European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 4 December 2009
Doc. Ref: EMA/CHMP/697798/2009

WITHDRAWAL ASSESSMENT REPORT FOR

MERSAREX
(iclaprim mesylate)

EMEA/H/C/1057

Day 180 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu. http://www.emea.europa.eu

TABLE OF CONTENTS

I. RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for Mersarex (iclaprim), in the "the treatment of complicated skin and soft-tissue infections (cSSTI)", is not approvable since identified "major objections" have not been resolved. These objections preclude a recommendation for marketing authorisation at the present time. The major efficacy and safety objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

- The applicant's answers to the major efficacy objections and other concerns in relation to the efficacy results from the two pivotal ASSIST studies do not provide convincing clinical evidence in support of the non-inferiority of iclaprim to linezolid in the sought indication at large. Consequently, there is insufficient evidence to support a favourable efficacy conclusion for the use of iclaprim in the treatment of adult patients with cSSTI at the recommended dosage of 0.8 mg/kg twice daily (with a maximum of 100 mg per dose) up to 14 days.

  The dosage regimen is not adequately supported by the rather limited clinical data especially in severe cSSTI nor the pharmacokinetic profile and experimental findings concerning T/>MIC; the major objection in relation to pharmacodynamics is not resolved whereas the assessment of the susceptibility table in section 5.1 of the SPC cannot be finalised.

- Iclaprim at the recommended dose level has a narrow cardiac safety margin. Iclaprim has demonstrated propensity to induce a dose dependent QTc interval prolongation in healthy subjects. The applicant's clarifications and available limited database on iclaprim do not provide assurance for the safe use of Mersarex at the recommended dose level in the targeted population of patients at large.

- Similarly, there is insufficient assurance based on the limited available data that iclaprim is not hepatotoxic at the recommended dose level. It remains unclear why increase in ALT values develops long after stopping iclaprim despite the observation that in vitro mitochondrial toxicity data on human hepatocytes did not reveal adverse effects. Present limited patient database and analyses do not allow identification of patients (with normal or slightly increased LFT values at baseline) with increased risk for liver function test elevations in order to include targeted precautions in the SmPC for such patients. Although, in the light of present limited patient database a risk factor analysis (e.g. patients with underlying conditions, concomitant medications) is not expected to generate conclusive findings the applicant should conduct risk factor analysis with the available data collected in clinical programme in order to identify patients with increased risk for liver function test elevations.

Overall, the provided response of the applicant to CHMP Day 120 List of Questions does not change the earlier conclusion of the CHMP that on the basis of available data, the major cardiac and hepatic concerns outweigh the questioned benefit whereas there is no sufficient clinical evidence provided that Mersarex is beneficial in special patient groups failing other antibiotics or intolerant to standard antibiotics used in the treatment of cSSTI.

Proposal for Questions to be posed to additional Experts
N/A

Proposal for Inspection.
N/A

II. EXECUTIVE SUMMARY

II.1 Problem statement

Skin and soft tissue infections (SSTIs) comprise a broad range of clinical presentations. These infections are typically classified as complicated (cSSTIs) if they require surgical intervention, involve deeper soft tissue such as fascia or muscle, or occur in patients with significant underlying disease that complicates (diabetes mellitus, neoplastic disease, HIV or peripheral vascular disease) the response to treatment. cSSTIs may be community-acquired, health-care associated or nosocomial as the result of hospitalisation itself or surgical intervention. They include infections complicating local traumatic injury or bite injury, burns, surgical procedures, major abscesses, cellulitis, fasciitis, diabetic foot infection (DFI), infected ischemic or decubitis ulcers, complicated erysipelas. Besides anti-microbial therapy, surgical intervention is commonly required in cSSTIs, such as surgical debridement[1] and/or incision and drainage of abscesses and amputation of diabetic foot.

In clinical practice, postoperative surgical site infections represent up to 25% of all nosocomial infections, and their treatment generally requires hospitalization. The pathogens involved in cSSTIs mainly depend on the location of infection and reflect the bacterial flora at the anatomical site of the infection. Most frequently isolated pathogens in cSSTIs are gram-positive aerobes like *S. aureus* and *Str. pyogenes,* followed by gram-positive anaerobic species and gram-negative bacteria like *Pseudomonas* and *Enterobacter* species. According to the SENTRY Antimicrobial Surveillance Program in the United States and Canada, the major pathogens isolated from SSTIs include: *S. aureus* (45.9%), *P. aeruginosa* (10.8%), *Enterococcus sp*ecies (8.2%), *E. coli* (7.0%), *Enterobacter sp*ecies (5.8%), and *Klebsiella sp*ecies (5.1%). *Proteus mirabilis* (3.0) and *beta -hemolytic streptococci (5.1%)*[2]. Gram-negative bacteria are isolated more frequently in severe and polymicrobial infections.

Diabetic patients with infections involving the foot represent an important subgroup of patients with cSSTI.

Methicillin-resistant *S. aureus* (MRSA) prevalence in skin and skin structure infections varies greatly among countries in Europe with an incidence of MRSA was 1% to 10% in Germany, Sweden, Denmark, Finland, the Czech Republic, and Iceland, 10% to 25% in Austria, Belgium, and Luxembourg, and more than 25% in the United Kingdom, Spain, Ireland, Italy, Greece, Portugal, Bulgaria, and Malta. In the United States, the proportion of MRSA isolates increased from 2% in 1975 to 35% in 1996, and was most recently reported to be the cause of nearly 60% of infections in patients presenting to emergency rooms for treatment with skin infections. The widespread emergence of Panton-Valentine leukocidin gene (PVL)-positive MRSA has exacerbated the problem and created the potential for more virulent infections. In areas where the prevalence of MRSA is high or in high risk patients, an empiric therapy that covers MRSA is required.

Since MRSA is also resistant to many other antimicrobial agents, both beta–lactams and non-beta-lactams (e.g. clindamycin, rifampicin), glycopeptides, especially vancomycin, and more recently approved agents such as linezolid, daptomycin, and tigecycline, have been considered as appropriate, empiric treatment for infections suspected or proven to be caused by methicillin-resistant organisms. With a single exception, tigecycline, these agents have no or negligible activity against gram-negative bacteria. There is a need for new anti-MRSA drugs among others due to the emergence of strains with decreased susceptibility to glycopeptides or full-blown glycopeptide resistance and the potential for the emergence of resistance to linezolid the first available alternative to the glycopeptides, especially among *S. aureus.*

[1] See e.g. N Engl J Med 355:724, August 17, 2006 *Editorial*

[2] Rennie RP, Jones RN, Mutnick AH, and the SENTRY Program Study Group (North America). Occurrence and antimicrobial susceptibility patterns of pathogens isolated from skin and soft tissue infections: Report from the SENTRY Antimicrobial Surveillance Program (United States and Canada, 2000). Diagn Microbiol Infect Dis 2003,45:287–293. EDMS-PSDB-6795896.

Iclaprim binds to target Gram-positive bacterial DHFR with an affinity many-fold higher than TMP. This results in an 8-10 fold increased *in vitro* activity compared to TMP, expanding the spectrum of activity of iclaprim to include TMP-resistant *S. aureus* in addition to MRSA. Iclaprim has a bactericidal mode of action.

Iclaprim does not show cross resistance to glycopeptides, linezolid or other anti MRSA drugs. Hence this drug seems to have the potential to further expand the choice of drug classes available to treat serious cSSTI infections caused by Gram-positive organisms, especially MRSA.

It is active against clinically relevant gram-positive pathogens in cSSTI: *Staphylococcus aureus* (including MRSA), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae* subsp. *Equisimilis,* Group G streptococci, *Enterococcus faecalis.*
It has no clinically relevant activity against gram-negative bacteria.

The presently sought slightly revised therapeutic *indication* for Mersarex is "Mersarex is indicated for the treatment of complicated skin and soft-tissue infections (cSSTI). See section 4.4 for the limitations of the studied population. Iclaprim is active against Gram positive bacteria (see section 5.1). Combination therapy may be indicated if a concomitant Gram-negative pathogen is documented or suspected. Consideration should be given to official guidance on the appropriate use of antibacterial agents".

The slightly revised standard *recommended dosage* regimen is administration of 0.8 mg/kg body weight, administered intravenously twice daily (every 12 hours) for 8-14 days (see section 5.1). The maximum single dose of Mersarex to be administered is 100 mg.~~or until the infection is resolved (see Section 5.1)~~.
Mersarex is given by intravenous infusion (see section 6.6) and administered over a 30-45 minute period. The concentrate solution is to be diluted in 250 ml of 0.9% sodium chloride injection solution or Dextrose 5% solution may be used for the infusion solution. Each dose of Mersarex should not exceed 100 mg.

No dose adjustment is required in patients with renal insufficiency. No dose adjustment is necessary when administering Mersarex to patients with mild hepatic insufficiency (Child-Pugh Class A) (see Section 5.2). A dose reduction of 50% is recommended for patients with moderate hepatic insufficiency (Child-Pugh Class B). No data are available in patients with severe hepatic insufficiency (Child-Pugh Class C); as requested these patients are contraindicated now the present SmPC.

Mersarex is not recommended for use in children below age 18 due to insufficient data on safety and efficacy.

II.2 About the product

Iclaprim mesylate is an antibiotic drug, a diaminopyrimidine derivative belonging to the class of DHFR inhibitors. It is developed as a parenteral formulation intended for serious infections. The mesylate salt was chosen because it formed a stable salt and could be formulated into an aqueous physiological solution. The racemate was chosen because both isomers of iclaprim have similar antimicrobial properties against a panel of 28 isolates of *S. aureus*". One ampoule of the formulation contains 5 ml concentrate of in total 81.4 mg of iclaprim mesylate corresponding to 64 mg of iclaprim base (12.8 mg iclaprim base in 1 ml), 0.7 w/V % of sodium chloride, 30 w/V % of dehydrated alcohol for injection to overcome the low solubility of iclaprim mesylate in physiological salt solution (1 mg/ml), 8.4 w/V % of povidone to inhibit the crystallisation of the drug substance during storage, and sodium hydroxide for pH adjustment to pH 5.0.

Iclaprim has a potent and selective action against microbial DHFR, including DHFR isolated from trimethoprim (TMP)-resistant and multidrug-resistant *S. aureus*, In addition, the particularly high potency against Gram positive pathogens is thought that it may allow the use of iclaprim as mono-substance, in contrast to TMP which needs the combination with a sulphonamide for sufficient

antibacterial efficacy. Pre-clinical studies demonstrated that iclaprim exhibits a rapid bactericidal action against important gram-positive bacterial pathogens, including multidrug resistant MRSA, and displays a minimal post-antibiotic effect.

II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

One Phase II study and two pivotal Phase III studies in patients (≥ 18 years of age) with cSSTI infections have been conducted as part of the iclaprim clinical programme in support of the sought clinical indication.

The clinical evidence of efficacy and safety of iclaprim in the sought indication is based on the results of two pivotal randomised double-blind comparative Phase III studies in various types of skin and soft tissue infections. See the table below.

Table 1. Phase II and III cSSTI Efficacy and Safety Studies

Study	Design	Iclaprim Dose	Location
AR-100-SSTI-001	Phase II, double- blind, efficacy and safety of Mersarex vs. vancomycin in patients with cSSTI	IV infusion: Patients were randomised (1:1:1) to receive Iclaprim 0.8 mg/kg, Iclaprim 1.6 mg/kg base or Vancomycin 1 g, b.i.d. All treatments for 10 days.	7 centres Germany, Latvia, Lithuania
ICLA-08-CSI1 (ASSIST-1)	Phase III, evaluator-blinded, comparative with Mersarex vs. Linezolid in patients (≥18 years of age) with cSSTI (at least in part) due to gram-positive pathogens.	Iclaprim: 0.8 mg/kg Iclaprim base i.v. q12h over 30 minutes (+15 min if indicated) infusion; Linezolid: 600 mg b.i.d. over 30 minutes i.v. infusion. Both treatments for 10-14 days	43 active centres North America and EUR
ICLA-09-CSI2 (ASSIST-2)	Phase III, evaluator-blinded, comparative with Mersarex vs. Linezolid, in patients (≥18 years of age) with cSSTI (at least in part) due to gram-positive pathogens.	Iclaprim: 0.8 mg/kg Iclaprim base i.v. q12h over 30 minutes (+15 min if indicated) infusion; Linezolid: 600 mg b.i.d. over 30 minutes i.v. infusion. Both treatments for 10-14 days	93 centres North America, EUR and South Africa

Note: Patients in whom Gram staining of culturable material indicated the presence of Gram-negative organisms were permitted to receive aztreonam. Patients who had anaerobic pathogens isolated from their infection site were allowed to receive metronidazole as a concomitant antibiotic.

As requested by the CHMP, the Phase III studies were confirmed to be evaluator blinded.

Supplementary safety data are derived from Phase I data.

At the initiation of the Mersarex development programme, the available therapeutic options with activity against Gram-positive bacteria, including MRSA, were quinupristin/dalfopristin, linezolid and daptomycin

The applicant has sought Scientific Advice on the development programme and/or application strategy from a few European regulatory authorities as follows:

Prior to initiation of the Phase 3 programme, scientific advice was requested from the EMEA in September 2004 and this advice was provided in December 2004. Specific points concerning protocol design raised by the regulatory authority were implemented into the Phase 3 study design. These included the following:

- Drug-Drug Interaction studies: The CHMP questioned the rationale for studying co-administration with ketoconazole. The applicant took into account emerging pharmacokinetic data as the major cytochromes involved in iclaprim metabolism are CYP 3A4 and CYP 2C19. Given that ketoconazole is a well-established inhibitor of CYP 3A4 and omeprazole is a well-established inhibitor of CYP 2C19, these compounds were further investigated in drug interaction studies.
- Phase II study design: The CHMP observed that the inclusion/exclusion criteria used in Phase 2 did not fully support Phase 3 plans. The recommendation regarding more stringent inclusion criteria for signs and symptoms of cSSTI was implemented in Phase III studies. See clinical assessment.
- Dosing: The CHMP asked why iclaprim dosing is on a mg/kg basis, suggesting that a single dose for adult patients (at least with normal hepato-renal function) should be explored. This is done but the dosing regimen is not substantially changed. See the clinical assessment.
- Dosing regimen: The CHMP advised that twice-daily dosing of a DHFR inhibitor based on an elimination half-life of 3 hours needs to be explained. The explanation is given, however, this is not entirely satisfactory, see the clinical and non-clinical assessment.
- QT prolongation: The CHMP advised the applicant to adhere to ICH Guidance E14. This advice was closely followed. The company attempted to do so. The results are not entirely satisfactory see clinical assessment.
- Choice of comparator: The CHMP noted that if vancomycin was used as the comparator, this would have to be justified based on the expectation of a high rate of encountering MRSA at sites chosen for the study. The applicant decided to use linezolid as the sole comparator because it is indicated for both MRSA and non-MRSA Gram-positive cSSTIs. In addition, like iclaprim, linezolid has a b.i.d. dosing regimen, which therefore facilitated blinding of the studies. Furthermore, inclusion criteria were changed to require a more stringent degree of patient's signs and symptoms of cSSTI.
- Non-inferiority margin: The CHMP noted that the choice of 12.5% as the clinically irrelevant difference would require adequate justification. Depending on the final inclusion criteria and, hence the nature of the population to be studied, the applicant was advised to consider using a delta of 10% or less for the sample size calculation and for the planned primary analysis of efficacy. The two Phase 3 studies were designed to be essentially identical and used the same comparator and number of patients in order to allow a combined analysis powered for -10%. However, to allow for replication of the results between studies, both individual studies were powered for -12%. See further clinical assessment.

Procedural pre-submission meetings were held with EMEA and with the Rapporteur.

The NfG on the Clinical Evaluation Medicinal Products Indicated for Treatment of Bacterial Infections (CPMP/EWP/558/95 rev.1) is applicable for this application.

II.4 General comments on compliance with GMP, GLP, GCP

All pivotal toxicity and safety pharmacology studies were done in compliance with GLP.

The applicant declared that all studies were conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice (GCP) and the Declaration of Helsinki.

II.5 Type of application and other comments on the submitted dossier

1. Legal basis
This is an application for a new active substance according to Article 8 (3) of Directive 2001/83/EC.
This is agreed upon.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Introduction

Mersarex was presented as ampoules filled with a concentrate for solution for infusion containing 12.8 mg/ml (64 mg/5 ml) of iclaprim mesylate (which corresponds to 16.28 mg/ml iclaprim mesylate base). Besides the active substance each ampoule would also contain the following excipients: ethanol, povidone and sodium chloride.

Active substance

Iclaprim (as mesylate) is the INN for the chemical substance 5-[((2*RS*)-2-Cyclopropyl-7,8-dimethoxy-2*H*-chromen-5-yl)methyl]pyrimidine-2,4-diamine methanesulfonate. The molecular formula is $C_{20}H_{26}N_4O_6S$ and the relative molecular mass 450.52 g/mol. There is no monograph for iclaprim mesylate in the Ph. Eur. Iclaprim mesylate is a racemic molecule and appears as a white to light yellow crystalline powder. It is a non-hygroscopic molecule which is soluble in methanol, sparingly soluble in water and slightly soluble in ethanol (at 23°C). Iclaprim mesylate is known to exist in different polymorph forms.

- Manufacture

Iclaprim mesylate active substance would be supplied by one active substance manufacturer. No Ph.Eur. Certificate of suitability has been issued for the active substance and consequently full information on the active substance has been provided by the active substance manufacturer. No Active Substance Master File (ASMF) procedure has been used for this marketing authorisation application.
The manufacturing route comprises three consecutive synthetic steps followed by a purification and milling step. Purification is achieved by recrystallisation.

- Specification

The iclaprim mesylate specifications include appropriate tests for appearance (visual examination), identity (IR-spectrophotometry, HPLC), heavy metals (Ph Eur), colour of solution (Ph Eur), pH (Ph Eur), loss on drying (Ph Eur), residue on ignition (Ph Eur), assay (HPLC), related substances (HPLC), residual solvents (HS-GC), phenylamine (GC-FID), methylmethane sulfonate and ethylmethane sulfonate (GC-MS) and finally, bacterial endotoxins (Ph Eur). The justification for the specifications is considered acceptable. In general an adequate drug substance specification is proposed. All issues related to potential formation of methylmethane sulfonate and ethylmethane sulfonate have been adequately settled, and adequate specifications are applied. Where necessary, the analytical methods have been adequately described and validated.

- Stability

The results of stability studies (up to 36 months data under long term and up to 6 months data under accelerated conditions) have been provided. In addition, the effects of temperature, oxidation and photolysis on iclaprim mesylate as well as its susceptibility to hydrolysis across a wide range of pH values were tested in forced degradation studies. The studies are performed in accordance to the ICH guidelines. The applicant claims a shelf life of 2 years in the proposed packaging without specific storage temperature (room temperature), The applicant committed to complete the on-going stability studies.

Medicinal Product

- Pharmaceutical development

The medicinal product is an ampoule containing 64 mg iclaprim (calculated as base) in a 5 ml concentrate for solution for infusion. One ampoule of 5 ml contains 81.4 mg of iclaprim mesylate corresponding to 64 mg of iclaprim base (12.8 mg iclaprim base in 1 ml), 0.7 w/v % of sodium chloride to achieve a close to physiological osmotic pressure, 30 w/v % of dehydrated alcohol for

injection to overcome the low solubility of iclaprim mesylate in physiological salt solution (1 mg/ml), 8.4 w/v % of povidone to inhibit the crystallisation of the drug substance during storage, and sodium hydroxide for adjustment to pH 5.0.
Regarding ethanol anhydrous the maximum daily dose based on 200 mg base will contain 4.69 g ethanol. It is remarked that this quantity of ethanol will be administered in diluted form (in ca. 781 ml). This daily intake of ethanol by two infusions of at least 30 min each does not have a toxicological significance.
During the maximum dosing the maximum intake of povidone will be 15.625 ml x 8.4% = 1.3125 g, being sufficiently below the ADI from WHO of 70 kg x 50 mg = 3.5 g, acceptable.
The pharmaceutical development is further well based.

