L-1512

Clinical Efficacy of Iclaprim in Complicated Skin and Skin Structure Infection (cSSSI): Results of Combined ASSIST Phase III Studies

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ABSTRACT

Background: The clinical efficacy of iclaprim (ICL) vs linezolid (LZD) was evaluated at the test-of-cure (TOC) visit using the combined data set of two essentially identical randomized, multicenter, double-blind, Phase III clinical trials.

Methods: Patients with cSSSI were treated for 10–14 days with IV ICL 0.8 mg/kg *q* 12 hours or IV linezolid (LZD) 600 mg *q* 12 hours.

The efficacy endpoint was clinical cure rate at the TOC visit (7–14 days post-treatment) in the intent-to-treat (ITT), the per protocol (PP) and modified clinically evaluable (MCE) populations.

Results: The ITT, PP and MCE populations comprised 991 (ICL: 500; LZD: 491), 823 (ICL: 415; LZD: 408) and 885 (ICL: 440; LZD: 445) patients, respectively.

The distribution of the infection types was very similar in both treatment groups and encompassed: wound infections (30%)*, cellulitis (38%), major abscesses (26%)**, infected ulcers (11%) and first- or second-degree burns (10%).

Staphylococcus aureus (591 isolates) accounted for 69.9% of all Gram-positive pathogens and 39.9% were methicillin-resistant *S. aureus* (MRSA).

High clinical cure rates were observed in the ITT, PP and MCE populations and were 82.2% (95% CI = 78.6–85.5%), 92.3% (95% CI = 89.3–94.7%) and 87.0% (95% CI = 83.5–90.0%) respectively for ICL and 85.3% (95% CI = 81.9–88.4%), 97.8% (95% CI = 95.9–99.0%) and 89.7% (95% CI = 86.5–92.3%) respectively for LZD.

Conclusions: ICL showed high efficacy in patients with cSSSI, which was comparable to LZD. ICL could be an important new therapeutic option for treatment of cSSSI, especially those caused by MRSA.

*Corrected from 19% in submitted abstract

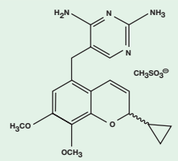
** Corrected from 25% in submitted abstract

BACKGROUND

- Complicated skin and skin structure infections (cSSSI) account for approximately 10% of hospital admissions. *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]) and *Streptococcus pyogenes* comprise the most common Gram-positive pathogens in this indication.[1]
- The increasing prevalence of MRSA in hospital and community infections[1–3] and the potential for resistance or emergence of resistance during therapy to available therapeutic options such as vancomycin,[4,5] linezolid (LZD)[6,7] and daptomycin[8] has created a need for additional therapeutic agents.[9,10]
- Iclaprim (ICL), a new generation diaminopyrimidine compound, has recently completed pivotal Phase III trials for the treatment of patients with cSSSI.[11,12] ICL has a differentiated mechanism of action compared with drugs used in this indication and inhibits bacterial dihydrofolate reductase, a critical enzyme in the bacterial folate synthesis pathway. ICL exhibits potent *in vitro* activity against predominant Gram-positive pathogens associated with cSSSI, including MRSA.[13,14]
- This poster describes the combined results from the two essentially identical double-blind, randomized, multicenter, Phase III clinical trials (ASSIST-1 and ASSIST-2). The primary objectives of this combined analysis were to compare (1) the clinical and microbiological efficacy of ICL with that of LZD and (2) the safety and tolerability of ICL with that of LZD.

The results show that ICL demonstrates high clinical and microbiological cure rates and is well-tolerated in patients suffering from cSSSI. The lower bound of the confidence interval of the treatment difference for the ITT, PP and MCE populations is within -10% for the combined studies.

Figure 1: Molecular structure of iclaprim mesylate.



Iclaprim mesylate

ICAAC/IDSA 2008

METHODS

(1) Study design

- Both ASSIST studies were randomized, multi-centre, double-blind, Phase III studies of essentially identical design.
- Based on the identical design of the two ASSIST studies, a combined analysis was possible by merging the datasets into a single database to evaluate the efficacy and safety of ICL in a larger population.
- Male and female patients with cSSSI infections, ≥18 years old, compliant with inclusion/exclusion criteria were enrolled in the studies.
- Patients were treated for 10–14 days with either
  - ICL 0.8 mg/kg infused over 30 minutes every 12±2 hours
  - or LZD 600 mg infused over 30 minutes every 12±2 hours.
- Concomitant medications:
  - Permitted: aztreonam and metronidazole for the treatment of Gram-negative and anaerobic involvement, respectively, in mixed infections.
  - Prohibited: other systemic or topical antibiotics, steroids or class IA/III anti-arrhythmic drugs.
- Clinical status determined at Test-of-Cure (TOC) 7–14 days post-treatment, is presented.

