprim but was dosed with linezolid.
[3] Patient 100-011, who did not complete the study, was randomized to the linezolid arm but was dosed with iclaprim.

Treatment Emergent Adverse Events

The overall incidence of TEAEs (sorted by preferred term) in ASSIST-1 and ASSIST-2 was 49.8% (249 of 500 patients) in the iclaprim treatment group and 52.3% (257/491) in the linezolid treatment group.

- The most commonly reported TEAE between the two groups was nausea, which was observed in 39 (7.9%) of 491 linezolid patients and 30 (6%) of 500 iclaprim patients. Similarly, 53 (10.8%) in the linezolid group experienced one of the following symptoms: nausea, vomiting or dyspepsia; compared to 43 (8.6%) in the iclaprim group.
- The most commonly reported TEAEs among the iclaprim-treated patients was elevation in alanine aminotransferase (ALT). Thirty six (36) patients (7.2%) experienced an elevation in either ALT or aspartate aminotransferase (AST), or both. Similarly, in the Linezolid group, 34 (6.9%) experienced a transaminase elevation.
- TEAEs that occurred with increased frequency in the iclaprim-treated group were those reporting at least one of the following: pyrexia, chills, feeling cold, cold sweat or increase in body temperature. There were 47 (9.4%) in the Iclaprim group, and 26 (5.3%) in the linezolid group. Also, the emergence of an abscess (regardless of location) occurred in 17 (3.4%) iclaprim-treated patients, compared to 10 (2%) in the linezolid group.
- Diarrhea or frequent bowel movements occurred in 29 (5.8%) of iclaprim-treated patients compared to 23 (4.7%) of linezolid-treated patients. Among those reporting abdominal pain (as discomfort, tenderness or distension) there were 17 (3.4%) patients in linezolid group, and 10 (2%) in the iclaprim group.

The most common TEAE (listed by preferred term) are described in the table 7.5.

Table 7.5: AEs in at Least 2% of the Iclaprim-Treated Group

Preferred Term	Iclaprim n = 500	Linezolid n = 491
ALT increased	33 (6.6%)	32 (6.5%)
AST increased	32 (6.4%)	27 (5.5%)
Headache	32 (6.4%)	30 (6.1%)
Nausea	30 (6.0%)	39 (7.9%)
Diarrhea	29 (5.8%)	22 (4.5%)
Constipation	27 (5.4%)	20 (4.1%)
Pyrexia	26 (5.2%)	11 (2.2%)
Pruritus	20 (4.0%)	18 (3.7%)
Anemia	18 (3.6%)	20 (4.1%)
Dizziness	16 (3.2%)	10 (2.0%)
Insomnia	16 (3.2%)	18 (3.7%)
Rash	14 (2.8%)	17 (3.5%)
Hypertension	12 (2.4%)	11 (2.2%)
Pain in extremity	12 (2.4%)	8 (1.6%)
Vomiting	12 (2.4%)	12 (2.4%)
Anxiety	11 (2.2%)	5 (1.0%)
C-reactive protein increased	11 (2.2%)	8 (1.6%)
Body temperature increased	10 (2.0%)	3 (0.6%)

Data relate to numbers of patient events and percentages of patients

Renal Adverse Events

There were two patients, who were reported to have a serious renal adverse event associated with the use of iclaprim at a dosage of 0.8 mg/kg bid for up to 14 days. One of these events was reported in association with a death (subject 306-034) and was previously discussed. The FDA

reviewer determined that the development of acute renal failure in this patient and death were possibly related to treatment with iclaprim.

The second event occurred with subject 133-01. He was a 38-year old male, who was treated with iclaprim for cellulitis of the elbow starting on the (b)(6). He only received two days of therapy before the investigator discontinued the study medication as the patient was not responding to treatment. His therapy was switched to clindamycin and vancomycin, and he was transferred to another hospital, where Zosyn and azithromycin were added to his treatment regimen. On (b)(6), his laboratory investigations showed an elevated creatinine level (4.4 mg/dL). A subsequent renal biopsy revealed acute tubular necrosis. With the new antibiotic agents, his arm began showing improvement and creatinine levels returned to normal. The FDA reviewer determined that the development of this SAE was possibly related to treatment with Iclaprim.

Renal adverse events comprised of 2.8% of all AEs reported in the iclaprim group. There were no drug discontinuations due to treatment emergent renal failure or azotemia.

Cardiac Adverse Events

The findings of pooled clinical observations and QT measurements from ASSIST-1 and ASSIST-2 were consistent with pre-clinical studies demonstrating a dose-dependent increase in QTc with iclaprim. In comparison to linezolid, iclaprim demonstrated a higher mean ΔQTc, and exposure-response analyses revealed a significant association between iclaprim AUC_{0-12} and QTc increases > 30 ms. Additionally, the incidence of iclaprim-treated patients who exceeded QT/QTc prolongation threshold of 60 ms occurred at approximately twice the rate seen with linezolid across all risk groups.