- Manufacture of the product

Iclaprim ampoules 64 mg/5 ml are manufactured by straightforward pharmaceutical procedures involving preparation of the bulk solution, sterile filtration, filling, and terminal heat sterilisation.-The manufacturing process has been demonstrated to be robust and to produce a finish product of the desired quality within the agreed finished product specification.

- Product specification

The specification for Mersarex includes tests for: appearance of the ampoule and of the solution (visual examination), clarity, colour and pH of the solution (Ph Eur), identity of iclaprim (HPLC), assay of iclaprim base (HPLC), related substances (HPLC), methyl methane sulfonate and ethyl methane sulfonate (GC-MS), sub-visible particles (Ph Eur), bacterial endotoxins and sterility (Ph Eur).
In general adequate specifications for the drug product are applied including the Ph. Eur. test 2.9.40 Uniformity of dosage units.
All tests included in the specification have been satisfactorily described and validated, according to the state of the art. Appropriate data have been presented to justify the release specification for each quality characteristic that is controlled. Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety. Impurity levels are in accordance with the NfG on the limits of genotoxic impurities. However, the applicant improved the HPLC method for assay and impurities, and stated that the current method will be soon replaced by the improved method. Therefore, the applicant is asked to update relevant sections in the drug product and to provide batch analysis results and stability data based on the new improved HPLC method, and to define – based on found results – appropriate release and shelf-life specifications on total impurities.

- Stability

Stability studies have been carried out under long-term (25ºC, 60%RH), intermediate (30ºC, 65%RH), and accelerated (40ºC, 75%RH) conditions. The parameters tested are the same as those tested at release. In addition, forced degradation studies were performed with iclaprim concentrate for solution for infusion ampoules in order to ensure that the method for the determination of impurities and active substance content in iclaprim 64 mg/5 ml concentrate for solution for infusion ampoules is stability-indicating with regard to unspecified degradation products. The stress test experiments included samples stored under the following stress conditions: light, heat, acid/base hydrolysis and oxidation
At the time of the withdrawal, the applicant was asked to give further clarification on stability batches. In addition the applicant was asked to give further explanation on the different stability results and the two HPLC methods used for this purpose. The claimed shelf-life would be definitively assessed upon receiving responses on the issues above.

III.2 Non clinical aspects

Pharmacology
Iclaprim belongs to the diaminopyrimidines and is a competitive inhibitor of bacterial dihydrofolate reductase (DHFR). Iclaprim significantly inhibited bacterial DHFR. For toxicological implications, it is important whether iclaprim also inhibits human DHFR. IC50 for iclaprim against human DHFR is high (IC50 > 300 μM) compared to human iclaprim levels (Cmax approximately 0.8 μg/ml = 0.002 μM). However, in animal studies, effects were observed that indicate that there was effect on DHFR in animals: effects on red blood cell parameters and reproductive toxicity.

Chromosomal mutations in the *dfrB* gene of which F98Y is the most frequent in *S. aureus* corresponded to lower MICs in strains exposed to iclaprim than in strains exposed to TMP. For TMP all tested strains carrying the F98Y mutation were resistant whereas for iclaprim part of the tested strains were still susceptible. However, the majority of iclaprim-exposed strains with the F98Y mutation had MICs higher than 0.25 µg/ml. Because of the lower breakpoint for iclaprim (susceptible ≤ 0.25 µg/ml) compared to that of TMP (susceptible ≤ 2 µg/ml), reflecting a.o. the lower dose and shorter half life of iclaprim, this advantage of iclaprim is therefore for a large part annihilated. Also baseline MICs against *S. aureus* were shown to be already above the susceptibility breakpoint, in the new study MI-16 and in data previously submitted. In the spontaneous mutation study described in MI-16, baseline MICs for iclaprim against *S. aureus* (0.03-0.5 µg/ml) were already partly above the susceptibility breakpoint. In data from the first submission: MRSA MIC_{90} 1 µg/ml; *S. agalactiae* MIC_{90} 0.25 – 0.5 µg/ml; *E. faecalis* MIC_{90} 0.12 – 4 µg/ml).

The most important mechanism of resistance to the related compound trimethoprim in Gram-positive bacteria is the occurrence of point mutations in gene for DHFR.
It was shown by the applicant that increased MICs due to point mutations against *S. aureus* were indeed lower for iclaprim than for TMP. *S. aureus* carrying exogenous genes such as S1DHFR/*dfrA* and S3DHFR/*dfrG* were resistant against iclaprim and TMP. A considerable post-antibiotic effect of 8 hours was observed for *S. aureus* and *S. pyogenes* in the presence of sub-MIC concentrations of iclaprim. It was insufficiently addressed that the susceptibility breakpoint of iclaprim is lower than that of TMP and that part of baseline MICs of relevant micro organisms were already above the susceptibility breakpoint and that after serial passage experiments, MICs of *S. aureus* were around 1 µg/ml which seems low but is above the susceptibility breakpoint. This indicates that, of relevant organisms, a considerable part of isolates of *S. aureus*, *Streptococci* except *S. pyogenes*, and *Enterococcus*, have MICs that are already in the resistant range, or risk to become resistant quite soon (considering the result of the passage experiments with *S. aureus* and the fact that organisms are resistant already at MICs > 0.25 µg/ml).

Against MRSA, iclaprim activity was comparable to TMP/SMZ and higher than the activity of TMP, erythromycin, clindamycin, tetracycline, ciprofloxacin, levofloxacin, teicoplanin, vancomycin and linezolid. Against vancomycin-intermediate *S. aureus*, activity was comparable to TMP/SMZ, teicoplanin and vancomycin. Activity was higher than the activity of TMP and tetracycline. Iclaprim was less active than erythromycin, clindamycin, ciprofloxacin, levofloxacin, linezolid and oxacillin (based on MIC90). Against vancomycin-resistant *S. aureus*, the activity of iclaprim was higher than the activity of TMP, tetracycline, teicoplanin and vancomycin. The activity was lower than the activity of TMP/SMZ, erythromycin, clindamycin, ciprofloxacin, levofloxacin, linezolid and oxacillin (based on range of MICs).

MBC_{90} (Minimal bactericidal concentrations for 90% of strains) of iclaprim against S. *aureus* was 2-4 times higher than MIC_{90} (same ratio as in case of trimethoprim). In case of β-haemolytic streptococci and enterococci this ratio was more than 16.

The observed postantibiotic effect (PAE) is very short for the relevant major Gram-positive micro-organisms in cSSTI based on in vitro data reported in studies M31 and M32 at 10 times the MIC value PAEs for MSSA and MRSA were up to 1.8 hrs and 1 hr resp.; at 1 X MIC value the respective PAEs were 1 and 0.5 hr. For *S. pyogenes* and *S. agalactiae* PAEs were up to 0.6 and 0.9 hrs resp. at 10 times the MIC value and 0.6 and 0.5 hr at 1 X MIC value. The PAE values were generally shorter for a number of the used strains especially for MRSA. However, the post-antibiotic effect in the presence of low concentrations of drug (sub-MIC concentrations) was considerable, especially when sub-MIC concentrations mimicked clinical plasma concentration profiles: prolongation of the antibiotic effect for 8 hours was observed for *S. aureus* and *S. pyogenes*. See also clinical comment under Pharmacodynamics below.

Iclaprim consists of two enantiomers. The two enantiomers demonstrated similar potency (MIC) against a series of isolates *S. aureus* and *S. pneumoniae.*

Of the major metabolites, M13 was the most active metabolite with a four-fold less activity compared to iclaprim. Activity of metabolites M6/7 and M10 was negligible.

In the SPC the applicant proposes one susceptibility breakpoint of 2 mg/L (equal to trimethoprim). This proposed breakpoint has not been assessed by EUCAST yet. However, the plasma concentration of iclaprim at the end of the infusion (30 min) is only 0.8 mg/L, the mean plasma half-life is short, 2.3 h, and the dosing interval is long, 12 h. So the lower in-vitro MICs of iclaprim and its higher in-vitro activity as compared to trimethoprim are neutralised by the lower plasma concentrations of the compound as compared to trimethoprim, which can be dosed orally at a much higher dose (160 mg) and has a much longer half-life (11 h). Based on these pharmacokinetic parameters and considering the very short post-antibiotic effect, currently a breakpoint concentration of 0.1 mg/L iclaprim at the most is acceptable at this stage.

Complete eradication of bacterial burden was not observed in the animal studies, either because it was not investigated (only ED50 values given) or because complete eradication was not achieved. PK/PD modelling based on rodent studies was complicated by the low activity of iclaprim the PK/PD studies, due to high thymidine concentrations in the animals. In vivo efficacy will for the major part have to be established in clinical studies. PK/PD studies in mice showed that AUC/MIC correlated best with efficacy, followed by T>MIC.

The applicant has presented a short discussion on secondary pharmacology aspects of iclaprim. Iclaprim was shown to inhibit human dihydrofolate reductase in a competitive manner with an IC_{50} of 22 µM and a Ki of 0.75 µM. In a study in HepG2 cells inhibition was bi-phasic and the first phase abolished by the addition of leucovorin also indicating that inhibition is directly related to dihydrofolate reductase inhibition. A screening study (Cerep) that included receptors, ion channels, transporters and enzymes did not indicate any apparent clinically relevant non-desirable target activity of iclaprim not already identified. Taken together the data presented is considered to provide an adequate response to the issue.

Iclaprim was investigated in a series of safety pharmacology studies assessing its effects on cardiovascular, respiratory, and central nervous systems in both in vitro and in pharmacological responsive animals.

With the exception of the cardiovascular system, iclaprim did not induce any adverse effects on respiratory, and central nervous system. However, as opposed to the negative CNS findings in the safety pharmacology studies, repeated dosings of iclaprim caused convulsions, respiratory changes, tremors, agitation, overactivity and anxiety in marmoset and minipig, indicating CNS-related effects.

In cells transfected with human hERG cDNA, iclaprim and its enantiomers selectively inhibited the hERG-mediated potassium current. In isolated rabbit purkinje fibres, iclaprim induced a concentration-dependent increase in action potential duration and the highest concentration induced early after-depolarisations in 2/6 experiments. In vivo, no treatment related effects on ECG intervals were found following a single intravenous injection with iclaprim to conscious telemetered dogs. However, the outcome of the vitro results suggests that iclaprim ought to be further evaluated for any potential cardiovascular effects and, in particular, for the potential to induce QT prolongation. In contrast to its enantiomer AR101, iclaprim significantly inhibits the hERG potassium current in different cardiovascular *in vitro* systems (there was a tenfold difference in IC50 between the two enantiomers). Moreover, in clinical studies iclaprim significantly induces QT prolongation. The possibility of using AR-101 instead of the racemate would however only be important if higher dosing could be possible because of this difference. Based on the difference in IC50 in the hERG channel assay, higher dosing could be possible for AR-101 compared to the racemate; this would however only be useful if the higher dose of AR-101 more than compensates for the slightly lower efficacy of AR-101 based on ED50. However, higher dosing would most likely not be possible because of the narrow hepatic safety margin. Therefore, the possibility of higher dosing due to the use of the AR-101 enantiomer seems not a realistic option.

In vitro determination of synergism or antagonism of iclaprim with other significant antibiotic drug class representatives was undertaken using MIC checkerboards. Synergism was observed with sulfonamides. No antagonism was observed.

Pharmacokinetics
The pharmacokinetics of iclaprim has been studied adequately, especially the IV and PO administration route in rat and marmoset. The chiral and non-chiral HPLC-UV methods for the measurement of the enantiomers AR-101 and AR-102 has been validated adequately in rat, rabbit, minipig and marmoset plasma.

Iclaprim was rapidly absorbed after PO administration. In rats and marmosets, the bioavailability of the enantiomer AR-101 appeared to be slightly higher than that of the enantiomer AR-102. A slightly higher metabolism of AR102 than AR101 in rat and human hepatocytes confirms this finding. Comparison of AUC after IV and PO administration revealed that the level of bioavailability was 28-31% in rats, 26% in minipig, 50% in the marmoset, and 40% in human. Absorption is probably greater than bioavailability due to first-pass effect after oral dosing. Based on single dose studies, no conclusion can be drawn on the dose-linearity of iclaprim. This is mainly due to the different administration routes, and the limited number of different doses per animal species. Toxicokinetic studies showed that pharmacokinetic parameters did not change following repeat-dose administration, and no accumulation of iclaprim in plasma was seen in marmoset and male rat. However, the systemic exposure was increased in female rats following repeated oral doses.

Following administration of ^{14}C-iclaprim in rats and marmosets, the highest concentrations were found in all tissues already at the first sampling time point, which indicated very rapid absorption and distribution. Particularly high concentrations of radioactivity in rat were found in intestine, adrenal glands, stomach wall and lung. High concentrations of radioactivity in marmoset were found in bile, liver, and lung. The lowest concentrations in both rat and marmoset were found in the brain. Radioactivity declined with increasing time in all tissues. The decrease of radioactivity in the eye was very slow, after 21 days more than 50% of the initial radioactivity was still present. This was most likely due to melanin binding. Hence, accumulation is expected to occur in the eye with repeated dosing

Iclaprim showed the highest protein binding in rabbit plasma (95%), followed by human (93%), minipig (88%), marmoset (85%), and rat (77%). In all species, iclaprim had a higher concentration in plasma than in red blood cells, indicating low binding of radioactive material to erythrocytes. Iclaprim-related material crossed the placenta in pregnant rats, but the foetal exposure is minimal.

Iclaprim is extensively metabolised in vivo by phase I and phase II processes in rat and marmoset. The major metabolites in rat plasma, urine and bile are M6, M7, M10, M13 and M17. Most of the phase II metabolites are detected in urine, whereas phase I metabolites are found in faeces (M10 and M14).The major metabolites in marmoset are M7, M10, M13ii and M20. The metabolite profiles are broadly similar after PO and IV administration. All metabolites observed in humans were also detected in rat and/or marmoset, and the major human metabolites were also major metabolites in these two species. In vitro studies have demonstrated that iclaprim is metabolised primarily by CYP3A4 and by CYP2C19. Iclaprim does not induce any of the CYP isoenzymes in vivo in marmoset. Iclaprim does not significantly inhibit the CYP isoenzymes with the exception of CYP3A4, although at high concentrations (IC_{50} = 11.9 μg/ml).

^{14}C-iclaprim is mainly excreted via faeces and bile in rats, while the route of excretion in marmoset is mainly via the kidney. ^{14}C-iclaprim-derived radioactivity was excreted in milk, with radioactivity detected until 6 hours postdose. The daily exposure for the pup is 0.13% or 0.025% of the maternal dose following IV and PO administration, respectively.

Interactions with other drugs via protein binding are not expected in rat and marmoset, since iclaprim is bound moderately to plasma proteins (74.1-77% in rat and 80.5-84.6% in marmoset). Preclinically, no drug-drug interactions through inhibition or induction of the major CYP isoenzymes and P-glycoprotein were observed.

Toxicology
Single dose toxicity studies were carried out in mice and rats, using the intravenous and the oral route. In mice and rats, deaths were seen after single intravenous doses of ≥ 75 and ≥ 150 mg/kg respectively. Acute toxicity signs in mice were lethargy, convulsions, absence of righting reflex, fast respiration, pallor to skin, bruising at injection site (tail), and in rats sedation, dyspnoea, ruffled fur, lost tail tip. When administered orally at 2000 mg/kg, no deaths or clinical signs were found in mice and rats.

Repeated dose toxicity studies were done in rats and marmosets. Marmosets were used in stead of dogs which are known to poorly tolerate diaminopyrimidines. At intravenous administration in both rats and marmosets heavy injection site damage precluded longer-term studies. Therefore, intravenous studies up to 4 weeks duration were done, supplemented by oral gavage studies up to 13 weeks.

The major toxicity in the intravenous studies in rats (major study: 4 weeks, doses 0, 10, 30 and 80-60 mg iclaprim expressed as mesylate/kg/day) consisted of decreased activity, several signs of local tissue damage to the tail, and at the high dose small effects on plasma chemistry which may be due to the local tissue reactions. In a 2 week preliminary oral gavage rat toxicity study with a dose of 1000 mg iclaprim base/kg/day marked toxicity was found with decreased food consumption, body weight, body temperature and clear haematological changes (decreased neutrophils, lymphocytes, monocytes, large unstained cell counts, eosinophil counts, total leucocyte counts, platelets, and RBC- and related parameters, but increased mean cell Hb concentration). In oral gavage studies of 4 (doses: 0, 50, 150, 500 iclaprim expressed as base/kg/day) and 13 weeks duration (the 13 week study including a 6 week recovery phase, doses: 0, 30, 100, 400 iclaprim expressed as base/kg/day) the major toxicity consisted of increased organ weight accompanied by histological effects of liver (centrilobular hepatocyte hypertrophy), thyroid (follicular cell hypertrophy), adrenals (increased incidence of cortical vacuolation) and spleen (increased germinal centre development), and effects on plasma (decreases of plasma protein, albumen, A/G ratio, AST, and some plasma ions) and urinary parameters (chlorine, sodium). At high doses in the 4 week study also low white blood cell counts were found. In a special hepatotoxicity study with 4 daily oral doses up to 800 mg/kg/day for a period of 18 days slight decreases of food intake and body weight gain were found, decreased APTT, and slight increases of ALAT and AST, and of liver (accompanied by centrilobular to diffuse hepatocyte hypertrophy) and kidney weight. After the recovery phase of the 13 week study the only effect which had not fully recovered was increased splenic germinal centre development. The overall NOEL of the repeated dose oral rat studies was 30 mg iclaprim base/kg/day, corresponding with AUC values of 925 and 1070 ng.hr/ml (males and females on day 1) to 1270 and 2540 ng.hr/ml (males and females on day 85) respectively. The human AUC at the recommended dose is 1980 ng.h/ml. Therefore, at the end of the study the exposure at the NOEL in the rat study was similar to the exposure in humans, however, the average exposure during the study will have been lower (because exposure increased during the study).

In intravenous repeated dose studies of 2 - 4 weeks in marmosets, also injection site reactions were found at all dose levels. In addition clinical acute toxicity signs (retching, emesis, unsteady appearance at ≥ 45 mg iclaprim expressed as mesylate/kg/day, convulsions and deaths at ≥ 60 mg/kg/day) were seen at high doses in 2 week preliminary studies. In the 4 week repeated dose study (0, 5, 12 and 30 mg iclaprim mesylate/kg/day) only injection site reactions were observed. Two additional oral gavage 4 (doses: 0, 15, 50, 160-100 mg/kg/day) and 13 weeks (doses: 0, 15, 40, 100 mg/kg/day) repeated dose studies were done. In the 4 week study decreased total cholesterol and total plasma protein were found at 50 – 100 mg/kg and in the 13 week study total cholesterol was decreased at all doses and blood haematocrit and haemoglobin at 40 and 100 mg/kg. The observed effects on plasma protein and cholesterol indicated effects on the liver, however, no histopathological changes were found. In the marmoset, based on the decreased total cholesterol at the lowest tested dose in the 13 week study, the NOEL was < 15 mg/kg/day. The systemic exposure in marmosets at an oral dose of 15 mg/kg (LOEL) was 1.17 (males) -1.63 (females) µg/ml on day 1 and 2.46 (males)-2.71 (females) µg.h/ml on day 91 respectively. So the average exposure in this study was similar to that in humans at the therapeutic dose (see above).

A number of questions the answers to which are needed for the interpretation of these studies and partially also for the interpretation of the reproduction toxicity studies were asked. These related to the interpretation of increases of foamy alveolar macrophages in the lungs and adrenal cortical vacuolation in male rats in the oral 13 week rat study, the possible significance of germinal cell centre development in the spleen in rats in different repeated dose studies, the inhibitory potency of iclaprim regarding the DHFR of the laboratory animals used in the repeated dose studies and the reproduction toxicity studies, and the possible interaction of plasma thymidine levels in the different laboratory animal species with the effects of iclaprim in the toxicity studies and the possible implications for interspecies extrapolation of effects. The responses to these questions were insufficient to allow firm conclusions, therefore additional data were requested. In particular, the company is asked to study the formation of potential antigens due to binding of iclaprim and/or metabolites to proteins, as has been published for trimethoprim. In addition, due to a lack of data regarding the sensitivity of the DHFR receptor of the used pivotal animal species for iclaprim compared to humans and to a lack of data regarding the possible impact of plasma thymidine levels in the pivotal animal species, extrapolation from the laboratory animals to humans is difficult. However, the applicant indicated that the observed hepatic toxicity might be a direct effect on the mammalian DHFR receptor. The company was asked to provide the experimental data needed for proper extrapolation of the animal data to humans.