Table 1: Study populations

Patients populations	
Intent-to-Treat (ITT)	Includes all randomized patients who received at least one dose of study medication
Modified Intent-to-Treat (MITT)	Includes all patients in the ITT population who had an infecting Gram-positive pathogen isolated at baseline
Per Protocol (PP)	Those in the PP population met all of the following conditions: 1. *Met clinical criteria for study infection and all inclusion/exclusion criteria.* 2. *Had no major protocol violations.* 3. *Were treated for a minimum of 4 calendar days and received at least seven doses of study medication.* 4. *Did not receive other systemic antibacterial therapy (except permitted aztreonam or metronidazole) before TOC assessment.* 5. *Had the necessary clinical evaluations performed i.e., EOT and TOC evaluations, and were classified as cure or failure.*
Modified Clinical Evaluable (MCE)	Same as the PP population but included clinically evaluable patients whose only protocol violation was use of additional systemic or topical prohibited antibiotics or high-dose steroids
Microbiologically Evaluable (ME)	Three ME populations were evaluated: • MEPP: All patients in the PP population who had an infecting Gram-positive pathogen at baseline • MITT: All patients in the ITT population who had an infecting Gram-positive pathogen at baseline • MEMCE: All patients in the MCE population with an infecting Gram-positive pathogen at baseline

(2) Patient selection

- Inclusion criteria:
  - Hospitalized patients diagnosed with cSSSI suspected or proven to be caused by Gram-positive pathogens.
  - Minimum of three local and one systemic sign or symptom of infection.
  - Severity of infection was assessed by the presence of two or more signs/symptoms of Systemic Inflammatory Response Syndrome (SIRS), and/or severe tenderness or erythema at infection site and/or positive blood culture at baseline.

(3) Microbiological assessment

- Examination of Gram stain was carried out before cultures were performed to identify pathogens isolated from the site of infection. Identification of pathogens and susceptibility testing were performed on all isolates by Eurofins Medinet (Washigton, DC, USA) according to current CLSI broth microdilution standards.

(4) Efficacy assessment

Evaluation of clinical cure was based on the following criteria:

- Resolution of signs and symptoms attributed to cSSSI present at baseline, or clinically relevant improvement of local and systemic signs and symptoms of cSSSI.
- No application of any systemic or topical antibacterial treatment up to and including the TOC visit.
- Minimum of 4 days of treatment and ≥ seven doses of study drug.

Evaluation of bacteriological eradication for each causative pathogen was based on the following criteria:

- Eradication/Presumed Eradication if the causative pathogen isolated at baseline was no longer present from any culture(s) at the TOC assessment or if the patient was a clinical cure at TOC and no material was available for culture from the original site of infection.

An overall therapeutic response was defined at TOC by assessing the number of patients for whom clinical outcome was Cure and bacteriological outcome was Eradication/Presumed Eradication.

(5) Safety Assessment

- All safety tabulations and listings are based on the Safety (ITT) population, defined as all subjects who received at least one dose of study medication.
- Assessment of safety included report of AEs, and changes in laboratory parameters, evaluation of ECGs* and vital signs. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA), version 8.0.

* QT data are the object of a separate poster (number L-1513) presented at this meeting.

RESULTS

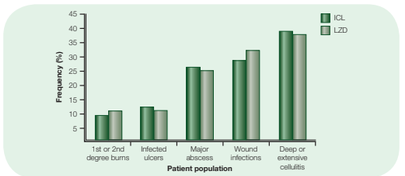
Clinical efficacy

Table 2: Demographic data (ITT population).

	ICL (n=500)	LZD (n=491)
Mean Age, years (SD)	48.5 (15.2)	47.0 (14.9)
Age range	18.3 – 87.7	18.1 – 85.9
Gender, n (%)		
Male	322 (64.4%)	329 (67.0%)
Female	178 (35.6%)	162 (33.0%)
Mean BMI, kg/m² (SD)	26.7 (5.3)	26.3 (5.4)
BMI range	17.0 – 49.0	15.0 – 43.0

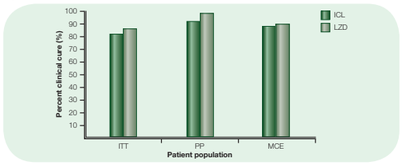
- Both treatment groups were well-balanced with respect to demographics at baseline.
- 92.4% of the patients in the ICL group and 92.9% of patients in the LZD group were categorized as having a severe infection. In addition, 46.4% (ICL) and 46.4% (LZD) were diagnosed as having SIRS.

Figure 2: Frequency of infection type in the ITT population at baseline.



- The frequency of infection types was comparable in both treatment groups (patients could have more than one infection type).