Summary of ΔQT, Combined Phase 3

	Iclaprim	Linezolid
Day 1		
Mean ΔQT	12.1	4.3
95% CI	10.77, 13.41	2.94, 5.59
n > 30 ms	54 (11.0%)	13 (2.7%)
n > 60 ms	0	1 (0.2%)
Day 4 ± 1		
Mean ΔQT	22.3	17.3
95% CI	19.80, 24.89	14.74, 19.83
n > 30 ms	184 (38.3%)	140 (29.2%)
n > 60 ms	48 (10.0%)	26 (5.4%)

Summary of ΔQTc (Friderica)

	Iclaprim	Linezolid
Day 1		
Mean ΔQTcF	8.9	2.6
95% CI	7.90, 9.98	1.51, 3.61
n > 30 ms	16 (3.2%)	4 (0.8%)
n > 60 ms	1 (0.2%)	1 (0.2%)
Day 4 ± 1		
Mean ΔQTcF	10.6	6.1
95% CI	9.05, 12.18	4.55, 7.68
n > 30 ms	58 (12.1%)	24 (5.0%)
n > 60 ms	3 (0.6%)	2 (0.4%)

Summary of ΔQTc (Friderica), female patients

	Iclaprim	Linezolid
Day 1		
Mean ΔQTcF	8.3	3.5
95% CI	6.54, 10.07	1.68, 5.34
N > 30 ms	7 (4.1%)	3 (1.9%)
N > 60 ms	0	0
Day 4 ± 1		
Mean ΔQTcF	11.0	8.2
95% CI	8.38, 13.65	5.50, 11.00
N > 30 ms	19 (11.2%)	11 (7.1%)
N > 60 ms	0	1 (0.6%)

Summary of ΔQTc (Friderica), male patients

	Iclaprim	Linezolid
Day 1		
Mean ΔQTcF	9.3	2.1
95% CI	7.99, 10.57	0.81, 3.38
N > 30 ms	9 (2.8%)	1 (0.3%)
N > 60 ms	1 (0.3%)	1 (0.3%)
Day 4 ± 1		
Mean ΔQTcF	10.4	5.1
95% CI	8.46, 12.34	3.19, 7.00
N > 30 ms	39 (12.5%)	13 (4.0%)
N > 60 ms	3 (1.0%)	1 (0.3%)

Certain patient sub-groups of particular interest were also more closely analyzed. Day 1 and Day 4±1 mean ΔQTcF data revealed similar effects on ΔQTcF in men and women, as shown above.

Other high-risk subgroups were also specifically evaluated: patients with baseline cardiovascular disease, QTcB ≥ 420 ms, patients 65-74 years of age at study enrollment, or patients who were on concomitant CYP3A4/5 inhibitors. In these subgroups, mean QTcF at day 4 was generally a bit higher for iclaprim-treated patients than linezolid patients. Two patients taking CYP3A4/5 inhibitors accounted for 3 of the patients in the iclaprim group who exceeded ΔQTcF thresholds on Day 4±1 with a measurement > 60 ms.

In the combined Phase 3 studies, there were no reported severe AEs, such as torsade de pointes or ventricular arrhythmias related to QTc prolongation, associated with the use of iclaprim for up to 14 days at a dosage of 0.8 mg/kg bid. No significant differences were noted in the incidence of abnormal vital signs between the two treatment groups. However, there are reports of two deaths in ASSIST-1 that may have had a cardiac etiology. Patient 306-033, who was "found unconscious", had two preceding QTcF measurements that were prolonged in post-dose measurements (ΔQTcF's on Days 1 and 4, were +33.7 ms and +16 ms respectively). Likewise, patient 306-034, was "found unconscious" and had prolonged QTcF measurements compared to baseline (ΔQTcF were +7.3 ms on Day 1 and +44 ms on Day 4).

Two patients in the iclaprim group were withdrawn from the study due to QTc prolongation on 12-lead ECG. At the time of the study, patient 802-02 was 81 years of age and had a history of hypertension and peripheral arterial disease. She received only one study dose, and her post-dose mean QTcF increased to 413 ms from a baseline of 405 ms. One patient was withdrawn from the study due to two consecutive ECG readings with an increase of QTc from baseline of more than 60 ms: Patient 619-23 received four days of iclaprim, and on the third and fourth day of treatment she had elevations from baseline > 60ms. At the time of the study, she was 56 years of age and had a history of MI, cirrhosis and was on an escalating dose of methadone. The investigator and FDA reviewer determined that these events were probably related to the use of iclaprim. Two patients in the linezolid group were also discontinued for the same reason.

The data on drugs that prolong the mean QT/QTc interval by more than around 5 and less than 20 ms are inconclusive, but some of these compounds have been associated with pro-arrhythmic risk.