No evidence was found for genotoxicity of iclaprim methanesulfonate (drug substance) in a full battery of genotoxicity assays, for induction of gene mutations in mammalian cells by the major metabolite (also degradant) M10, or for induction of gene mutations in bacteria by the formulated drug product. However, it is noted that in the bacteria only low concentrations could be tested due to the high toxicity of iclaprim to the test organisms. So if genotoxic impurities would occur in the drug product, it is highly unlikely that the provided study would be able to detect effect of such impurities.

Considering the short duration of the clinical use, it is acceptable that no carcinogenicity studies were done.

Reproductive and developmental toxicity studies were done in rats (fertility, embryo-foetal development and pre/postnatal development) and mini-pigs. The mini-pig was chosen because preliminary studies in rabbits showed high maternal toxicity, which confirms the known poor tolerance of antimicrobials by this species.

Effects on male and female fertility were studied in two intravenous studies in rats. Due to the high toxicity at intravenous administration, a limited range of doses could be studied. For male as well as female fertility the established NOEL (male: 40 mg/kg/day, female: 20 mg/kg/day) was the highest tested dose at which fully assessable data were obtained. The AUC at the NOEL for female fertility is of the same magnitude as human plasma exposure.

Three full embryo-fœtal toxicity studies were done: one intravenous and one oral gavage study in rats and one intravenous study in mini-pigs. In rats, both studies showed that iclaprim mesylate is teratogenic in this species. In mini-pigs, no teratogenicity was found after intravenous administration, but clear increases of minor anomalies and aberrant skeletal ossification indicated at least some embryo-fœtal toxicity. A small number of major anomalies were found which were not contributed to treatment. However, considering the lower numbers of these anomalies in the control and the historical controls, this interpretation seems uncertain. For both species no NOEL could be established and the AUC values at the LOEL are similar to or slightly higher than those at the therapeutic dose in humans.

An oral gavage rat prenatal/postnatal study confirmed the teratogenic effect of iclaprim in rats, in addition decreased litter size, prolongation of gestation length, decreased pup survival on the first postnatal day were found. The difference between post-natal development of offspring from control and treated dams was a lower body weight gain of males after the 4th postnatal day; it is not certain whether this is really a treatment effect. Plasma iclaprim exposure was not assessed in this study, but based on data from the other studies; the AUC at the NOEL is about a factor 10 higher than human therapeutic exposure.

Bright yellow staining of the cage paper was noted in some toxicology studies and red urine in reproduction toxicity studies. The applicant has made clear that it is unlikely that a metabolite is implicated, but an alternative cause for the observation and the potential clinical relevance were not adequately discussed. The applicant should provide data on the comparability of the commercial formulation with human blood.

No juvenile toxicity studies were done. Mersarex is not recommended for use in children below age 18.

Primary local irritation studies in rabbits showed that after local application to the skin or the eye, iclaprim is not irritating. After intravenous injection in laboratory animals, iclaprim induced severe local tissue damage. Studies using the clinical formulation did not show any significant issues with respect to paravenous or intraarterial tolerance.

A phototoxicity test in albino guinea pigs was provided, in which topical administration of iclaprim (as aqueous slurry) did not induce a phototoxic response. However in a dermal study, the exposure differs from the exposure after intravenous administration. In the distribution studies, iclaprim was found to accumulate in light exposed tissues. However, provided additional data regarding the absorption in the UV/visible range showed relatively little absorption by iclaprim and its major metabolites beyond 300 nm was observed in these experiments.

The results of a local lymph node assay suggested that iclaprim is a skin sensitiser. However, based on these data it is not known whether iclaprim may also have sensitising properties after IV administration. Since in the repeated dose rat studies an increased splenic germinal centre development was found, which may be due to formation of sensitising metabolites this point could not yet be completely closed (see above).

AR-001-0332, an iclaprim degradant and also a metabolite in rats, marmosets and humans, has been sufficiently investigated in the toxicity studies and a separate *in vitro* mammalian gene mutation assay, which provided no evidence of genotoxic potential.

Two impurities, AR03 and AR04, (possibly) contain structural alerts for genotoxicity, and a third impurity, 3-phenylamino-propionitrile, has been identified as a mutagenic component in a Salmonella assay. In response to a question regarding genotoxicity of these impurities the company provided bacterial genotoxicity assays which showed that AR3 and AR04 were negative under the conditions of the assay, but that 3-phenylamino-propionitrile was weakly positive. The proposal to apply the TTC approach for the latter compound was acceptable.

The outcome of the environmental risk characterisation shows that none of the criteria for further testing in Tier B is fulfilled, except partly the trigger for testing on effects to sediment dwelling organisms. Although iclaprim may formally exceed the criteria for Tier B, since the parent residue was slightly above 10% in the sediment of one test system on Day 14, testing on sediment dwelling organisms is considered not necessary with regard to the fate of iclaprim in aquatic system (DT50 3 to 5 for the whole system including sediment) and the low risk indicated for aquatic organisms particularly invertebrates (PEC/PNEC ratio << 1).

It is concluded that iclaprim is unlikely to present a risk to the aquatic environment and no effects on the microbial community of STP are to be expected. However, the PBT assessment cannot be completed until the study report of the log K_{ow} test is provided by the applicant. The log K_{ow} has not been determined according to the OECD 107 guideline. The log K_{ow} can not be accepted at this moment since there are some uncertainties with respect to the determination. Based on the $PEC_{surfacewater}$ calculated in the phase I assessment, a phase II assessment should be performed. In order to complete this phase II assessment, a study on the effects of iclaprim to cyanophyta is required.

III.3 Clinical aspects

Pharmacokinetics

Absorption:
As the formulation concerns a concentrate for solution for i.v. infusion, the bioavailability of iclaprim is 100%. However, oral formulations indicate that the absolute bioavailability after oral administration is about 40%.

Iclaprim AUC values increased linear with dose after single dose over the dose range of 0.4 – 3.2 mg/kg and after twice daily dosing over the dose range of 60 – 120 mg (30 min. infusion). For iclaprim, time dependency in pharmacokinetics is not observed. Elimination half-life and clearance were independent of dose and not affected by repeated administration. Steady state is to be expected within one day, as iclaprim has a short elimination-half-life (about 2 - 4h).

Inter-individual variability in iclaprim pharmacokinetics (AUC, C_{max} and Cl) is low (<20%). Intra-individual variability in iclaprim pharmacokinetics was not evaluated.

One study was carried out applying b.i.d. dosing and using a dose of 60 mg (about 0.8 mg/kg) being the recommended dose in the SPC. At this dose the trough values were below the limit of detection of 4 ng/ml or just above (up to 14 ng/ml). However, a relationship between efficacy of iclaprim and trough levels and/or AUC could not be obtained (see section Pharmacodynamics).

Distribution:
The volume of distribution is 1.4 l/kg. Protein binding is rather high (93%), however concentration independent over the range of 200 – 2000 ng/ml. Iclaprim concentrations in the fluid from cutaneous suction blisters 1 h post-dose was about 30%-60% of those found in plasma. Data obtained with a more representative method such as micro-dialysis method are not available. Iclaprim penetration into subcutaneous tissues has not been investigated. As the skin is the target tissue for the claimed indication, it is considered important to have additional supportive data with regard to distribution into the skin and to discuss the relation to plasma concentrations, The presently observed concentrations are rather low and of questionable value to support of the target efficacy attainment, assuming T/>MIC as an important correlate for efficacy. Therefore, the applicant was requested to obtain supplementary data using a more representative method, like the micro-dialysis. The latter analysis data were not provided. An adequate quantitative relationship to plasma concentrations is not available to be used in eventual PK-PD analysis for break-point determinations. See assessment of response to Pharmacodynamic objection and other concerns below.

An AUC of iclaprim was increased almost twice in severely obese subjects compared with non-obese subjects (study HKI-004). This suggests that iclaprim distributes into non-fat tissues. Protein displacement due to interaction is not expected. Indeed the warfarin interaction study showed no pharmacokinetic interaction (see section Interactions).

Iclaprim is well distributed over the body. Iclaprim was not actively taken up in red blood cells. Animal data indicate that iclaprim may be excreted into mother milk, and may cross the placenta.

Metabolism:
In vitro studies showed that iclaprim is metabolised mainly by CYP2C19 and CYP3A4. CYP2C19 is subject to polymorphism, however it is expected that the CYP3A4 pathway will compensate metabolism in poor metabolisers. In response to the question of the CHMP, the applicant indicated that data on poor metabolisers are available, but did not provide those data. The applicant should submit these data. Moreover, as AR-102 showed a more pronounced effect on QTc interval prolongation in vitro, the potential to inhibit this enantiomer compared to AR-101 should be further substantiated in vitro.

In vivo, after i.v. administration, it appeared that iclaprim is extensively metabolised. In plasma the major drug compound was iclaprim.

Elimination:
After 168 h, 74.1 ± 4.2% of the radioactivity was excreted in urine, and 20.1 ± 3.1% in faeces (total 94.2 ± 3.1%). Most of it was excreted within 24 h after administration. Iclaprim is almost completely excreted as metabolites. Less than 2% could be recovered as intact drug. The total body clearance is about 0.5 l/h/kg, and the elimination half-life 2 – 4 h.

Enantiomers:
Iclaprim is a racemate. Both enantiomers are equally active, however, AR102 showed an almost 10-fold more potency to reduce the hERG current indicative for QTC prolongation, which may be of concern (see Preclinical assessment). In vitro limited interconversion (<5%) is observed.

The pharmacokinetics of the single enantiomers are in line with that of the racemate. Clearance of the enantiomer AR102 was about 10% higher than that of AR 101.

It is not clear whether different enzymes contribute in the elimination pathways of the separate enantiomers. This should be further substantiated.

Special patient groups:
A clinically relevant gender effect is not observed after i.v. dosing. Age (elderly) did not affect the pharmacokinetics of iclaprim.

As could be expected, a renal impairment had no influence on the pharmacokinetics of iclaprim. The SPC states that no dose adjustment has to be applied which is agreed. However, as iclaprim is mainly excreted as metabolites, accumulation may occur. Increased plasma levels of metabolites may be a safety concern. This should be elucidated.

A mild impaired hepatic function has a slight effect on the exposure of iclaprim (30% increase). AUC more than doubled in subjects with a moderate hepatic impairment. In case the dose was halved, AUC was only a little higher than the AUC observed in normal subjects. The SPC recommends no dose adjustment for subjects with a mild hepatic impairment, and a dose reduction of 50% for patients with a moderate hepatic impairment, which is agreed based upon the pharmacokinetic results.

No study is carried out in subjects with severe hepatic impairment. The SmPC states that no data are available under section 4.2 Posology and method of administration. However, as can be expected that in patients with severe hepatic impairment iclaprim exposure may be more pronounced increased, and considering the cardiac safety concerns, this patient group should be contra-indicated (see Clinical part, Safety evaluation). In response to the question of the CHMP, the applicant adjusted the Contraindication section of the SmPC.

Pharmacokinetics of iclaprim in target population was studied in two Phase III efficacy studies applying sparse sampling. A population pharmacokinetic model was developed to predict the demographic and physiologic parameters which could affect the pharmacokinetics characteristics of iclaprim. Overall, 500 subjects across both studies were assigned to be treated with iclaprim 0.8 mg/kg bid. Blood samples were obtained from each subject treated with iclaprim on two occasions. Three samples were obtained upon administration of the first dose, and 3 samples were obtained on the 4th day (+/- 1 day) of treatment. The data was best fitted to a two-compartmental model. Pharmacokinetic parameters for patients with cSSTI predicted from the population pharmacokinetic model were similar to those in healthy volunteers from Phase I studies.

A linear relationship was observed between AUC and body mass index. After i.v. dosing AUC was increased in obese subjects (64% in mild to obese subjects and 110% in severe obese subjects). Obese patients are subject to an ‘overexposure’ when the mg/kg dosing strategy is applied. A Monte Carlo simulation indicates that applying a fixed dose results in a consistent exposure over the different weight groups. Instead of proposing a fixed dose, the SPC recommends the 0.8 mg/kg dose, with a maximum dose of 100 mg. The mg/kg dose is still proposed as the pivotal studies were carried out on a mg/kg base. A fixed dose regimen would be preferable, however, based on the available data, the

outstanding major cardiac and hepatic concerns there is inadequate basis to conclude on an efficacious and safe fixed dose regimen. The rational to use the cut off of 100 mg is to limit the overexposure in obese subjects, however, no further support is submitted. To be able to use the population PK model for further simulations regarding upper dose limit as well as pharmacokinetic-pharmacodynamic modelling, additional reassurance of the appropriateness of the model should be provided.

No specific studies were carried out in patients below the age of 18 years.

Interactions:
In vitro studies indicate that iclaprim is metabolised mainly by CYP2C19 and 3A4. Indeed, ketoconazole, a CYP3A4 inhibitor, increased the AUC of iclaprim by 70%. Furthermore, omeprazole, a CYP2C19 inhibitor, increased the AUC by about 20%, however, omeprazole is considered not to be a potent CYP2C19 inhibitor. The SPC states that the dose has not to be adjusted. The increase of 70% may be clinically relevant with regard to cardiac safety issues. The applicant should support the dosing advice. Moreover, the applicant should also address the possibility of inhibition of both pathways. In addition also the aspect of the polymorphism of CYP2C19 should be taken into account, especially those for poor metabolisers of CYP2C19.

No interactions studies have been carried out with CYP inducers, which should be addressed.

Iclaprim showed in vitro an inhibition potential for 3A4. Indeed, iclaprim increased the AUC of R-warfarin, a CYP3A4 substrate, only by 14%. No increase in INR was observed. The applicant should support the usefulness of warfarin as a representative CYP3A4 substrate to study the in vivo inhibition of CYP3A4.

No interaction is observed with digoxin.

No information is submitted whether iclaprim may induce CYP enzymes. This may be relevant as iclaprim should be dosed for 8 – 14 days. The applicant should elucidate this.

Moreover, in vitro data showed that iclaprim may inhibit P-gp (IC50 14 μM). The applicant should discuss the possibility of inhibition in vivo.
In response to the question of the CHMP, the applicant provided additional clarifications. The interaction potential has been partly resolved in the SPC. Iclaprim inhibition potential regarding CYP3A4 is limited, as is for induction of CYP enzymes. Moreover, iclaprim does not inhibit P-gp. Increase in iclaprim plasma levels is of concern, as iclaprim causes dose dependent QTc prolongation. CYP2C19 and CYP3A4 are involved in the metabolism of iclaprim. Inhibition of one of these enzymes will reflect the possible overall effect of inhibition of one enzyme, and metabolism of the other enzyme. It is still unclear what the overall result is when both enzymes are cocomitant inhibited, or in case of poor metabolisers of CYP2C19, if the CYP3A4 enzyme is inhibited. The applicant indicated that data on poor metabolisers are available, but did not provide those data. The applicant should submit these data.
Moreover, as AR-102 showed a more pronounced effect on QTc interval prolongation in vitro, the potential to inhibit this enantiomer compared to AR-101 should be further substantiated in vitro.

The SPC has been changed by the applicant. Regarding inhibitors of CYP2C19 and CYP3A4, it states now that:
"Mersarex might act synergistically with drugs known to prolong the QT interval, thus potentially increasing the risk for ventricular arrhythmia. Iclaprim should not be co-administered in combination with other drugs that inhibit CYP3A4 and 2C19".
With regard to inducers, the SPC states:
Iclaprim should not be co-administered with other drugs that induce cytochrome P450 iso-enzymes, in particular CYP3A4 and 2C19".
The proposed text is conservative, however it should be taken into account, that the observed QTc prolongation is concentration dependent. Therefore, the SPC changes are considered acceptable provided that the text with regard to CYP3A4 and 2C19 inhibitors is changed as indicated in the SPC recommendations.

Pharmacodynamics

Primary pharmacology. Iclaprim has a high affinity for Gram-positive DHFR especially *S. aureus* DHFR, which includes mutant DHFR resistant to trimethoprim. Iclaprim has a narrow activity spectrum limited to most prevalent Gram-positive pathogens in cSSTI including. The applicant claims that iclaprim is active against TMP- resistant *S. aureus* (F98Y DFHR mutation), and its activity is independent of susceptibility to methicillin/oxacillin. In vitro activity iclaprim against *S. aureus*/MRSA and beta-haemolytic streptococci is bactericidal.

The applicant claims that Iclaprim has a post-antibiotic effect (PAE) at sub-MIC concentrations. The observed postantibiotic effect (PAE) is very short for the relevant major Gram-positive micro-organisms in cSSTI based on in vitro data: at 10 times the MIC value PAEs for MSSA and MRSA were up to 1.8 hrs and 1 hr resp.; at 1 X MIC value the respective PAEs were 1 and 0.5 hr. For *S. pyogenes* and *S. agalactiae* PAEs were up to 0.6 and 0.9 hrs resp. at 10 times the MIC value and 0.6 and 0.5 hr at 1 X MIC value. The PAE values were generally shorter for a number of the used strains especially for MRSA. As requested, additional data were provided by the applicant. Based on these data, the claimed inhibition of bacterial growth by this PA-SME during the entire dosing interval in the presence of clinically relevant drug concentrations (between 0.025 and 0.05 mg/L) should be interpreted with caution because of the limited number of species tested and the less consistent finding for 1/5 MRSA strains e.g. PAE MRSA NRS192 (No. 800101). Using available PK/PD data and MICs distributions, it is difficult to support proposed breakpoint for Gram-positive bacteria (Sensitive: ≤ 0.25 mg/L).

The bactericidal activity of iclaprim is essentially time-dependent. Whilst iclaprim is 93% protein bound plasma has shown little or no effect on the *in vitro* activity of iclaprim including time-kill assays.

As mentioned in the non-clinical assessment the provided data are insufficient to show that the development of resistance to iclaprim in-vitro is slower than the development of resistance to trimethoprim. More species and strains per species should be investigated and the results should be subjected to statistical analysis to proof.

Secondary pharmacology related to safety. Two double-blind, randomised, placebo-controlled, crossover studies (AR-100-ECG-002 and ECG-003) in healthy volunteers evaluated PK and pharmacodynamic effects on *cardiac parameters* such as ECGs, QTc intervals and safety using single IV doses of iclaprim- therapeutic and higher doses (levels: 0.4 mg/kg, 0.8 mg/kg, 1.6 mg/kg and 3.2 mg/kg).

These studies revealed that iclaprim exerted a dose-dependent prolongation of the QT interval that is transient, rapidly reversible and not influenced by gender. Maximal QTc prolongations were observed around C_{max}. The first indications of QTc prolongation were detected with the 0.8 mg/kg dose. The placebo-corrected mean prolongation around C_{max} was 10 msec on average.

PK / PD

The applicant claims that AUC/MIC has been shown in several animal models of infection to be the pharmacodynamic parameter that correlated best with efficacy: "PK/PD studies performed to date have generally shown that AUC/MIC correlates best with the efficacy of iclaprim, followed by T/>MIC. Time likely plays a role in such studies since the drug requires to be administered relatively frequently due to the poor pharmacokinetics of iclaprim in small rodents. All studies have shown that Cmax/MIC does not correlate with the observed efficacy".

Due to the antagonistic effects of thymidine levels present in animals used in such experimental models (in contrast to humans) a conclusive meaningful numerical ratio could not be established. Due to this antagonism, activity of iclaprim was investigated in a mouse abscess infection model using TK-deficient *S. aureus* mutants. AUC/MIC correlated best with efficacy.

Thymidine levels in humans are low and do not antagonise the activity of iclaprim and other diaminopyrimidines such as TMP. Consequently, the proposed single breakpoint of 2 mg/l (which is equal to that of trimethoprim) for target Gram-positive pathogens are primarily based on *in vitro* MIC distributions and clinical outcome at each MIC. The observed very short PAEs are of questionable importance for their claimed supportive value for the claimed breakpoints or dosing frequency for iclaprim.