Figure 3: Clinical cure at TOC visit (ITT, PP and MCE populations)



- ICL exhibited high clinical cure rates across all study populations.
- ICL cure rates were comparable to those of LZD in all study populations.

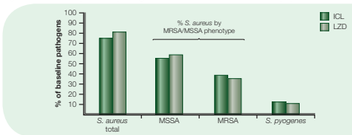
Table 3: Statistical analysis of clinical cure at TOC visit – ITT, PP and MCE populations

Patient populations	ICL	LZD
ITT	(n=500)	(n=491)
Clinical cure	82.2%	85.3%
95% CI	78.6%–85.5%	81.9%–88.4%
PP	(n=415)	(n=408)
Clinical cure	92.3%	97.8%
95% CI	89.3%–94.7%	95.9%–99.0%
MCE	(n=440)	(n=445)
Clinical cure	87.0%	89.7%
95% CI	83.5%–90.0%	86.5%–92.3%

- The protocol defined primary end point was fulfilled for both studies and for each of the co-primary populations (ITT and PP).
- The lower bound of the 95% CI for the treatment difference (ICL-LZD) was within -10% for all populations (ITT, PP and MCE) based on the combined study data.

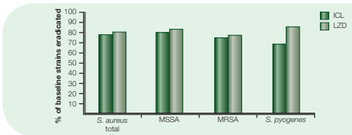
Microbiological efficacy

Figure 4: The most prevalent pathogens isolated at baseline in the MITT population.



- *S. aureus* was the most commonly-isolated baseline pathogen (over 75%) in both treatment groups.
- Approximately 40% of *S. aureus* isolates were MRSA.
- *S. pyogenes* was the second most common pathogen at baseline (13% of Gram-positive isolates).

Figure 5: Eradication/presumed eradication (%) of baseline pathogens (MITT population).



- ICL exhibited high eradication rates for both MRSA and MSSA comparable to those of LZD;
- MRSA eradication rates for ICL (76.4%) were similar to those for LZD (78.7%).
- Eradication rates in the ICL group were similar for the most common cSSSI pathogens: 79.5%, 76.4% and 70.7% for MSSA, MRSA and *S. pyogenes*, respectively.

Table 4: MIC_{50} and MIC_{90} of ICL and LZD against Gram-positive pathogens most frequently isolated at baseline.

Pathogen	# isolates	ICL		LZD	
		MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Total *S. aureus*	584	0.12	0.25	2	2
MSSA	349	0.12	0.25	2	2
MRSA	235	0.12	0.12	2	2
S.pyogenes	112	0.015	0.12	1	1
β-haemolytic streptococci*	51	0.12	0.25	1	1

**S. agalactiae* and *S. dysgalactiae* subsp. *equisimilis*

- ICL was the most active compound tested with MIC_{90} values several-fold lower than those for LZD, or vancomycin (data not shown), for MRSA and MSSA respectively.
- No changes from baseline MICs were observed for ICL for any of the isolates.

Safety and tolerability profile

Table 5: Adverse events (AEs) in the ITT population.

	ICL (n=500)	LZD (n=491)
	Total number of patients (%)	
Total AEs	245 (49.0)	249 (50.7)
Total AEs possibly/probably related to study drug	113 (22.6)	137 (27.9)
AEs possibly/probably related to study drug (by preferred term in at least 1% of patients) by system organ class:		
Gastrointestinal disorders	37 (7.4)	51 (10.4)
General disorders and administration site conditions	21 (4.2)	19 (3.9)
Investigations	42 (8.4)	48 (9.8)
Nervous system disorders	24 (4.8)	32 (6.5)
Skin and subcutaneous tissue disorders	21 (4.2)	22 (4.5)

- AEs were less frequent in the ICL group when compared to LZD group.

CONCLUSIONS

- **>90% of patients in the ASSIST studies were classified as having severe infections**
- **The demographics and baseline conditions were well balanced and comparable between the ICL and LZD treatment groups**
- **All populations (ITT, PP and MCE) met an NI margin of -10% for the combined study data.**
- **ICL showed high clinical cure rates in all study populations and these rates were similar to those observed for LZD.**
- **The most common pathogens isolated at baseline were *S. aureus* and *S. pyogenes*.**
- **MRSA accounted for approximately 40% of *S. aureus*.**
- **ICL exhibited high eradication rates for all major causative organisms, including MRSA, MSSA and *S. pyogenes*.**
- **No changes from baseline MICs were observed for ICL for any of the isolates.**
- **Safety and tolerability of ICL compared favourably with that of LZD.**
- **In conclusion, based on the clinical experience to date, ICL appears a safe and effective potential alternative for the treatment of cSSSI, including those caused by MRSA and group A Streptococcus.**

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