Hepatic Adverse Events

One patient experienced a severe hepatic adverse event in ASSIST-2. Patient 455-007 experienced elevations in aminotransferases, which the FDA reviewer determined to be possibly due to iclaprim-associated hepatotoxicity. At consent, the patient was a 23 year-old white male, who had a post-traumatic infected wound of the left calf. He received 10 days of therapy with iclaprim. At TOC (13 days after his last dose of iclaprim), blood test results showed abnormal liver function tests. A flow chart of liver function tests are summarized in the following table:

Liver function Tests for patient 455-007

	AST (U/L)	ALT (U/L)	Bilirubin (µmol/L)	ALP (U/L)
Baseline	19	15	2.4	82
Day 3	19	17	5.6	83
Day 10 (EOT)	14	17	5.0	76
Day 21 (TOC)	314[b]	1007[b]	18.0	122[a]
Day 34	57	264		
Day 42 (LFU)	51[a]	88[a]	10.3	98

[a] greater than the upper limit of normal (ULN), [b] >3x ULN, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, EOT: end of therapy, TOC: test of cure, LFU: Long-term follow-up

He was on no other concomitant medications during the course of his therapy or prior to the abnormal blood tests. The patient did not have any clinical signs or symptoms and was referred to a specialized hepatology clinic for additional assessment, where viral hepatitis was ruled out. Direct bilirubin was not detected. Abdominal ultrasound revealed no changes in the liver, gallbladder or biliary tract, and no signs of portal hypertension were detected. The patient experienced nausea, vomiting, and asthenia during the hospitalization period and his treatment included a diet and glucose infusions. On Day 35, the patient was prescribed an oral combination of essential phospholipids (Essentiale) tablets and discharged. Subsequently, his ALT and AST levels decreased to within the normal ranges, and the patient recovered.

There were no study drug discontinuations due to elevation in aminotransferases, bilirubin or alkaline phosphatase in the iclaprim group. None of the deaths in the iclaprim group were associated with abnormal liver function tests or indications of hepatotoxicity. Additionally, there were no cases that met criteria for Hy's Law [aminotransferase elevation greater than three times the upper limit of normal (ULN) with findings of cholestasis or elevation of total bilirubin >2xULN]. However, evaluation of clinical chemistry values revealed that there were a higher number of patients treated with iclaprim who experienced elevations of ALT >3xULN at TOC and LFU, and slightly more patients at LFU up who were found to have elevations in AST >3xULN. Neither patient group demonstrated a pattern of elevation in bilirubin or alkaline phosphatase or an excess in elevation in comparison to the other.

Summary of liver function tests: Number of Patients with Extreme values

ALT >3xULN	Iclaprim	%	Linezolid	%
EOT	14	2.92	17	3.62
TOC	18	3.87	13	2.86
LFU	24	5.25	8	1.83

AST >3xULN	Iclaprim	%	Linezolid	%
EOT	6	1.25	9	1.92
TOC	14	3.01	13	2.86
LFU	15	3.28	10	2.28

Bilirubin >2xULN	Iclaprim	%	Linezolid	%
EOT	0		0	
TOC	1	0.22	0	
LFU	0		0	

ALP >3xULN	Iclaprim	%	Linezolid	%
EOT	3	0.60	3	0.61
TOC	2	0.40	2	0.40
LFU	2	0.40	1	0.20

The drugs that have caused severe liver injury in humans generally have not shown dose-related toxicity, and generally have caused low rates of severe injury in humans (1 in 5,000 to 10,000 or less). Such idiosyncratic reactions due to iclaprim may not be revealed in a safety population of approximately 500.

Hematologic Adverse Events

Anemia was reported as a treatment emergent adverse event in 18 (3.6%) patients treated with iclaprim, which was comparable to linezolid (4.1%). There were no reported severe adverse reactions or adverse hematologic events in the iclaprim group that resulted in study drug discontinuation. Anemia was listed as an adverse event associated with the deaths of two patients (306-027 and 306-033) that were treated with iclaprim; however, no direct relation can be confirmed as both patients had multiple co-morbid conditions.

Except for platelet count, no considerable differences were seen between the two groups' hematologic parameters, either outside the normal range at each study visit or by change in mean values between baseline and each study visit. An increase in platelet count during the treatment period was somewhat more marked in the iclaprim group (108.25/mm^3, with a standard deviation of 184.45), as compared to the linezolid arm (36.87/mm^3, with a standard deviation 135.27). Leukocyte counts were elevated in both treatment groups at baseline, which is consistent with the patients having an infectious disease.

VIII. ISSUES FOR DISCUSSION

1. Do the data presented demonstrate the safety and effectiveness of iclaprim for the treatment of cSSSI?

- If your answer is yes, are there any specific issues that should be addressed in labeling?
- If your answer is no, what additional data/studies are needed?

2. Should there be any limitations on the use of iclaprim? In your response, discuss the following:

- The comparative outcomes for iclaprim and linezolid from the phase 3 trials
- The specific clinical situations where iclaprim should be used
- The basis for any specific restrictions