PK/PD breakpoints were not calculated as there was no strict correlation between clinical cure and MIC in both phase III registration trials. Overall, however, the reasons for the choice of BID dosing frequency are not entirely convincing; based on the rather limited clinical data especially in severe cSSTI and the pharmacokinetic profile and animal findings that T/>MIC correlates also with the efficacy of iclaprim a safe and more frequent dosing regimen to avoid suboptimal drug levels should have been explored. The applicant should provide supplementary analyses for target efficacy attainment assuming T/>MIC as an important correlate for efficacy. The presently observed low skin blister fluid concentrations should be also taken into account. The present data are not supportive of proposed breakpoint for Gram-positive bacteria (Sensitive: ≤ 2 mg/L). In response to CHMP question, the applicant did not provide supplementary analyses for target efficacy attainment assuming T/>MIC as an important correlate for efficacy. The skin concentration data had also to be taken into account in these analyses. See also non-clinical assessment of breakpoints. Overall, this major objection is not resolved.

The proposed susceptibility breakpoint, needs further scrutiny by the EUCAST in accordance with the SOP "Harmonization of European Breakpoints set by EMEA/CHMP and EUCAST" (SOP/H/3043). In addition, this criticism has its consequence for the micro-organisms listed in the susceptibility table in section 5.1. The present response of the applicant does not allow finalisation of the assessment of susceptibility data in the table and breakpoints.

From the clinical point of view, the number of baseline isolates with elevated MIC values for *S. aureus* and MRSA (≥0.25 µg/ml) and for *S. pyogenes* (>0.06 µg/ml), was too small to allow appropriate conclusions on the relationship between clinical outcomes and iclaprim MIC values although numerically more failures were observed in the latter category of isolates. See clinical results section. This should be taken into account in the breakpoint assignment.
The potential for the emergence of resistance after clinical use is assessed under results of clinical efficacy studies. See also non-clinical assessment part. See further clinical dose response data below.

Clinical efficacy
Three studies were conducted to support the indication of cSSTI: one Phase II proof-of-concept study (AR-100-SSTI-001) and two Phase III pivotal studies (ICLA-08-CSI1/ASSIST-1; ICLA-09-CSI2/ ASSIST-2).

Dose-response studies
Dose selection of iclaprim for the Phase III studies was based on the safety results from the Phase I studies and the Phase II proof-of-concept study which compared the efficacy of treatment regimens with 0.8 mg/kg *q* 12 hours iclaprim versus 1.6 mg/kg *q* 12 hours iclaprim versus vancomycin. See below.

In healthy subjects there was a correlation between the occurrence of AEs and iclaprim dose. Repeated b.i.d. administration of 1.6 mg/kg iclaprim for > 10 days occasionally resulted in increases of > 3x ULN in liver transaminases.

Local injection site intolerability was observed when the concentration of the infusion exceeded 3 mg/ml. As a consequence, iclaprim infusions are applied in concentrations not exceeding 1 mg/ml. Taken together, the results suggested that the recommended dose of 0.8 mg/kg b.i.d. IV iclaprim (at an infusion concentration of 1 mg/ml) provided the optimal balance between safety and efficacy.

The CHMP Scientific Advice noted that if vancomycin was used as the comparator, this would have to be justified based on the expectation of a high rate of encountering MRSA at sites chosen for the

study. The applicant argued that linezolid was chosen instead as the comparator because it is indicated for both MRSA and non-MRSA Gram-positive cSSTIs. In addition, like iclaprim, linezolid has a b.i.d. dosing regimen, which therefore facilitated blinding of the studies.

Proof-of-concept study
The population in the Phase II proof-of-concept study included 92 patients (≥18 years of age) with cSSTI.

The treatment groups had similar demographics and baseline conditions.The study protocol requested that two out of the five signs and symptoms of cSSTI be present for patient inclusion in the study. The CHMP Scientific Advice observed that the inclusion/exclusion criteria used in Phase II did not fully support Phase III plans. The applicant argued that a retrospective data analysis of this study revealed that 98% of patients exhibited five of the five signs and symptoms of cSSTI: 100% of patients had signs and symptoms of erythema, swelling, tenderness to palpitation, localised warmth, and > 90% of patients had pain, discharge and heat. The majority of patients in each study arm had infected ulcers (35%) followed by burns (25%), cellulitis (22%) and major abscesses (15%). The distribution of Gram-positive pathogens was similarly balanced between the treatment groups. The most common Gram-positive pathogen was *S. aureus* (50 cases), of which 5 were cases were MRSA.

A TOC evaluation was conducted on Day 30 (± 5 days) or approximately 20 days after therapy 7 to 10 days after the end of therapy.

Main clinical studies
The designs of the two Phase III studies (ICLA-08-CSI1 and ICLA-09-CSI2) were consistent with the guidelines of the U.S. Food and Drug Administration (FDA) and the Committee for Proprietary Medicinal Products (CPMP), for antimicrobial drug development.

Primary objective of the studies was to demonstrate the non-inferiority of iclaprim compared with linezolid based regimens with respect to the clinical cure rate.

They had essentially identical design and used a single comparator (linezolid). Accordingly, it was prospectively defined that the combined study population would be used for final primary efficacy assessment with the two individual trials, meeting their protocol-defined endpoints independently, providing further supporting evidence. Both studies were monitored for safety by the same unblinded DMC. The studies were planned to follow two stages, with the safety data from both studies pooled and evaluated. In the first phase patients with a QTc > 470 msec are excluded and after the first 200 patients, an unblinded data monitoring committee (DMC) would consider data and recommend requirements to amend the protocol. No concerns were raised by the unblinded DMC during the trials and for both ASSIST-1 and ASSIST-2 Phase 3 trials this restriction of the QTc entry criterion was eliminated by a protocol amendment.

Both studies were evaluator-blind, randomized (1:1 for both trials), multicenter, controlled non-inferiority studies where the efficacy of iclaprim therapy was compared with that of a comparator in patients (≥18 years of age) with cSSTIs due to suspected or proven gram-positive infection.

Only the pharmacist was unblinded but the necessary precautions were taken to keep the blind for all pesonnel involved in the treatment. The pharmacist prepared all treatments using the material provided for blinding, which included infusion bags, infusion lines and hard-plastic, nontransparent blinding shells for each infusion. However, although the protocols mentioned that the studies were evaluator blinded the applicant's Clinical Overview and Clinical and Summaries mention that the studies were double-blind. The applicant is requested to confirm and detail blinding procedures with regard to treating physician/ investigator/ evaluator and patients. In response, the applicant gave explanation that seems to allow the conclusion and confirmation that the pivotal studies are most probably evaluator-blinded.

Based on the Phase II study results iclaprim base 0.8 mg/kg body weight infused over 30 minutes *q* 12 hours (± 2 hours) was chosen for the Phase III trials. Iclaprim mesylate i.v. solution in 300 ml N-saline

was administered for 10 to 14 days. The infusion duration was not to be shorter than 30 minutes but could be extended to 45 minutes. In response to CHMP Scientific Advice the applicant argues that the same dose regimen as in the Phase II study was used since at that time, the extent of QT prolongation in a cSSTI population was not known. In addition, the pharmacokinetic profile of iclaprim in a cSSTI population had not been elucidated. Retrospectively, a fixed dose of 64 mg can be considered based on Monte Carlo Simulation analysis (see PK assessment).

The CHMP advised that twice-daily dosing of a DHFR inhibitor based on an elimination half-life of 3 hours needs to be explained. The applicant subsequently reviewed PK and PD data from animal studies. These studies have generally shown that AUC/MIC correlates best with the efficacy of iclaprim, followed by T/>MIC. Time likely plays a role in such studies since the drug requires to be administered relatively frequently due to the poor pharmacokinetics of iclaprim in small rodents. In addition, the bactericidal activity of iclaprim (which is time dependent) together with a high distribution into tissues and strong post-antibiotic effect (PAE) observed would support the adequacy of twice-daily dosing. Finally, the efficacy results seen in the Phase II study justified the choice of the dosing regimen. However, claimed evidence of PAE for iclaprim could not be accessed in the dossier. Hence, this argumentation is not entirely satisfactory especially in relation to the chosen breakpoint and efficacy of the 0.8 mg/kg BID regimen. Overall, the reasons for the choice of BID dosing frequency are not entirely convincing; based on the rather limited clinical data especially in severe cSSTI and the pharmacokinetic profile and animal findings that T/>MIC correlates also with the efficacy of iclaprim a safe and more frequent dosing regimen to avoid suboptimal drug levels should have been explored. A fixed dose BID is not used in the Phase III studies because the same dosing regimen as in the Phase II study was used since at that time, the extent of QT prolongation in a cSSTI population was not known. In addition, the pharmacokinetic profile of iclaprim in a cSSTI population had not been elucidated. Retrospectively, a fixed dose of 64 mg can be considered based on Monte Carlo Simulation analysis (see PK assessment). Overall, the argumentation of the applicant can be accepted; the studies are already completed and since the cardiac safety issues are important for this agent- dose & Cmax dependent- a mg/kg dosing is the safer option for the targeted population at large. On the other hand, the applicant recommends not exceeding 100 mg per dose whereas this is not mentioned as such in the protocols. The applicant should comment. The applicant explained that in the ASSIST studies only 8 patients were treated with iclaprim in a dose exceeding 100 mg per dose. From the point of view of efficacy and safety this is a very limited database. It remains unclear how many patients were exposed to fixed dose between 64 mg (based on the mean body weight of 80 kg in the Phase III studies, dosed with 0.8 mg/kg) and 100 mg.

The applicant has justified the choice of linezolid as the comparator antibacterial agent in the two pivotal comparative studies with iclaprim for the treatment of cSSTI caused by MRSA as well as non-MRSA Gram-positive pathogens arguing that published data supported the use of linezolid to treat cSSTI caused by MRSA as well as non-MRSA Gram-positive pathogens (Weigelt et al 2005).

Both studies allowed the concomitant use of metronidazole and aztreonam to provide activity against anaerobic pathogens and gram-negative pathogens respectively.

Outpatient antibiotic treatment (OPAT) was possible under certain circumstances. In eligible patients, after initial hospital treatment for 4±1 days (i.e., subsequent to completion of Day 4±1 ECG tests) study medication could be continued in an outpatient setting (e.g., outpatient facility or through home health nursing service) if all study procedures could be guaranteed. The OPAT option often suggests that the patient is not having sufficiently severe infection to be kept hospitalised and there is a higher risk of non-adherence to protocol prohibited co-medications. European countries usually do not accept OPAT in contrast to the USA. This may affect the objective to study patients with severe cSSTI needing hospitalisation. See further comments under results.

Clinical efficacy in the cSSTI pivotal studies was assessed at the TOC visit, which was 7 to 14 days after the last dose of study drug therapy and at late follow-up (LFU) visit, which was 7-14 days after the TOC visit.

Primary endpoint was the clinical cure rates at the test-of-cure visit (TOC) based on all patients in the PP and ITT populations.

Secondary efficacy endpoints included: Clinical efficacy at TOC for all non-primary populations and at EOT for all study populations; time to resolution of systemic and local signs and symptoms of cSSTI; bacteriologic outcome in the ME population; bacteriologic eradication rates of baseline (BL) pathogens; clinical efficacy at TOC by MIC analysis.

The primary efficacy variable was clinical cure at the TOC visit for the ITT, PP, and CE populations. The ITT population included all randomized patients who received at least one dose of study medication. The modified ITT (MITT) population included all patients in the ITT population who had an infecting Gram-positive pathogen isolated at baseline. The clinically evaluable (CE) patients in the ITT population were those who met major criteria of the PP population. The PP population was defined as the subset of the ITT population and included 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 (EOT and TOC evaluations, and were classified as cure or failure). The restrictive definition of the PP as compared to a clinically evaluable population, excludes patients treated with prohibited antibiotics (which could be a sign of sub-optimal success with the study medication).

However following a preliminary analysis of the data, a strong imbalance in the use of prohibited antibiotics was observed (twice as frequent in the linezolid as compared to the Mersarex group in ASSIST-2, with the same tendency, although not such extreme in ASSIST-1). In order to address the effect of this imbalance (as required by ICH E9 guideline) and to analyse the mismatch between the ITT and PP datasets, an additional population was identified named the "modified clinically evaluable" (MCE) population. It is important to note that all protocol violators - including the medical judgement if the prohibited antibiotic use in a particular patient could have contributed to the clinical outcome - were identified during the blinded phase of both studies.

The MEPP population included all patients in the PP population who had an infecting Gram-positive pathogen at BL. The MECE population included all patients in the CE population who had an infecting Gram-positive pathogen at BL.

A patient was considered clinically ***cured*** if, in the opinion of the investigator, there was resolution of all signs and symptoms of the infection; 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 on the EOT or TOC (as applicable for the assessment); and received at least four days of treatment and at least seven doses. (See criticism under results).

A patient was considered clinically a ***failure*** when conditions for "Cure" were 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 or 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. Note: Any patient classified as "Failure" at EOT also was classified as "Failure" at the TOC visit (carry-forward).

Patients response was considered ***Indeterminate*** when 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 fulfil all other criteria for "Cure."
- For TOC: patients who had <4 days or <7 doses of treatment but did not fulfil all other criteria for "Cure" or patients with "Cure" at EOT but no TOC visit.

The *by-pathogen bacteriological response* for each causative organism identified at baseline (BL) was evaluated. Acceptable causative pathogens were *S. aureus*, *S. pyogenes*, *S. agalactiae*, *E. faecium*, and *E. faecalis*. All other organisms classified as pathogens by the study site or the microbiologist at the site's local laboratory were to be reviewed by a review board blinded to treatment allocation with regard to their appropriate classification as a valid pathogen of cSSSI for the purposes of efficacy analysis. The organisms named above were automatically considered causative pathogens but other Gram-positive, Gram-negative, and anaerobic organisms were also to be assigned as pathogens by the blinded reviewers.

Recovered isolates at the local laboratory were identified and tested at the central laboratory using a standard procedure approved by the CLSI subcommittee on Antimicrobial Susceptibility Testing. Response was defined as follows:

- Eradication: BL causative organism could not be isolated from any culture(s) at the TOC assessment.
- Presumed Eradication: The patient was a clinical cure at EOT or TOC, and there was no appropriate material for culture from the original site of infection.
- Persistence: The BL causative pathogen (based on susceptibility profile or molecular typing) was isolated at EOT or TOC (as appropriate for the assessment).

(Note: Persistence at EOT was carried forward to TOC if no appropriate material for culture was available at TOC).

The *by-patient bacteriological response* pertained to patients with at least one (and only) Gram-positive BL pathogen. Eradication or presumed eradication in this case meant that all BL Gram-positive causative organism(s) had a response of eradication or presumed eradication (as mentioned above). Similarly, Persistence or Presumed Persistence etc. were defined.

The *overall therapeutic response* was also analysed. This was defined separately for the EOT and TOC visits as follows: Success included patients with clinical response of cure and the by-patient bacteriological response was Eradication or Presumed Eradication. Indeterminate meant Clinical or by-patient bacteriological responses were Indeterminate and none of these two is Failure, Persistence, or Presumed Persistence. Failure: All other outcomes.

Patients without a BL pathogen were not included in this analysis.

Main *inclusion/exclusion criteria of pivotal studies* were:
The inclusion and exclusion criteria for both studies were similar. *Included* patients were those patients aged ≥18 years who were hospitalized at baseline or who required hospitalization and presented with cSSTI (at least in part due to Gram-positive pathogens).

Presence of purulent or seropurulent drainage or at least three of the following five signs and symptoms had to be present 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 localised warmth; and (5) pain and/or tenderness to palpation. These were graded on a scale of 0 to 3 (0=none, 1=mild, 2=moderate, or 3=severe). In addition, at least one of the following conditions was to be pathogen-related: (1) fever > 38°C; (2) Elevated total peripheral white blood cells >10,000/mm^3 and/or (3) > 15% immature neutrophils (bands), regardless of total peripheral WBC count.

Patients had suspected or proven infection with gram-positive pathogen(s) with accessible biological fluid/tissue samples available from infected lesion at baseline for microbiological culture. Patients were characterized as having *severe infection* at BL if they met one or more of the following criteria:

- Fulfilled the published definition for Systemic Inflammatory Response Syndrome (SIRS) by having two or more of the following findings:
    - body temperature >38°C or <36°C;
    - heart rate >90 bpm;
    - respiration rate >20 breaths/minute; and
    - WBC >12000/mm3 or <4000/mm3 or >10% bands.

- Evaluated as having severe tenderness or severe erythema at the infection site; or
- Positive blood cultures at BL.

In response to question during the Scientific Advice inclusion criteria were changed to require a more stringent degree of patient's signs and symptoms of cSSTI to ensure that only patients with truly complicated infections were enrolled.

Excluded patients were among others those patients with infected diabetic foot or decubitis ulcers, infections due to animal or human bites, immunocompromised or neutropenic patients, obese (BMI index >40 or body weight >150 Kg), patients with SSSI that could be treated by surgery alone, patients with severely impaired arterial blood supply, osteomyelitis, necrotizing fasciitis or gangrene, patients with infections associated with a prosthetic device. Infections that would require > 10 days of IV therapy, only 14 days therapy allowed (!). Patients with severe renal impairment, or hepatic disease, patients with cardiovascular disease or patients requiring high dose steroids were excluded.

The following patients with cardiovascular conditions and treatment:
- QT/QTc interval outside the normal range defined as QTc >470 ms (Stage A only).
- Patients known to have congenital or sporadic syndromes of QTc prolongation;
- Type IA or III anti-arrhythmic drugs;
- Non-sustained ventricular tachycardia (NSVT) defined as ≥10 consecutive ventricular beats at a rate of >120 beats per minute (bpm) with a duration of <30 s;
- Bradycardia (<50 bpm); and/or

Patients were also excluded if they had abnormal blood electrolyte levels, as defined below, that could not be corrected before study inclusion; Potassium ≤3.0 mmol/L, and/or Magnesium ≤0.5 mmol/L (1.2 mg/dl).

cSSTI suspected or documented as being due exclusively to Gram-negative or anaerobic organisms based on epidemiological grounds or on direct examination of a specimen with Gram's stain was excluded. Patients with mixed cSSSI in which both Gram-positive and Gram-negative pathogens were isolated were enrolled if the clinician suspected that the predominant causative pathogen was Gram-positive.

Patients who had received for more than 24 hours any systemic antibiotic or any topical antibiotic on the infection site with Gram-positive activity within the previous seven days prior to enrollment were excluded. [It is unclear whether patients with endocarditis, septic arthritis, or toxic shock syndrome or shock, episiotomy infection, peri-anal cellulitis, infection extended to the oropharyngeal, gastrointestinal, urogenital or gynaecological tract) were excluded].

Non-inferiority margin
The Phase III studies were powered to test non-inferiority with a one-sided alpha of 0.025, 85% clinical cure rate and a 12.5% delta (although regulatory guidance would require setting that at 10%).

In the ITT population, the lower bound of the CI for treatment difference in each trial was >-12.5% achieving the primary efficacy endpoint for both co-primary populations ITT and PP. Thus in retrospect it is in alignment with regulatory guidance for such studies and recent registration cSSTI trials. Analysis of the combined dataset showed a delta of -7.9% (ITT) and -8.7% (PP), well within the predefined limits. The chosen non-inferiority margin is sufficiently discussed and justified in an additional document.

Interim analyses
No formal interim analyses were planned for ASSIST-1. However, to reassess the planned sample size, the non-evaluability rate and the overall clinical cure rate were evaluated based on blinded data when approximately 50% of the patients completed the TOC visit, as foreseen in the protocol.

Following a preliminary analysis of the data (before data unblinding), a strong imbalance in the use of prohibited antibiotics was observed (twice as frequent in the linezolid as compared to the Mersarex group in ASSIST-2, with the same tendency, although not such extreme in ASSIST-1). As required by

ICH E9 guideline, this imbalance was further analysed (protocol violators were identified during the blinded phase of the study) referred to as the modified clinically evaluable (MCE) population, in which patients in the PP population who were potential treatment failures were not excluded, thus improving the quality of the study analysis. Analysis of the MCE population in both Phase III studies demonstrated the lower bound of the CI for the treatment difference to be <10% in the individual studies as well as the combined studies (-7.0% to 1.8%).

Results

Pivotal studies

Overall, ≥90% of patients in both pivotal studies (ASSIST-1 and ASSIST-2) completed the study. The most common reasons for premature termination of treatment were withdrawn consent, AE, and infection-related reasons with some variations between studies. In ASSIST-2 more linezolid-treated patients withdrew prematurely from the study than iclaprim treated patients, with the greatest treatment difference being within the infection-related reasons category. The demographic characteristics (overall and by geographic regions) of ITT, PP, MITT, MCE, MEPP and MEMCE populations in the two treatment groups were similar to each other.

All patients were hospitalised and over 90% of patients had severe infection. A tendency for more severe infections in ASSIST-1 was noted: in this study essentially all patients (98.8%) had a so-called severe infection, versus approx. 86% in ASSIST-2. Overall 46.4% of patients were diagnosed with Systemic Inflammatory Response Syndrome [SIRS].

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; infected ulcers and burns were less frequent with some variation between studies. See the following table.

Table E1: 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.

Overall, the distribution of infection types was similar for both treatment groups and for all study populations. However, a geographic variation was seen in the ITT population.

80.4% and 79.0% of patients in the iclaprim and linezolid arm respectively had a wound infection classified as severe. However, only 10 (2.2%) and 14 (2.8%) of patients, in the iclaprim and linezolid arm respectively, had a *positive blood culture* in the combined (ITT) data set. There was also a clear regional difference in the frequency of blood cultures done, which was much higher in the US; in addition, the percentage of US patients was much higher in ASSIST-2. In ASSIST-1 blood cultures were not done in approx. 82% of the patients whereas in ASSIST-2 blood cultures were done in seemingly over approx. 70% of the patients.

More than 70% of enrolled patients had a Gram-positive pathogen assigned at baseline, the species distribution of which was well-balanced between treatment groups with *S. aureus* predominating (69.9% of isolates), 39.9% of *S. aureus* were MRSA. The majority of the MRSA strains were from the ASSIST-2 study. Among the MRSA isolates, approximately 70% were resistant to erythromycin and the same proportion were resistant to levofloxacin while approximately 10% of the MRSA were resistant to clindamycin. The resistance rates were similar between the 2 treatment arms. Among the isolates resistant to TMP/SMX, 5 were from patients in the iclaprim arm and at TOC 4/5 patients were

considered as overall therapeutic successes. Among the *S. pyogenes* isolates, 6% were resistant to erythromycin. All of the *E. faecalis* isolates were susceptible to vancomycin and ampicillin. No resistance to linezolid was encountered. All phenotypically methicillin-resistant strains that were tested were found to carry *mecA*. Additionally, there were 2 MSSA strains that were positive for *mecA*, and they may represent heterogeneously oxacillin resistant strains that were not detected by MIC determination.

There were clinically relevant differences between patient populations in both studies. In ASSIST-1, the use of *pre-study antibiotics* was recorded in 39.8% in the iclaprim group and 36.7% in the linezolid group; the use of analgesics was reported for iclaprim in 57% cases and for linezolid in 64%). For ASSIST-2, the use of pre-study antibiotics was recorded in 12.7% in the iclaprim group and 20.2% in the linezolid group; the use of analgesics was more evident in the iclaprim treatment group (iclaprim: 27.9%; linezolid: 20.2%).

The most widely used *concomitant medication* type was analgesics, these were used in a similar proportion of patients in both studies and in both treatment groups (range 54% - 62%).

In ASSIST-1, the overall percentage of patients who received a portion of their study medication course as *outpatients* was small (ITT: 23/249 and 29/248, PP: 17/206 and 23/213 in the iclaprim and in the linezolid arm, respectively). In ASSIST-2, a substantial proportion of the patients of both treatment groups received OPAT following an initial 3-4 days of in-patient study medication treatment: OPAT was used in 105/251 (41.8%) and 110/243 (45.3%) of patients in the iclaprim and linezolid groups, respectively. This is explained by the geographical differences in the treatment of cSSTI e.g. in the US the percentage of OPAT treatment after 4 days in the hospital was high, whereas in the EU and rest of the world (ROW) regions most patients stayed in the hospital for the entire treatment duration.

Clinical efficacy results. The results obtained in both studies were similar. The clinical cure rates at the TOC visit for iclaprim was consistently slightly lower than for linezolid to that of linezolid in both studies and across the different analysis populations although lower bound of the CI for the treatment difference remained within the predefined values (<12.5%). However, for the ITT and PP populations the lower bound of the CI for treatment difference across the two trials did not achieve consistently values <10%. For the combined studies the lower bound of the CI for the treatment difference was -7.9% for the ITT population and -8.7% for PP population, see the following composite table. Analysis of the MCE population (patients using prohibited antibiotics as co-medication were not excluded, other exclusion criteria were the same as for the PP population) demonstrated the lower bound of the CI for the treatment difference to be <10% in the individual studies as well as the combined studies.

Table E2: Clinical Cure Rate at TOC – ITT and PP Populations 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%	75.9% – 85.9%	76.5% – 86.5%	78.6% – 85.5%	81.9% – 88.4%
Treatment difference and 95% CI	-5.6% [-11.72% to 0.6%]		-0.6% [-7.7% to 6.5%]		-3.1% [-7.9% to 1.6%]	
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% – 93.7%	92.7% – 98.5%	89.3% – 94.7%	95.9% – 99.0%
Treatment difference and 95% CI	-4.4% [-8.4% to -1.0%]		-6.5% [-11.8% to -1.2%]		-5.5% [-8.7% to -2.4%]	
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	84.6% – 93.2%	88.3% – 95.6%	79.3% – 89.2%	81.4% – 90.9%	83.5% – 90.0%	86.5% – 92.3%
Treatment difference and 95% CI	-3.1% [-8.8% to 2.5%]		-2.0% [-8.8% to 5.0%]		-2.6% [-7.0% to 1.8%]	

CI=confidence interval, ITT=Intent-to-treat, MCE=modified clinically evaluable (patients using prohibited antibiotics as co-medication were not excluded; other exclusion criteria were the same as

for the PP population), PP=per protocol (*note*: patients using prohibited antibiotics as co-medication were excluded), TOC=test of cure.

The CIs presented in this table were calculated using SAS-generated 95% CI. The ASSIST-1 analysis used the Newcombe-Altman formula.

The clinical cure rates at the TOC visit in the non-primary populations MITT, ME_{PP} and ME_{MCE} were consistent with the results of the primary populations, see the following display.

Table E3: Clinical Cure Rate at TOC – 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	76.8% – 88.2%	83.7% – 93.1%	75.0% – 86.5%	75.2% – 86.9%	77.9% – 85.9%	81.3% – 88.8%
Treatment difference & 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 & 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 & 95% CI	-2.7% [-9.1 to 3.4%]		-2.3% [-10.1% to 5.6%]		-2.8% [-7.8% to 2.1%]	

MEMCE= microbiologically evaluable and modified clinically evaluable, MEPP=microbiologically evaluable and per protocol, MITT=modified intent-to-treat, TOC=test of cure.

The clinical outcome at the EOT visit for all populations was similar to the outcomes of the primary efficacy variables (not shown here).

Efficacy by type of infection. In study ASSIST-1, the clinical cure rates were relatively consistent across the types of infection. In the iclaprim wound-infection subgroup, there were 5/29 and 3/22 failures in ITT and PP populations, respectively. In the linezolid wound-infection subgroup, there were 1/43 and 1/36 failures in the ITT and PP populations, respectively. The numbers obtained were too small to draw any conclusions of statistical significance.

No similar analysis by type of infection is presented for ASSIST-2, whereas in the integrated efficacy/safety summary document the response by type of infection is briefly commented and relevant tables of the results are presented. From these tables the combined results in the MCE and PP populations can be summarised as follows.

In the leading diagnosis with number of patients approx. 100 or more the results seem to favour linezolid.

Table E4: Clinical Cure Rates at the TOC Visit in combined data set (MCE and PP Analysis Sets)

	-- Iclaprim --			--- Linezolid ---		
	N	n	%	N	n	%
MCE Analysis set						
Infected ulcers	54	49	90.7	54	47	87.0
1st & 2nd degree burns	44	39	88.6	50	44	88.0
Major Abscesses	114	96	84.2	106	95	89.6
Deep & extensive Cellulitis	167	136	81.4	166	148	89.2
Wound infections	119	104	87.4	139	123	88.5
PP Analysis set						
Infected ulcers	52	49	94.2	50	47	94.0
1st & 2nd degree burns	39	39	100	44	44	100
Major Abscesses	107	96	89.7	99	95	96.0
Deep & extensive Cellulitis	153	136	88.9	150	148	98.7
Wound infections	112	104	92.9	126	123	97.6

Note: n is the number of patients with a clinical outcome of Cure.

The applicant should provide a comprehensive discussion for the results by type of infection in the relevant clinically and bacteriologically evaluable data sets. Differentiated results by pathogen (mono and mixed) involved and severity per type of infection should also be addressed and the necessary sensitivity analyses should be provided. Special emphasis should be put on the results in patients with at least three or more of the SIRS criteria for severity of infection (including body temperature >38°C).

Overviews of the type of wound infections (post-surgical, trauma etc.) and abscesses (major, location etc.) are not discussed in the reports. These overviews should be presented and discussed.

Based on the overall results for all patients the applicant claims non- inferiority of iclaprim versus comparator regimens for the clinical cure rate at the TOC visit in each study and integrated combined study analysis. However, this conclusion cannot be accepted at this stage because of importabnt issues noted in the assessment of these studies:

- Definitive interpretation of the present results concerning the primary efficacy endpoints is hampered by the used definition of cure in the trials; namely cure included alternatively the definition “Clinically relevant improvement of the local and systemic signs and symptoms of cSSTI 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 on the EOT or TOC (as applicable for the assessment); and received at least four days of treatment and at least seven doses”. The applicant is requested to present separate analyses of the cure rates by considering patients who showed full resolution of the clinical signs and symptoms and did not need further antibiotic therapy at the TOC and LFU visits separately from those whose cure outcome was based on the just mentioned alternative improvement definition. Due to these lacking data it cannot be concluded at this stage that this coined definition is adequate to assess definitively that involved two treatments in the trials will exhibit clinically similar efficacy (see NfG for Guidance on Evaluation of Medicinal Products indicated for Treatment of Bacterial Infections (CHMP/EWP/558/95).
- No systematic presentation and discussion by type of infection per study (for ASSIST-2 not presented), whereas in the integrated efficacy/safety summary document the response by type of infection is briefly commented. From these tables the combined results in the MCE and PP populations for the leading diagnosis with number of patients approx. 100 or more seem to favour linezolid.

– Overviews of baseline data for clinical signs and symptoms and at TOC and LFU should included for each analysis. Furthermore, for the assessment of the consistency of the results across subgroup analyses, particularly infection type and by causative agent (mono and mixed infections) per type in the relevant clinically and bacteriologically evaluable data sets should be systematically presented and discussed per study and in the integrated analysis. The necessary sensitivity analyses should be provided. Special emphasis should be put on the results in patients with at least three or more of the SIRS criteria for severity of infection (including body temperature >38°C).

As requested, additional analyses were given using the cure definition by considering patients who showed full resolution of the clinical signs and symptoms and did not need further antibiotic therapy at the TOC and LFU visits in the "modified clinically evaluable" (MCE) population. The MCE population includes all patients in the clinically evaluable population (CE) who had an infecting Gram-positive pathogen at baseline (BL) and corrects for the identified marked imbalance between treatment groups in the use of prohibited antibiotics which made the PP population questionable for a correct efficacy assessment since these potential failures who received concomitant prohibited antibiotics are excluded from the PP population (per definition in the SAP). Hence it is acceptable to consider the MCE population as the pivotal analysis population to assess the clinical efficacy.

The provided analyses up to date confirm original conclusion of the CHMP that numerically and rather consistently lower cure rates were observed iclaprim treated groups especially in important subgroups with >38°C and >=2 additional SIRS criteria, with the leading diagnoses abscess and cellulites and those with *S. pyogenes* infection. This holds also for patients (with ≤8 BL symptoms with scores 2 or 3) due to MRSA constituting most MRSA infected patients. See for instance results in the following display.

Table E.4.1: MCE Population – No Individual Score at TOC >1

	All BL scores			≤8 BL scores 2 or 3			9-12 BL scores 2 or 3	
	Iclaprim	Linezolid		Iclaprim	Linezolid		Iclaprim	Linezolid
All								
Cure %	82.0	83.4		82.4	83.5		81.6	83.2
Δ% ICL-LIN		-1.3			-1.1			-1.6
N	440	445		255	260		185	185
No SIRS								
Cure %	83.3	84.5		83.9	82.1		82.4	88.5
Δ% ICL-LIN		-1.1			1.8			-6.2
N	234	238		149	151		85	87
SIRS								
Cure %	80.6	82.1		80.2	85.3		81.0	78.6
Δ% ICL-LIN		-1.5			-5.1			2.4
N	206	207		106	109		100	98
SIRS with 38°C								
Cure %	77.6	81.2		73.3	82.5		82.1	79.3
Δ% ICL-LIN		-3.6			-9.2			2.8
N	58	69		30	40		28	29
Abscess								
Cure %	80.7	86.8		83.3	89.3		73.3	80.6
Δ% ICL-LIN		-6.1			-6.0			-7.3
N	114	106		84	75		30	31
Burn								

	All BL scores			≤8 BL scores 2 or 3			9-12 BL scores 2 or 3	
	Iclaprim	Linezolid		Iclaprim	Linezolid		Iclaprim	Linezolid
Cure %	88.6	84.0		83.3	80.0		100.0	93.3
Δ% ICL-LIN		4.6			3.3			6.7
N	44	50		30	35		14	15
Cellulitis								
Cure %	77.8	83.7		75.3	78.7		80.0	87.9
Δ% ICL-LIN		-5.9			-3.3			-7.9
N	167	166		77	75		90	91
Ulcers								
Cure %	72.2	66.7		77.8	75.0		69.4	63.2
Δ% ICL-LIN		5.6			2.8			6.3
N	54	54		18	16		36	38
Wounds								
Cure %	84.0	82.0		83.3	80.2		85.4	86.8
Δ% ICL-LIN		2.0			3.1			-1.5
N	119	139		78	101		41	38
S. aureus								
Cure %	84.0	85.1		85.5	87.0		81.9	82.6
Δ% ICL-LIN		-1.1			-1.4			-0.7
N	250	276		145	161		105	115
MRSA								
Cure %	84.0	83.8		83.8	88.5		84.6	70.4
Δ% ICL-LIN		0.2			-4.7			14.2
N	100	105		74	78		26	27
S. pyogenes								
Cure %	71.7	88.2		68.4	89.5		73.5	87.5
Δ% ICL-LIN		-16.5			-21.1			-14.0
N	53	51		19	19		34	32

A similar pattern of efficacy results seem to emerge also in the corresponding analyses of available data for LFU evaluations; difference between iclaprim and linezolid efficacy profiles seemed to be also more pronounced in favour of linezolid although the latter results should be interpreted with caution due to the noted deficiencies in the trial design with respect to the LFU efficacy evaluations. See for instance results in the following display.

Table E.4.2:MCE Population – No Individual Score at LFU >1

	ALL BL scores			≤8 BL scores 2 or 3			9-12 BL scores 2 or 3	
	Iclaprim	**Linezolid**		**Iclaprim**	**Linezolid**		**Iclaprim**	**Linezolid**
All								
Cure %	80.0	86.9		80.4	84.7		79.6	90.2
Δ% ICL-LIN		**-6.9**			**-4.4**			**-10.6**
N	215	213		112	131		103	82
No SIRS								
Cure %	84.2	84.6		86.2	80.2		81.6	92.9
Δ% ICL-LIN		**-0.3**			**5.9**			**-11.2**
N	114	123		65	81		49	42
SIRS								
Cure %	75.2	90.0		72.3	92.0		77.8	87.5
Δ% ICL-LIN		**-14.8****			**-19.7***			**-9.7**
N	101	90		47	50		54	40
SIRS with 38°C								
Cure %	64.5	88.2		60.0	89.5		68.8	86.7
Δ% ICL-LIN		**-23.7***			**-29.5**			**-17.9**
N	31	34		15	19		16	15
Abscess								
Cure %	77.6	90.7		81.3	92.1		70.6	87.5
Δ% ICL-LIN		**-13.2**			**-10.9**			**-16.9**
N	49	54		32	38		17	16
Burn								
Cure %	76.9	80.0		73.7	76.9		85.7	88.9
Δ% ICL-LIN		**-3.1**			**-3.2**			**-3.2**
N	26	35		19	26		7	9
Cellulitis								
Cure %	77.5	88.3		82.8	79.4		75.0	95.3
Δ% ICL-LIN		**-10.8**			**3.3**			**-20.3****
N	89	77		29	34		60	43
Ulcers								
Cure %	69.6	66.7		66.7	77.8		71.4	50.0
Δ% ICL-LIN		**2.9**			**-11.1**			**21.4**
N	23	15		9	9		14	6
Wounds								
Cure %	80.0	77.3		80.6	77.6		79.2	76.5
Δ% ICL-LIN		**2.7**			**3.0**			**2.7**
N	60	66		36	49		24	17
S aureus								
Cure %	79.1	89.7		82.5	90.8		75.0	88.0
Δ% ICL-LIN		**-10.6***			**-8.2**			**-13.0**
N	115	126		63	76		52	50
MRSA								

	ALL BL scores			≤8 BL scores 2 or 3			9-12 BL scores 2 or 3	
	Iclaprim	**Linezolid**		**Iclaprim**	**Linezolid**		**Iclaprim**	**Linezolid**
Cure %	80.9	89.4		85.3	91.9		69.2	80.0
Δ% ICL-LIN		**-8.5**			**-6.6**			**-10.8**
N	47	47		34	37		13	10
S. pyogenes								
Cure %	78.4	94.1		80.0	92.3		77.8	95.2
Δ% ICL-LIN		**-15.7**			**-12.3**			**-17.5**
N	37	34		10	13		27	21

* $p < 0.05$

** $p < 0.01$

The latter results based on an important proportion of patients with useful LFT assessment remain of important clinical concern for the sought cSSTI indication at large.

The applicant's reliance on the statistical non-inferiority- with observed non-inferiority margin within -10% for clinical cure as defined by the protocol at TOC for both studies and combined dataset- in the MCE population becomes less relevant in the light of above described results. Even then numerically iclaprim global cure rates were lower than for linezolid. Furthermore, in the analysis of therapeutic success in the microbiologically evaluable MCE population which is acknowledged to be an important indicator of clinical efficacy, iclaprim showed consistently less favourable results than linezolid across all analysis sets and in both studies. The lower non-inferiority margin exceeded the -12.5% value per study and the -10% for the combined data in favour of linezolid.

Overall, in the combined dataset results from these pivotal studies, clinical cure rates as defined in the SAP at TOC in patients in MITT population as well as MCE populations for the leading diagnosis seem to favour linezolid. This is also reflected in the bacteriological eradication and persistence results for the predominant pathogens *S. aureus* (both MSSA and MRSA) and *S. Pyogenes* of severe infection based on the given SIRS definition. Similarly, despite the given detailing of the applicant cure rates in patients from the linezolid arm were higher than those in the iclaprim arm (97.0% versus 63.0%) in the small group (approx. 41-50 patients per group) of patients with 2 or more Gram-positive pathogens identified at baseline.

Time to resolution of clinical symptoms
Median time to resolution of clinical symptoms was 8 days for iclaprim and 7 days for linezolid regimens in study ASSIST-1 whereas this was 5 days and 6 days respectively in study ASSIST-2 (not shown here).

The greater majority of the patients (≥65%) in both treatment groups had baseline body temperature of > 37.8°C. Median time to defervescence (defined as the first of 2 days with a body temperature of < 37.2°C) was 4 days in both treatment groups in ASSIST-1 whereas this was 3 days for iclaprim and 2 days for linezolid in ASSIST-2.

The majority of patients (≥ 80%) in both studies had *CRP values* above the normal range at baseline. At Day 3 the majority of patients had still elevated values. In ASSIST-1, the percentage of patients with CRP values above the normal range for the iclaprim and linezolid groups were 43.6% versus 35.2%, and 39.6% versus 31.2%, respectively, at the EOT and TOC visits. In ASSIST-2, the corresponding values were 35.9% versus 29.9%, and 35.9% versus 28.0%, respectively.

Clinical cure rates by pathogen. Results at the TOC visit against major causative pathogens (isolated from >10 patients in the pooled dataset) in MITT population for infection site isolates are presented in the following display.

Table E5: Clinical Cure Rates by Infecting Pathogen at TOC in MITT Patients for Combined Pivotal Phase III cSSTI Studies

	Clinical Cure at TOC (n=cured; N=patients with the respective pathogen)	
	Iclaprim n/N (%)	Linezolid n/N (%)
Staphylococcus aureus, total	236/287 (82.2)	262/304 (86.2)
- MRSA	95/119 (79.8)	98/117 (83.8)
- MSSA	141/166 (84.9)	163/185 (88.1)
Streptococcus pyogenes	46/58 (79.3)	49/56 (87.5)
Enterococcus faecalis	24/29 (82.8)	25/28 (89.3)
Streptococcus agalactiae	5/8	8/11
Streptococcus dysgalactiae subsp. equisimilis	6/7	6/6

MITT=modified intent-to-treat, MRSA=methicillin-resistant *S. aureus*, MSSA=methicillin-sensitive *S. aureus*, TOC=test-of-cure.

The results seem to be similar although a trend towards lower cure rates is visible on the iclaprim treated patients.

Concurrent bacteraemia at baseline was present in 10 patients in the iclaprim and 14 patients in the comparator treatment group in the pooled ITT dataset. Clinical and bacteriological results could not be accessed in the dossier. This should be provided. As requested, the applicant explained that of the 10 patients in the iclaprim group, 7 were assessed for clinical response at TOC and of these 5 were considered to have clinical cure. For comparison, 14 patients who received linezolid had a positive blood culture at baseline; of these 12 patients were assessed at TOC and 7 of these were considered to have clinical cure. The number of bacteraemic patients remains very limited.
Furthermore, it can be criticised that blood cultures were not done systematically in the sought cSSTI indication; in ASSIST-1 blood cultures were not done in approx. 82% of the patients versus seemingly in <30% of the patients in ASSIST-2.

Overall, the pathogens isolated from the primary infection site at baseline in both treatment groups in both studies were predominantly Gram-positive organisms and primarily *S. aureus* (both MSSA and MRSA) followed by *Streptococcus pyogenes*. Clinical experience against other gram-positive pathogens other than these two pathogens is too limited to allow appropriate conclusions.

Bacteriological outcome by patient. Patient bacteriological cure rates against Gram-positive pathogens at TOC and EOT were analysed in the different analysis populations are displayed in the following table.

Table E6: 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 and 95% CI	-8.9% [-17.4% to -0.3%]		-1.2% [-9.9% to 7.6%]		-5.1% [-11.1% to 1.0%]	
MEPP	**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 and 95% CI	-7.6% [-15.2% to -0.1%]		-7.6% [-15.3% to 0.2%]		-7.7%[-13.0% to -2.4%]	
MEMCE	**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 and 95% CI	-6.7% [-14.9% to 1.5%]		-3.3% [-11.8% to 5.3%]		-5.1% [-10.9% to 0.7%]	

CI=confidence interval, MEMCE= microbiologically evaluable and modified clinically evaluable, MEPP=microbiologically evaluable and per protocol, MITT=modified intent-to-treat, TOC=test of cure.

The CI presented in this table were calculated using SAS-generated 95% CI. The ASSIST-1 analysis used the Newcombe-Altman formula.

Table E7: By-Patient Bacteriological Response at EOT 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 (%)	123 (67.2%)	175 (91.6%)	146 (76.0%)	158 (85.9%)	269 (71.7%)	333 (88.8%)
95% CI	59.9% – 74.0%	86.8% – 95.1%	69.4% – 81.9%	80.0% – 90.6%	66.9% – 76.2%	85.2% – 91.8%
Treatment difference and 95% CI	-24.4% [-32.5% to -16.0%]		-9.8% [-18.0% to -1.5%]		-17.1% [-22.8 to -11.2]	
MEPP	**N=150**	**N=167**	**N=165**	**N=149**	**N=315**	**N=316**
Eradication/Presumed Eradication, n (%)	107 (71.3%)	160 (95.8%)	129 (78.2%)	139 (93.3%)	236 (74.9%)	299 (94.6%)
95% CI	63.4% – 78.4%	91.6% – 98.3%	71.1% – 84.2%	88.0% – 96.7%	69.8% – 79.6%	91.5% – 96.8%
Treatment difference and 95% CI	-24.5% [-32.8% to -16.2%]		-15.1% [-23.0% to -7.1%]		-19.7% [-25.3% to -14.0%]	
MEMCE	**N=156**	**N=176**	**N=172**	**N=164**	**N=328**	**N=340**
Eradication/Presumed Eradication, n (%)	109 (69.9%)	164 (93.2%)	133 (77.3%)	145 (88.4%)	242 (73.8%)	309 (90.9%)
95% CI	62.0% – 77.0%	88.4% – 96.4%	70.3% – 83.4%	82.5% – 92.9%	68.7% – 78.5%	87.3% – 93.7%
Treatment difference and 95% CI	-23.3% [-31.8% to -14.7%]		-11.1% [-19.4% to -2.7%]		-17.1% [-23.0 to -11.2]	

ASSIST=Arpida's Skin and Skin structure Infection Study, CI=confidence interval, EOT=end of therapy, MEMCE= microbiologically evaluable and modified clinically evaluable, MEPP=microbiologically evaluable and per protocol, MITT=modified intent-to-treat, TOC=test of cure.

The CI presented in this table were calculated using SAS-generated 95% CI. The ASSIST-1 analysis used the Newcombe-Altman formula.

Overall eradication/presumed eradication rates of baseline pathogens were for iclaprim were consistently lower than the rates observed with linezolid across the analysis populations. Similar results were seen in both, ASSIST-1 and ASSIST-2 studies. The same holds for the results per specific prevalent gram-positive isolates including the most predominant pathogen *S. aureus* and MRSA.

The lower eradication/presumed eradication rates with iclaprim were also reflected in the results per specific prevalent gram-positive isolates including the most predominant pathogen *S. aureus* and MRSA, see the following table for the pooled data (>10 isolates in any arm, MITT population at TOC and EOT) from both studies. The treatment difference in favour of linezolid was more marked at EOT

Table E8: By-Pathogen Bacteriological Response at TOC & EOT Visits – MITT Population, combined analysis of ASSIST-1 &2

	TOC visit		EOT visit	
	Iclaprim	Linezolid	Iclaprim	Linezolid
S. aureus, total, n[1] (%)	**287 (57.4%)**	**304 (61.9%)**	**287 (57.4%)**	**304 (61.9%)**
Eradication	10 (3.5%)	9 (3.0%)	24 (8.4%)	54 (17.8%)
Pres. Eradication	213 (74.2%)	237 (78.0%)	180 (62.7%)	214 (70.4%)
MRSA, n (%)	**119 (23.8%)**	**117 (23.8%)**	**119 (23.8%)**	**117 (23.8%)**
Eradication	1 (0.8%)	1 (0.9%)	4 (3.4%)	7 (6.0%)
Pres. Eradication	90 (75.6%)	91 (77.8%)	87 (73.1%)	92 (78.6%)
MSSA, n (%)	**166 (33.2%)**	**185 (37.7%)**	**166 (33.0%)**	**185 (37.7%)**
Eradication	9 (5.4%)	8 (4.3%)	20 (12.0%)	47 (25.4%)
Pres. Eradication	123 (74.1%)	145 (78.4%)	93 (56.0%)	121 (65.4%)
S. pyogenes, total, n (%)	**58 (11.6%)**	**56 (11.4%))**	**58 (11.6%)**	**56 (11.4%)**
Eradication	2 (3.5%)	3 (5.36%)	5 (8.6%)	18 (32.1%)
Pres. Eradication	39 (67.2%)	45 (80.4%)	34 (58.6%)	36 (64.3%)
S. agalactiae, total, n (%)	**8 (1.6%)**	**11 (2.2%)**	**8 (1.6%)**	**11 (2.2%)**
Eradication	1 (12.5%)	3 (27.3%)	1 (12.5%)	4 (36.4%)
Pres. Eradication	4 (50.0%)	6 (54.5%)	4 (50.0%)	6 (54.5%)
E. faecalis, total, n (%)	**29 (5.8%)**	**28 (5.7%)**	**29 (5.8%)**	**28 (5.7%)**
Eradication	4 (13.8%)	6 (21.4%)	7 (24.1%)	10 (35.7%)
Pres. Eradication	18 (62.1%)	18 (64.3%)	15 (51.7%)	14 (50.0%)

ITT=intent-to-treat, MRSA=Methicillin-resistant *S. aureus*, MSSA=Methicillin-sensitive *S. aureus*, Pres.=presumed.

[1] Includes 5 and 10 isolates at TOC and EOT respectively of unknown methicillin susceptibility identified by local laboratories but failed to grow in the central laboratory.

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

This was also reflected in the per pathogen bacteriological (presumed) persistence results in this population analysis. The more marked treatment difference in favour of linezolid at EOT is not in support of a consistent clinically fourable efficacy of iclaprim vs. the comparator, this difference is not adequately addressed by the applicant.

Effect of PVL type. 540 isolates of *S. aureus* had PVL typing, 263 in the iclaprim arm and 277 in the linezolid arm.
Similar eradication/presumed eradication response of both treatments were seen at the TOC visit in the MITT population against PVL positive *S. aureus* [91/109 (83.5%) for iclaprim vs. 102/119 (85.7%)] and against PVL negative *S. aureus* [116/154 (75.3%) for iclaprim vs. 124/158 (78.5%) for linezolid]. A similar pattern was seen against MRSA PVL positive and PVL negative isolates: PVL positive *MRSA* [59/75 (78.7%) for iclaprim vs. 64/79 (81.0%)] and against PVL negative *MRSA* [28/38 (73.7%) for iclaprim vs. 21/29 (72.4%) for linezolid].

Efficacy by susceptibility (MIC) to Iclaprim
In the 2 Phase III cSSTI studies, iclaprim MICs were <0.25 µg/ml against the majority of the predominant pathogen *S. aureus* and MRSA isolated at baseline (with MIC90 of 0.25 µg/ml for the total *S. aureus*). For *S. pyogenes* isolates the MIC90 was 0.12 µg/ml.

There was no apparent relationship between favourable clinical outcomes and iclaprim MIC values of present isolates at baseline. However, the number of baseline isolates with elevated MIC values for

S. aureus and MRSA (≥0.25 µg/ml) and for *S. pyogenes* (>0.06 µg/ml), was too low to allow appropriate conclusions although numerically more failures were observed in the latter category of isolates. This should be taken into account in the breakpoint assignment.

Overall therapeutic success. In ASSIST-1 and ASSIST-2, the overall therapeutic success was defined as the combination of a clinical outcome of cure and a bacteriological outcome of eradication or presumed eradication. Overall therapeutic success for iclaprim was 75.2%, 83.5%, and 80.2% for the MITT, ME_{PP}, and ME_{MCE} populations, respectively, compared to the some what higher rates for linezolid (80.3%, 91.8% and 85.3%) at the TOC visit. Similar results were seen in both ASSIST-1 and ASSIST-2 studies. A similar pattern was apparent for the results at the EOT visit, however, the differences in response between the two treatment groups were more marked (e.g. for ME_{PP}, and ME_{MCE} populations iclaprim success rates were 74.3%, and 72.6% resp. compared to 94.3%, and 90.6% resp. for the comparator).

Clinically the overall therapeutic success is an important indicator of clinical efficacy in bacteriologically documented infections, in this analysis iclaprim therapeutic success appears to be consistently less favourable than for linezolid across all analysis sets and in both studies. The lower non-inferiority margin exceeded the -12.5% value per study and the -10% for the combined data in favour of linezolid.

See table below for the combined results at TOC and EOT visits.

Table E9: Overall Therapeutic Response at TOC and EOT Visits – MITT and ME Populations (Combined ASSIST-1 & 2)

	TOC visit		EOT visit	
	Iclaprim	**Linezolid**	**Iclaprim**	**Linezolid**
MITT	N=375	N=375	N=375	N=375
Success (%)	282 (75.2%)	301 (80.3%)	264 (70.4%)	330 (88.0%)
95% CI	70.5% – 79.5%	75.9% – 84.2%	65.5% – 75.0%	84.3% – 91.1%
TD & 95% CI	-5.1% [-11.2% to 1.1%]		-17.6% [-23.4% to -11.7%]	
MEPP	N=315	N=316	N=315	N=316
Success (%)	263 (83.5%)	290 (91.8%)	234 (74.3%)	298 (94.3%)
95% CI	78.9% – 87.4%	88.2% – 94.6%	69.1% – 79.0%	91.2% – 96.6%
TD & 95% CI	-8.3% [-13.6% to -3.0%]		-20.0% [-25.7% to -14.3%]	
MEMCE	N=328	N=340	N=328	N=340
Success (%)	263 (80.2%)	290 (85.3%)	238 (72.6%)	308 (90.6%)
95% CI	75.5% – 84.4%	81.1% – 88.9%	67.4% – 77.3%	87.0% – 93.5%
TD & 95% CI	-5.1% [-11.1% to 0.8%]		-18.0% [-24.0% to -12.0%]	

CI=confidence interval, TD= Treatment difference, MEMCE= microbiologically evaluable and modified clinically evaluable, MEPP=microbiologically evaluable and per protocol, MITT=modified intent-to-treat, TOC=test-of-cure, EOT=end of therapy.

Efficacy by Out patient antibiotic treatment (OPAT): In ASSIST-1, the number of failures in patients receiving OPAT in the ITT and PP populations were 5/23 and 4/29 in the iclaprim group versus 1/17 and 1/23, respectively in the linezolid group.
In ASSIST-2, a substantial proportion of the patients of both treatment groups received OPAT following an initial 3-4 days of in-patient study medication treatment (105/251 and 110/243 of patients in the iclaprim and linezolid groups, respectively). In this subgroup the results of both treatment were similar in the ITT population (cure rates of approx. 87% in both treatment groups) but linezolid gave more favourable results in the PP population [91/93 (98%) vs. 88/95 (93%) for iclaprim; failures in 2% and 7% of the patients resp.). For both treatment groups, clinical cure rates at TOC and among patients who received OPAT were higher than those who remained as in-patients (with aprox. 76-78% cure in the ITT population). The higher cure rates in the patients groups receiving OPAT could be at least partly explained by their less severe disease condition.

Subgroup analyses
There were no notable differences by *ethnicity* (predominant being the Caucasian and Hispanic), *age* (predominantly being <65 years of age, only 72/500 iclaprim treated patients were ≥65 years of age) or *gender*. The slightly lower cure rates seen in Hispanics is explained by 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, with generally numerically higher cure rates than for iclaprim in particular in the PP population. Higher cure rates for both linezolid and iclaprim were seen for Europe and Rest of World countries as compared to USA, despite European patients having a higher severity of illness. See the following table.

Table E10: 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%)
USA	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%)

ITT=intent-to-treat, PP=per protocol, TOC=test-of-cure.

A higher proportion of patients in ASSIST-2 had MRSA infection (reflecting the higher percentage of US patients). In the combined dataset the numbers of patients who had MRSA infection in the MITT population at TOC visit in Europe were 4-fold lower. The combined presumed eradication/eradication rates for MRSA in the USA were 76.0% for iclaprim versus 81.0% for linezolid.

Results by severity of infection. In patients with severe infection clinical cure rates at the TOC visit in the combined MCE data set were 351/404 (86.9%) and 369/413 (89.3%) in the iclaprim and linezolid treated patients resp. Cure rates in patients with sevrity of infection defined by SIRS are displayed below.

Table E11: Clinical cure rates by severity of infection based on SIRS definition at TOC – in MCE and PP combined data set

	Combined	
	Iclaprim	**Linezolid**
MCE		
Severe by SIRS definition	N=206	N=207
Clinical cure, n (%)	178 (86.4%)	187 (90.3%)
Not severe	N=234	N=238
Clinical cure, n (%)	205 (87.6%)	212 (89.1%)
PP		
Severe by SIRS definition	N=194	N=191
Clinical cure, n (%)	178 (91.8%)	187 (97.9%)
Not severe	N=221	N=217
Clinical cure, n (%)	205 (92.8%)	212 (97.7%)

MCE=modified clinically evaluable, PP=per protocol, TOC=test of cure.

Overall, numerically lower response in the iclaprim treatment group was observed especially when severetiy definition was based on SIRS definition. Note also that only approx. 47% of the patients in the PP population had severe infection based on the latter definition (191-4 patients per group).

Effect by treatment duration. Overall, cure rates for iclaprim and linezolid were comparable for treatment durations of 10 to 13 days. The majority of patients received treatment for 10 days; in this sub-group cure was reported in 276/299 (92.3%) of patients in the iclaprim arm and 295/314 (93.9%) of patients in the linezolid arm in the ITT population (and 97.1% and 99.7% resp. in the PP population). For patients who received 14 days or more of treatment, cure rates in the ITT population favoured linezolid, 69/82 (84.1%) vs. 78/100 (78.9%) of patients in the iclaprim arm (and 95.5% and 87.0% resp. in the PP population). Overall, for infections requiring $\geq$ 14 days therapy (which would often be the case for more severe complicated infections) cure rates were lower in the iclaprim group than in the compartaor group. As mentioned before, there were no patients who were treated longer than 15 days (as dictated by the protocol). Such patients were not included. The applicant should discuss data on the further treatment of patients in requested LFU dataset. The applicant explained that approx. 5% of iclaprim patients needed further antibiotic treatment. See LFU results above. The CHMP's concern is not entirely resolved. The sought indication at large may necessitate longer treatment duration than the recommended 14 days in severe complicated cases whereas the efficacy and safety of iclaprim in such cases is not studied.

Monomicrobial vs. polymicrobial infections. The majority (approx. 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 as shown in the following table. In the smaller group with 2 or more Gram-positive pathogens identified at baseline cure rates in patients from the linezolid arm were higher than those in the iclaprim arm (97.0% versus 63.0%). The same holds for cure rates were also indistinguishable in mixed infections with Gram-negative pathogens involved. Only one case with anaerobes was documented in the program.

Table E12: 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 (0%)

Effect by concomitant antibiotic use. Patients in the ITT population dataset received protocol allowed initial aztreonam and metronidazole to cover for eventual gram-negative and anaerobic infections respectively: 95 (19%) and 85 (17.3%) of patients from the iclaprim and linezolid arm, respectively received concomitant aztreonam and 69 (13.8%) and 67 (11.6%), respectively received concomitant metronidazole. These proportions are low and most probably are due to the stringent selection criteria used for inclusion in the trials. Apparently, conditions with known potential gram-negative and anaerobic aetiology or requiring longer therapy duration than 14 days were generally excluded or avoided.

For patients receiving aztreonam cure rates were similar in both treatment arms (73.7-74.1%) but lower than for patients receiving no aztreonam (84.2-87.7%). In the PP population the corresponding cure rates for patients receiving on concomitant aztreonam were (84.9-92.1%) and for patients receiving no aztreonam (93.9-98.8%).

For patients receiving metronidazole, cure rates were lower for iclaprim [43/69 (63.3%)] compared to linezolid [41/57 (71.9%)] in the ITT population as well as in the PP populations (78% and 95% cre rates in the resp. arms.). However, in a similar manner to aztreonam, cure rates in both arms were lower than for patients receiving no metronidazole with cure rates in the PP population 94.2% for iclaprim and 98.1% for linezolid treated patients.

Effect of body weight. Among the primary efficacy populations there were no differences in body weight distribution with equal distributions of patients in the extreme 0-10 and 90-100 percentiles in the combined data set. Cure rates for each body weight percentile subgroup were similar across the percentile categories within a treatment arm. In the predominant 59-101 kg category clinical cure rates in the PP population were 316/343 (92.1%) and 319/326 (97.9%) in the iclaprim and linezolid treatment groups respectively.

Surgical intervention during treatment. The number of patients who needed surgical intervention during treatment was very low and similar across treatment groups (16 and 11 patients in the combined ITT data set for iclaprim and linezolid resp.); clinical cure rates in these patients were 13/16 (81.3%) and 10/11 (90.9%) resp. Of note, when a surgical procedure is required as adjunct or F/U therapy was considered failure of the study medication. The CHMP requested further analysis of the data. The given analysis on the infection site surgery and outcome analyzed depending on whether surgical treatment was used or not particularly in the MCE population confirms the earlier efficacy profile; in the leading diagnoses infections requiring surgery intervention (thus implying more severe infections) iclaprim regimen results were less favourable than linezolid regimen results. See the following table.

Table E.12.1. Cure Rates for Patients with Surgical Procedure around Baseline (-1/+2 Days) vs. No Surgical Procedure around Baseline by Type of Infection - MCE Population

		ASSIST-1		ASSIST-2		COMBINED	
Type of Infection	Procedure	Iclaprim (N=218)	Linezolid (N=228)	Iclaprim (N=222)	Linezolid (N=217)	Iclaprim (N=440)	Linezolid (N=445)
Deep or extensive cellulitis	Patients with surgical procedure	33/37 (89.2)	51/53 (96.2)	25/32 (78.1)	23/25 (92.0)	58/69 (84.1)	74/78 (94.9)
	Patients with no surgical procedure	58/69 (84.1)	49/54 (90.7)	20/29 (69.0)	25/34 (73.5)	78/98 (79.6)	74/88 (84.1)
Wound infection	Patients with surgical procedure	6/8	16/16	39/40 (97.5)	36/40 (90.0)	45/48 (93.8)	52/56 (92.9)
	Patients with no surgical procedure	13/17 (76.5)	19/24 (79.2)	46/54 (85.2)	52/59 (88.1)	59/71 (83.1)	71/83 (85.5)
Major abscesses	Patients with surgical procedure	31/36 (86.1)	37/39 (94.9)	39/47 (83.0)	39/43 (90.7)	70/83 (84.3)	76/82 (92.7)
	Patients with no surgical procedure	7/8 (87.5)	6/8 (75.0)	19/23 (82.6)	13/16 (81.3)	26/31 (83.9)	19/24 (79.2)
Infected ulcers	Patients with surgical procedure	1/2	0/2	4/4	0	5/6	0/2
	Patients with no surgical procedure	32/33 (97.0)	33/34 (97.1)	12/15 (80.0)	14/18 (77.8)	44/48 (91.7)	47/52 (90.4)
Infected burns	Patients with surgical procedure	2/2	5/5	1/1	3/3	3/3	8/8
	Patients with no surgical procedure	25/28 (89.3)	20/23 (87.0)	11/13 (84.6)	16/19 (84.2)	36/41 (87.8)	36/42 (85.7)

Diabetics. A total of 118/991 (11.9%) of the ITT population were classified as diabetics. In the PP population in the combined data set the cure rates for iclaprim lower [39/48 (81.3%)] were than for the linezolid treated diabetic patients [38/40 (95.0%)] with a treatment difference of 13.7% (CI 95%: 83.1 to 99.4%). The corresponding cure rates for the non-diabetic patients in the respective treatment arms were 344/367 (93.7%) and 361/368 (98.1%) in the PP population and 344/357 (88.9%) and 361/391 (92.3%) in the MCE population.
In general, subgroup analyses demonstrate that the treatment effects (including observed trends in differences between treatments) were observed consistently across relevant sub-populations.

Analysis performed across trials (pooled analyses AND meta-analysis)
See data reflected in tables above.

Supportive study(ies)
In the Phase II trial (AR-100-SSTI-001) which evaluated iclaprim 0.8 mg/kg vs. iclaprim 1.6 mg/kg vs. vancomycin 1 g b.i.d. comparable rates of clinical efficacy of 26/28 (92.9%), 28/31 (90.3%), and 26/28 (92.9%) respectively were observed at the test-of-cure (TOC) visit in the ITT analysis. The eradication/presumed eradication of Gram-positive pathogens were observed in 89.7%, 80.0% and 72.0% cases respectively. The eradication/presumed eradication rates for *S.aureus* were 80%, 72.2% and 58.8% of the cases respectively (including all 5 cases of MRSA).

The study, however, had several issues which may have influenced on selecting the most appropriate dose (mostly highlighted in the EMEA scientific advice document): e.g. underpowered, with study groups of approximately 30 patients and with small numbers of most microorganisms except total number of *S. aureus.* At the same time the clinical response rate was very high for the indication of cSSTI and was much greater than initially expected (>90% vs about 80%, respectively), probably due to the very selected patient population. The comparator agent in the dose finding study was vancomycin an agent that most guidelines recommend for resistant organisms (mostly MRSA) only as its efficacy in cSSTI is modest being worse than that of beta-lactams and newer agents such as linezolid.

Overall, this study has an exploratory character and not sufficiently statistically powered to draw definitive conclusions with regard to iclaprim dosage although the results seem to support the choice of 0.8 mg/kg b.i.d regimen for the evaluation of the efficacy of iclaprim in the sought indication in the selected group of patients.

Emergence of resistance. In the non-clinical dossier the applicant mentions that a series of experiments were undertaken to determine the propensity for resistance development to iclaprim *in vitro*. These studies demonstrated that the potential for emergence of (acquired) resistance to iclaprim *in vitro* is very low, and no resistant strains were obtained. The clinical data seem to suggest lack of the development of resistance in pathogens during the clinical studies. However, the present clinical database should be interpreted with caution due to the controlled trial conditions and rather limited database. Furthermore, data on the clinical isolates from the clinical studies Phase II-III studies are not adequately discussed in relation to resistance development or decreased susceptibility to iclaprim. The applicant should discuss the failures at the TOC and LFU visits in relation to persistence and or emergence of less susceptible or resistant strains to iclaprim. A clear overview of the geno-and phenotyping results should be presented. As requested, the applicant gave additional analysis of the data.
See also non-clinical assessment. In ASSIST-1 or ASSIST-2, a full analysis of all isolates in of *S. aureus* and *S. pyogenes* revealed increase in iclaprim MIC >2-fold in five patients: 2 cases 0.25→ >16 µg/ml; 2 cases 0.06 →>16 µg/ml and 1 case 0.12 → >16 µg/ml. Most cases were associated with *superinfection* by an unrelated resistant strain of *S. aureus* (resulting from selection pressure). For the 35 patients with persistent bacteriological outcomes, iclaprim MICs of all isolates from the TOC visit were ≤1 doubling dilution of the baseline iclaprim MIC (only in 10/35 there was doubling of MIC values). Similarly for all patients who were considered as clinical failures, there was no incidence of the same baseline species being isolated at TOC visit in which the iclaprim MIC was increased by ≥1 doubling dilutions.
These data seem to indicate that the potential for the emergence of resistance after clinical use of iclaprim is not substantial. See, however, the Non-clinical assessment as to the potential mechanisms of resistance. As noted before the clinical data base is rather limited. Furthermore, due to the design of the studies no microbiology was performed in the Phase III studies at LFU visits (see comment above with regard to LFU evaluations).
From the clinical point of view presence at baseline and emergence of strains of *S. aureus* and MRSA strains with (≥0.25 µg/ml; and noted >16 µg/ml in several clusters from Latvia, Romania and Russia) during and after exposure to iclaprim remain of concern which impacts on the clinical efficacy profile of iclaprim at the recommended dose level. The number of baseline isolates with elevated MIC values

for *S. aureus* and MRSA (≥0.25 µg/ml) and for *S. pyogenes* (>0.06 µg/ml), was very small yet numerically more failures were observed in the latter category of isolates.

In the RMP the potential for developing antimicrobial resistance should be considered as a potential risk and as such is listed in the RMP. See RMP assessment.

Overall comment on efficacy data

The small exploratory Phase II trial (AR-100-SSTI-001) was not sufficiently statistically powered to draw definitive conclusions with regard to iclaprim dosage although the results seemed to support the choice of 0.8 mg/kg b.i.d regimen for the evaluation of the efficacy of iclaprim in the sought indication. The higher iclaprim 1.6 mg/kg did not reveal higher therapeutic results in the selected group of patients. In the light of the questioned clinical efficacy results from the two pivotal studies a new study investigating a more appropriate dosing regimen is deemed to be necessary.

Based on the results of the pivotal Phase III studies ASSIST-1 and ASSIST-2 the applicant claims non- inferiority of iclaprim versus comparator regimens for the clinical cure rate at the TOC visit in each study and integrated combined study analysis. However, this conclusion could not be accepted because of important issues noted in the assessment of these studies:

- Definitive interpretation of the present results concerning the primary efficacy endpoints was hampered by the used definition of cure in the trials; namely cure included alternatively the definition "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 on the EOT or TOC (as applicable for the assessment); and received at least four days of treatment and at least seven doses". Due to these lacking data it could not be concluded at this stage that this coined definition is adequate to assess definitively that involved two treatments in the trials will exhibit clinically similar efficacy (see NfG for Guidance on Evaluation of Medicinal Products indicated for Treatment of Bacterial Infections(CHMP/EWP/558/95). The applicant was requested to present separate analyses of the cure rates by considering patients who showed full resolution of the clinical signs and symptoms and did not need further antibiotic therapy at the TOC and LFU visits separately from those whose cure outcome was based on the just mentioned alternative improvement definition.
- At LFU approx. 92-3% of patients in ASSIST-1 and ASSIST-2 resp. were assessed, however, the results are not presented or discussed by the applicant**.** Overviews of baseline data for clinical signs and symptoms and at TOC and LFU should included for each analysis. Furthermore, for the assessment of the consistency of the results across subgroup analyses, particularly infection type and by causative agent (mono and mixed infections) and severity (by SIRS and Eron criteria) per type in the relevant clinically and bacteriologically evaluable data sets should be systematically presented and discussed per study and in the integrated analysis. The necessary sensitivity analyses should be provided. Special emphasis should be put on the results in patients with at least three or more of the SIRS criteria for severity of infection (including body temperature >38°C).
- No systematic presentation and discussion by type of infection per study (for ASSIST-2 not presented), whereas in the integrated efficacy/safety summary document the response by type of infection is briefly commented. From these tables the combined results in the MCE and PP populations for the leading diagnosis with number of patients approx. 100 or more seem to favour linezolid.
- The protocol-defined primary endpoint of both individual studies ASSIST-1 and ASSIST-2 was clinical cure at the TOC visit in the co-primary populations ITT and PP.
  In primary analysis of the cure rate in the PP population the lower bound of the CI for treatment difference across the two trials did not achieve consistently values <10% (the required non-inferiority margin). In both studies the entire 95% CI for the difference to comparator lies below zero, and for ASSIST-2 the lower limit also was below -10%. Therefore, statistically non-inferiority cannot be concluded. This concern is strengthened by the similar pattern of results in the ITT population. The applicant should provide a thorough discussion and justify the conclusion of non-inferiority.
- Overall, the pathogens isolated from the primary infection site at baseline in both treatment groups in both studies were predominantly Gram-positive organisms and primarily *S. aureus* (both MSSA

and MRSA) followed by *Strep. pyogenes*. Numerically clinical cure rates at TOC in MITT Patients for Combined Pivotal Phase III cSSTI Studies seem to favour linezolid. The numerically much greater bacteriological persistence rate especially in cases of *S. pyogenes* creates a real concern of using iclaprim empirically as is common in clinical practice. In the small group of patients with 2 or more Gram-positive pathogens identified at baseline (approx. 30 patients) cure rates in patients from the linezolid arm were higher than those in the iclaprim arm (97.0% versus 63.0%).

Clinical experience against gram-positive pathogens other than *S. aureus* and *Strep. Pyogenes* is too limited to allow appropriate conclusions.

- Numerically lower response in the iclaprim treatment group was also observed especially when severetiy was based on SIRS definition (only 191-4 patients per group in the PP population had severe infection based on the latter definition).
- Although the number of diabetic patients per arm in the combined data set is quite small, cure rates for iclaprim were lower than for the comparator.
- Clinically the overall therapeutic success is an important indicator of clinical efficacy in bacteriologically documented infections, in this analysis iclaprim therapeutic success appears to be consistently less favourable than for linezolid across all analysis sets and in both studies. The lower non-inferiority margin exceeded the -12.5% value per study and the -10% for the combined data in favour of linezolid.

Overall, these efficacy data constituted a major efficacy objection against the sought indication. In response to the major efficacy objections gave supplementary analyses and argumentation. The provided analyses up to date confirm original conclusion of the CHMP.

The robustness of the efficacy data to support the sought indication in adult patients with cSSTI remains seriously questioned based on the provided additional analyses using the cure definition by considering patients who showed full resolution of the clinical signs and symptoms and did not need further antibiotic therapy at the TOC and LFU visits in the "modified clinically evaluable" (MCE) population. The MCE population includes all patients in the clinically evaluable population (CE) who had an infecting Gram-positive pathogen at baseline (BL) and corrects for the identified marked imbalance between treatment groups in the use of prohibited antibiotics which made the PP population questionable for a correct efficacy assessment since these potential failures who received concomitant prohibited antibiotics are excluded from the PP population (per definition in the SAP). Hence it is acceptable to consider the MCE population as the pivotal analysis population to assess the clinical efficacy.

The provided analyses up to date confirm original conclusion of the CHMP that numerically and rather consistently lower cure rates were observed iclaprim treated groups especially in important subgroups with >38°C and >=2 additional SIRS criteria, with the leading diagnoses abscess and cellulites and those with *S. pyogenes* infection. This holds also for patients (with ≤8 BL symptoms with scores 2 or 3) due to MRSA constituting most MRSA infected patients. A similar pattern of efficacy results seem to emerge also in the corresponding analyses of available data for LFU evaluations; difference between iclaprim and linezolid efficacy profiles seemed to be also more pronounced in favour of linezolid although the latter results should be interpreted with caution due to the noted deficiencies in the trial design with respect to the LFU efficacy evaluations. The latter results based on an important proportion of patients with useful LFT assessment remain of important clinical concern for the sought cSSTI indication at large.

The applicant's reliance on the statistical non-inferiority- with observed non-inferiority margin within -10% for clinical cure as defined by the protocol at TOC for both studies and combined dataset- in the MCE population becomes less relevant in the light of above described results. Even then numerically iclaprim global cure rates were lower than for linezolid. Furthermore, in the analysis of therapeutic success in the microbiologically evaluable MCE population which is acknowledged to be an important indicator of clinical efficacy, iclaprim showed consistently less favourable results than linezolid across all analysis sets and in both studies. The lower non-inferiority margin exceeded the -12.5% value per study and the -10% for the combined data in favour of linezolid. Overall, in the combined dataset results from these pivotal studies, clinical cure rates as defined in the SAP at TOC in patients in MITT population as well as MCE populations for the leading diagnosis seem to favour linezolid. This is also reflected in the bacteriological eradication and persistence results for the predominant pathogens *S. aureus* (both MSSA and MRSA) and *S. Pyogenes* of severe infection based on the given SIRS

definition. Similarly, despite the given detailing of the applicant cure rates in patients from the linezolid arm were higher than those in the iclaprim arm (97.0% versus 63.0%) in the small group (approx. 41-50 patients per group) of patients with 2 or more Gram-positive pathogens identified at baseline.

In addition, a number of findings and issues can be criticised and raise the following concerns:
The extent of exposure is essentially limited to 14 days. Infections requiring ≥ 14 days therapy (which would often be the case for more severe complicated infections were generally excluded (as dictated by the protocol). There is a concern that for the indication at large in general practice treatment for longer duration in severe complicated cases may be needed whereas the efficacy and safety of iclaprim in such cases is not studied. The applicants's answer is not sufficiently reassuring; 5% of iclaprim patients needed further antibiotic treatment in the pivotal studies. The CHMP concerns despite reflection of limitations of the data in the SmPC is not entirely resolved but can be potentially resolved in the SmPC in case of any positive Opinion.

Data suggest that most patients had community-acquired and not nosocomial infection, the applicant should clarify this issue. The applicant did not give direct clarification as to the source of infection whether it was community-acquired or nosocomial infection; the applicant should have given a direct clarification based on the diagnoses and hospital acquired relationship.

Furthermore, important groups of patients with severe infection patients were excluded from the studies: diabetic foot infections or patients with decubitis ulcers, osteomyelitis, necrotizing fasciitis or gangrene, patients with infections associated with a prosthetic device, infections that would require > 10 days of IV therapy (only 14 days therapy allowed, whereas in section 4.2 of the SPC longer treatment till resolution of the infection is recommended), major burns comprising more than 20% of body surface, infections due to animal or human bites, immunocompromised or neutropenic patients, patients with severely impaired arterial blood supply, patients with severe cardiac disorders. It is unclear whether patients with septic arthritis, or toxic shock syndrome or shock, episiotomy infection, peri-anal cellulitis, and infection extended to the oropharyngeal, gastrointestinal, urogenital or gynaecological tract were excluded. The applicant gave additional clarifications and expanded the list of relevant patient groups in the listed limitations of the clinical data in section 4.4 of the SmPC.

The number of bacteraemic patients at baseline is very limited: only in 10 patients in the iclaprim and 14 patients in the comparator treatment group in the pooled ITT dataset. Clinical and bacteriological results were given in response to the request of the CHMP; however the numbers remain very limited. Furthermore, it can be criticised that blood cultures were not done systematically in the sought cSSTI indication; in ASSIST-1 blood cultures were not done in approx. 82% of the patients versus seemingly in <30% of the patients in ASSIST-2.

These issues make the representativeness of the evaluated patients for the sought indication cSSTI at large questionable.

There is no clinical evidence provided that iclaprim is beneficial in special patient groups failing other antibiotics or intolerant to standard antibiotics used in the treatment of cSSTI. The applicant discussed this issue as requested. The reviewed data based on the numbers of patients (per antibiotic and treatment arm) who received at least 2 days of treatment with antibiotics effective against Gram-positive pathogens prior to the study entry, and who were assessed as failures to this treatment allowing enrolment into the ASSIST studies are very small and the underlying diagnosis and pathogen involved are not specified. Of note again in the total MCE population iclaprim performed less well than linezolid in the defined subgroup. The presented retrospective analysis does not constitute sufficient clinical evidence that iclaprim is beneficial in special patient groups failing other antibiotics or intolerant to standard antibiotics used in the treatment of cSSTI. This conclusion will be carried forward to the benefit-risk assessment.

The applicant recommends not exceeding 100 mg per dose whereas this is not mentioned as such in the protocols. The applicant should comment. The applicant explained that in the ASSIST studies only 8 patients were treated with iclaprim in a dose exceeding 100 mg per dose. From the point of view of

efficacy and safety this is a very limited database. It remains unclear how many patients were exposed to fixed dose between 64 mg (based on the mean body weight of 80 kg in the Phase III studies, dosed with 0.8 mg/kg) and 100 mg.

Numbers and results of patients with perivascular disease and complicated erysipelas should be clarified. The applicant explained that in the combined data set only 4 patients presented with peripheral vascular disease (PVD) and 8 patients with complicated erysipelas (CE) in the iclaprim treatment arm versus 5 and 3 patients resp. in the linezolid arm in the MCE population. The few patients with PVD seemed to respond better on linezolid than on iclaprim whereas for the few patients with CE both treatments seemed to perform similarly. These very small numbers of patients do not allow definitive conclusions on efficacy in these described conditions; they illustrate once more the limitations of the database for sought cSSTI indication. This is taken into account in the present benefit-risk conclusion and SmPC assessment.

The potential for the emergence of resistance after clinical use of iclaprim cannot be denied. The clinical data seem to suggest lack of the development of resistance or less susceptible strains during the clinical studies. Although there was no apparent relationship between favourable clinical outcomes and iclaprim MIC values of present isolates at baseline, the number of baseline isolates with elevated MIC values for *S. aureus* and MRSA (≥0.25 µg/ml) and for *S. pyogenes* (>0.06 µg/ml), was too low to allow appropriate conclusions although numerically more failures were observed in the latter category of isolates. The present clinical database should be interpreted with caution due to the controlled trial conditions and rather limited database. Furthermore, data on the clinical isolates from the clinical studies Phase II-III studies are not adequately discussed in relation to resistance development or decreased susceptibility to iclaprim. The applicant should discuss the failures at the TOC and LFU visits in relation to persistence and or emergence of less susceptible or resistant strains to iclaprim. A clear overview of the geno-and phenotyping results should be presented. The applicant's answer allows the conclusion that provided analysis of all isolates in of *S. aureus* and *S. pyogenes* revealed increase in iclaprim MIC >2-fold in five patients: 2 cases 0.25→ >16 µg/ml; 2 cases 0.06 →>16 µg/ml and 1 case 0.12 →>16 µg/ml. Most cases were associated with *superinfection* by an unrelated resistant strain of *S. aureus* (resulting from selection pressure). From the clinical point of view presence at baseline and emergence of strains of *S. aureus* and MRSA strains with (≥0.25 µg/ml; and noted >16 µg/ml in several clusters from Latvia, Romania and Russia) during and after exposure to iclaprim are of concern which impacts on the clinical efficacy profile of iclaprim at the recommended dose level. The number of baseline isolates with elevated MIC values for *S. aureus* and MRSA (≥0.25 µg/ml) and for *S. pyogenes* (>0.06 µg/ml), was very small yet numerically more failures were observed in the latter category of isolates. This conclusion is relevant for the benefit-risk assessment and not finalised breakpoint setting.

Clinical safety

The applicant has provided the safety data on exposed healthy volunteers from Phase I studies and patients treated with iclaprim for sought indication in the Phase II-III studies. These studies comprised a total of 344 healthy subjects and 562 cSSTI patients exposed to iclaprim.

Phase 1 studies revealed a propensity for iclaprim to prolong the QTc interval at high doses. These first findings were thoroughly evaluated in two Phase 1 studies. Since a QTc prolonging propensity for iclaprim had been established, patients were monitored for QTc elevation in the Phase II-III studies.

Patient exposure
The source of the main data sets for safety analysis is displayed in the following table.

Table S1: Exposure to recommended iclaprim dose in phase II-III studies (ITT safety population)

Study	Dose	N
Phase II (AR-100-SSTI-001)	Iclaprim 0.8 mg/kg b.i.d. by IV infusion for 10 days	30
	Iclaprim 1.6 mg/kg b.i.d. by IV infusion for 10 days	32
Phase III (ASSIST-1 and -2)	Iclaprim 0.8 mg/kg b.i.d. by IV infusion for 10-14 days	500

In the Phase I studies the highest single IV infusion exposure was 3.2 mg/kg (infusion over 30 minutes), this was studied in the cardiac safety study AR-100-ECG-002.
The majority (approx. 60%) of patients in the two Phase III studies were treated for 10 days and approx. 19% of the patients received 14 days of treatment; none of the patients received iclaprim for >15 days.

Adverse events Phase III studies
In the pooled analysis of the two pivotal Phase III studies the incidence of possibly or probably treatment related AEs was 22.6% for the iclaprim treatment group, compared to 27.9% for the linezolid group. The majority of the treatment related AEs were mild or moderate in terms of severity and patients recovered without sequelae.

Table S2: Summary of Treatment-Emergent Adverse Events (TEAEs)
(Pooled Phase III Studies: ITT Safety Analysis Set)

	Iclaprim (N = 500)				**Linezolid (N = 491)**			
Number (%) of Patients Experiencing	**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 discontinuations	11	(2.2%)	6	(1.2%)	6	(1.2%)	6	(1.2%)
Deaths	6	(1.2%)	0	--	1	(0.2%)	0	--

* Related: Possibly or probably related to study drug or with missing rating on relationship to study drug)

If a specific AE occurred more than once in the same patient, each incidence (which had a start and a stop point) was counted as a separate event for the determination of the total number of TEAEs. If a stop date was missing (i.e. TEAE ongoing) in 1 record and the same TEAE was recorded again at a later date for the same patient, it was counted only once.

The most frequently reported individual AEs in the iclaprim group were increased alanine transaminase (ALT) (6.6%), increased aspartate transaminase (AST) (6.4%), headache (6.0%) and nausea (6.0%). The same AEs were reported for the linezolid treatment group, the most frequently reported AEs being 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 (at least 5 times more frequent in the linezolid group) and body temperature increase (at least 3 times more frequent in iclaprim group). However, fewer than 12 patients in each treatment group reported these events.

Drug-related adverse reactions with >1% incidence were generally similarly reported for iclaprim treated patients, although overall, more patients in the linezolid group (27.9%) than the iclaprim group (22.6%) experienced study-drug-related AEs. See the following table.

Table S3: AEs at least Possibly Related to Study Drug in At Least 1% of Patients in Either Treatment Group (Pooled Phase III Studies ASSIST-1 and -2: ITT Safety Analysis Set)

	Combined Phase III Data	
System Organ Class	**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. In ASSIST-1, possibly- and probably-related events were considered separately and the threshold of 1% applied to each category.

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

The ALT / AST elevations observed and reported as AEs were slightly higher in the linezolid group. A case of clostridium colitis of mild nature possibly related to iclaprim was reported in ASSIST -1. A detailed narrative is not presented. The applicant is requested discuss this in more detail and put it in a broader perspective of the potential of iclaprim to cause *C. difficile* associated diarrhoea and pseudomembraneous colitis.

Overall safety profile of iclaprim appeared to be similar to that of linezolid in the selected patient populations throughout both studies. However, as mentioned before the safety database is rather limited and the extent of exposure is essentially limited to 14 days. Infections requiring ≥ 14 days therapy (which would often be the case for more severe complicated infections were generally excluded (as dictated by the protocol). There is a concern that for the indication at large in general practice treatment for longer duration in severe complicated cases may be needed whereas the cardiac and liver safety of iclaprim in such cases is not studied. The applicant's answer to raised question did not give essentially new insight. The recruited patients in the Phase III trials were generally treated for a maximum of 14 days. The percentage of patients treated for 14 days was below the 20% of the patient population per treatment arm (see the following table from the response to question 41), whereas the number of patients who received antibacterial treatment between TOC and LFU (starting

at TOC) was 20 (4.5%) in the iclaprim group. Analysis of patient data by treatment duration of 10 days or 2-4 days longer suggest that the propensity for cardiac events or alterations in liver function tests are similar between these two groups of patients. However, as stated by the applicant the overall higher incidence of cardiac AEs in patients with 14 days of treatment as compared to the group with only 10 days of treatment might be a consequence of the more serious overall clinical condition of this group of patients. The latter observation remains a matter of concern. Overall, therefore, the present concern - that for the indication at large in general practice treatment for longer duration in severe complicated cases may be needed whereas the cardiac and liver safety of iclaprim in such cases is not sufficiently studied - is not resolved due to the limitations of the data. This conclusion is taken into account in the benefit-risk assessment.

Adverse events Phase I-II studies
In the Phase I studies, poor local tolerability was observed when doses of 60 and 120 mg were given at concentrations of 3 mg/ml and 6 mg/ml respectively (study HMR-01-014). Isolated cases of phlebitis were also reported. However, when the doses were diluted (in saline) and infused as a solution of 0.8 mg/ml iclaprim the 120 mg dose was well tolerated.

In the two placebo-controlled Phase I single-dose studies AR-100-ECG-002 and AR-100-ECG-003 which evaluated iclaprim's potential for QTc interval prolongation the following observations were made after single dose exposure:

AR-100-ECG-002 showed a dose-dependent reversible effect of iclaprim (administered as an infusion over 30 minutes in a volume of 150 ml diluted with N-saline) on the duration of the QTc interval based on the assessment of the effects of iclaprim on ECG measurements for a period of 12 hours post-dose. Administration of iclaprim induced prolongation of the QTc interval with an average maximum absolute prolongation from baseline of 34 ms for the 1.6 mg/kg dose and 51 ms for the 3.2 mg/kg dose, with individual maxima between 15 minutes and 45 minutes after start of the infusion. Mean QTc prolongation was most pronounced at the end of the iclaprim infusion period, when maximum plasma levels were attained. Prolongations exceeding 500 ms occurred in 2 subjects after 3.2 mg/kg iclaprim treatment. A maximum QTcB value of 501 ms was observed in 1 subject after 1.6 mg/kg iclaprim treatment.

Clinically relevant maximum QTc prolongations ≥ 60 ms were observed in 1 subject after 1.6 mg/kg iclaprim and in 8 subjects after 3.2 mg/kg iclaprim treatment. All changes were transient: 30 to 60 minutes after the end of the infusion of the 1.6 mg/kg dose, the placebo-corrected QTc prolongation dropped to below 10 ms and was not statistically significant. An increase in the number of abnormal ECGs occurred after iclaprim administration, being most pronounced after infusion of the 3.2 mg/kg dose, where such findings were reported for 88% of the subjects during the 12 hours following infusion. Non-specific T wave alterations were most frequently reported (83% of the subjects after the 3.2 mg/kg dose, 21% after the 1.6 mg/kg dose and 8% after placebo). T-wave alterations were reversible from 4 – 8 hours post-dosing.

No clinical signs and symptoms or ECG recordings indicating study drug-related cardiac arrhythmia were observed.

AR-100-ECG-003 evaluated the effect of a single intravenous dose of 1.6 mg/kg iclaprim given over 60 minutes and single doses of 0.4 mg/kg and 0.8 mg/kg iclaprim (in a volume of 150 ml diluted with N-saline) given intravenously over 30 min on the QTc interval as compared to placebo and as compared to baseline.

Administration of iclaprim prolonged mean QTc intervals to mean maximal values of 427 ms at a dose of 0.4 mg/kg, to 436 ms at a dose of 0.8 mg/kg and to 434 ms at a dose of 1.6 mg/kg. This resulted in a mean maximum prolongation from baseline of 23 ms for the 0.4 mg/kg dose and of 29 ms for both the 0.8 mg/kg dose infused over 30 minutes and the 1.6 mg/kg dose infused over 60 minutes. The time of the maximal effect was in good agreement with the time of maximal plasma levels of iclaprim. All changes were transient. 15 to 30 minutes after the end of infusion of the 0.8 mg/kg and 1.6 mg/kg

doses, the placebo-corrected prolongation (Bazett) dropped below 10 ms and was not statistically significant.

Inspection of the ECGs showed that post-dose findings were reported at approximately the same rate after active treatment and placebo overall. Rates varied between 55% of the subjects (0.4 mg/kg iclaprim), 63% (placebo), 68% (iclaprim 0.8 mg/kg) and 71% (iclaprim 1.6 mg/kg). Signs of arrhythmia and T-wave abnormalities were observed after all treatments at approximately the same rate.

Overall, the present QTc prolongation findings indicated dose dependent reversible effect of iclaprim (administered as an infusion over 30 minutes in a volume of 150 ml diluted with N-saline). Although no cardiac adverse events were associated with these QTc prolongations, clinically relevant (greater than 450 ms for men or 470 ms for females) prolonged maximum QTcF values occurred in these studies. In study *AR-100-ECG-002* these were observed in 3/24 subjects after exposure to single doses of 1.6 mg/kg iclaprim and in 13/24 subjects after exposure to 3.2 mg/kg iclaprim; prolongations exceeding 500 ms occurred in 1 and 2 subjects respectively. Clinically relevant maximum QTc prolongations ≥ 60 ms were observed in 1 subject after 1.6 mg/kg iclaprim and in 8 subjects after 3.2 mg/kg iclaprim treatment.

In study *AR-100-ECG-003* no subject had maximum QTc values >470 ms or > 500 ms whereas 2/22 subjects showed a QTcB prolongation ≥ 60 ms after 0.8 mg/kg iclaprim (administered as an infusion over 30 minutes) versus none on placebo. Placebo and baseline-corrected QTcB prolongations (individual subject- and time-matched) at the end of the infusion period were 10.3 ms (95% confidence interval: 3.3 to 17.3 ms) for the 0.8 mg/kg dose. This study shows that the recommended dosage of 0.8 mg/kg iclaprim is not totally void of clinically relevant QTc prolongation after single dose exposure.

An increase in the number of abnormal ECGs occurred after iclaprim administration, being most pronounced after infusion of the 3.2 mg/kg dose, where such findings were reported for 88% of the subjects during the 12 hours following infusion especially in the first study. Differences were less clear in the second study.

The spreading of the dose dependent effect over 2 studies and the relatively low numbers of subjects tested and absence of a positive control hampers the derivation of a more clear-cut conclusion with respect to the recommended 0.8 mg/kg iclaprim dose. Overall, these studies raise a concern that the safety margin of iclaprim is narrow with respect to QTc interval prolongation. Furthermore, data on the impact of eventually required more frequent dosing per day than the presently recommended BID regimen are not available (see also comment under dose response and PK/PD).

Of note, the CHMP advised the applicant to adhere to ICH Guidance E14. The applicant believes that this advice was closely followed. The applicant believes that according to ICH Guidance E14, no active-control QT study is needed but QT prolongation propensity has to be further evaluated in patients.

The applicant evaluated QTc in all patients in the Phase III studies at C_{max} (as suggested by the E14 guidance) on treatment days 1 and 4 using standardised equipment and a central laboratory for evaluation of the ECGs as an alternative justification for the absence of a positive control and based on the positive QTc prolongation findings in the formal placebo-controlled ECG Phase I studies. However, such studies were not specifically designed to assess the effect size of the QTc interval prolongation effects; in addition patients with additional risk factors for QTc prolongation or TdP were generally excluded from the two pivotal Phase III studies. See further assessment below under Special Safety Topics.

According to E14 the confidence in the ability of the study to detect QTc prolongation can be greatly enhanced by the use of a concurrent positive control group (pharmacological or non pharmacological) to establish assay sensitivity. Absence of a positive control should be justified and alternative methods to establish assay sensitivity provided. The applicant's answer did not provide new insights, the

applicant acknowledges the lack of a prospective positive control (e.g. moxifloxacin) study hampers the comparison to other marketed medicinal products which was done in the original submission. The given justification is not entirely satisfactory; however, the available cardiac safety data have already bearing on the CHMP raised objection from the safety point of view. The conclusion is taken into account in the benefit-risk assessment.

The applicant earlier claim in Section 4.4 of the SmPC that "Mersarex can cause QT interval prolongation; QT prolongation during or following Mersarex administration is similar to that of oral moxifloxacin" is deleted in response to CHMP comment that this comparison is not appropriate without prospective comparative study data in which moxifloxacin control was included.

In the Phase II study, possibly or probably treatment-related AEs reported in none of the iclaprim dose group 0.8 mg/kg patients and 6.3% of the patients in the 1.6 mg/kg dose group compared to 10% in the vancomycin group. 2 patients (6.3%) experienced 2 possibly related events (erythema and pruritus) in the iclaprim 1.6 mg/kg group and 3 patients (10.0%) experienced 3 possibly related events (tremor, pruritus and dermatitis medicamentosa) in the vancomycin group. Iclaprim was associated with transient increases (>3 X ULN) in ALT values with a few patients, in 2 and 4 patients in the iclaprim 0.8 mg/kg and 1.6 mg/kg dose groups resp.

Electrocardiographic safety monitoring was performed on a total of 48 patients in accordance with Protocol Amendment 3. Occasional and transient QTc prolongations of greater than 30 msec were observed in 8 patients with equal distribution to the 2 iclaprim and the vancomycin treatment arms. No treatment-related cardiac rhythm disturbances were observed.

Special safety topics
Non-clinical studies identified a potential associated with iclaprim for causing prolongation of QT interval, convulsive effects and to a lesser extent hepatotoxic effects. The applicant has also devoted a discussion to hypertension-related AEs. These selected issues are discussed below.

Cardiac effects. A review of cardiac AEs and effects on QTc reported across all studies was conducted by an independent cardiologist and is included in the Cardiac Safety Summary.

With respect to cardiac effects, results from the pooled Phase III clinical studies indicated that although the incidence of QTc prolongation was similar in the iclaprim and linezolid arm, there was a relationship between increased QTc and use of iclaprim when compared to linezolid. The mean increase in QTcF in the iclaprim group on Day 1 and Day 4±1 is about 8.9 ms (SD=12.069) and 11 ms (SD=18) resp.

No cases of QTc prolongations classified as treatment related "AE" were observed in these studies. Cardiovascular AEs reported as drug-related were equally reported in the iclaprim group and linezolid groups. (approx. 3%).

As noted by the external expert, these results were not gathered with the rigor of a well-controlled QT study, thus there were no restrictions on time of day and there was no pharmacodynamic comparison made with study drug levels, but they do support the earlier findings that associate an increased ΔQTcF with iclaprim therapy.

Mean ΔQTcF did not seem to differ much according to age, however, the number of elderly was small (approx.70).
Findings in the small group of patients (85-88 patients per group) who had concomitant medications which have a potential risk of inducing TdP confirmed that taking such medications seemed to increase the chance of having an ECG outlier such as for ΔQTcF > 30 ms. However, the frequency of such outliers in the iclaprim group was approx. 2-folds higher than in the linezolid group. There were also 2 cases ΔQTcF > 60 ms in the iclaprim group taking such medications. Similarly, in the Group of patients who had QTcF > 400 ms at baseline the frequency of outliers of ΔQTcF > 30 ms in the iclaprim group (n= 270) was approx. 2-folds higher than in the linezolid group. There was also 1 case

ΔQTcF > 60 ms in the iclaprim group. Note that by protocol patients with QTc>470 ms were excluded at baseline.

Similar findings were observed for the small group (21-23 per group) of patients using medications known to inhibit P450 3a4/5, but no outliers ΔQTcF > 60 ms were observed.

Data on QTc interval in risk patients such as those with impaired drug metabolizing capacity or clearance (e.g., renal or hepatic impairment) are not discussed.

Overall, although the incidence of QTc prolongation was similar in the iclaprim and linezolid arm, there was a relationship between increased QTc and use of iclaprim when compared to linezolid. Despite the amendment of the protocol to lift the exclusion of patients from the studies with a baseline QTc>470 ms, the maximum baseline value in the iclaprim group was 473 ms versus 525 ms in the linezolid group. Therefore, as such defined high risk patients were not really present in the cardiac safety assessment cohort of the pivotal studies. It is then not surprising those patients with QTc interval increases to QTc >500 ms were not observed.

The present rather limited data for patients at higher risk of developing QTc interval prolongation do not exclude the potential of iclaprim to increase the frequencies of clinically relevant outliers. This risk seems to be higher than for the used comparator (linezolid) in the pivotal studies.

Hepatic-related AEs
Overall, the increases in ALT and AST levels observed upon IV exposure using the therapeutic dose of iclaprim in the cSSTI population were similar to those observed with the comparator and were considered not to be of major clinical significance, since they were asymptomatic and without concomitant bilirubin increase. The potential for serious drug-induced hepatotoxicity remains an ongoing safety concern, an ongoing review of hepatic safety was warranted.

A review of all available clinical data was conducted by an independent hepatologist and is presented in the dossier.

The overall results obtained from studies indicate that iclaprim exhibits a dose-dependent effect on ALT/AST levels that is reversible.

In the case of IV iclaprim, the incidence of elevations (change from normal baseline) greater 3xULN in ALT/AST levels in the pooled data base in the cSSTI population was low (4.2%). In patients with elevated baseline values elevated >3xULN occurred in 23/108. There were no cases of hepatic failure or any cases conforming to the definition of Hy Zimmerman's Law or a "modified" Hy's law with concomitant rise in serum bilirubin. Most of the ALT/AST elevations occurred after the course of treatment was completed, with no evidence that patients with pre-existing LFT abnormalities at baseline developed any signs of hepatic impairment. In the linezolid group similar findings were noted; the incidence of elevations (change from normal baseline) >3xULN in ALT/AST levels was 4.1%.

Overall, the available data suggest similar frequencies of elevated liver enzyme levels for iclaprim and linezolid. However, due to the rather limited clinical experience the possibility of a narrow hepatic safety margin cannot be dismissed.

Convulsive effects. There were no cases of drug-related convulsive AEs. 1 case of epilepsy of moderate severity (recovered) was reported but was assessed to be not related to iclaprim.

Hypertension related AEs. A retrospective iclaprim exposure-effect analysis was done based on the population pharmacokinetic model for the combined data of the Phase 3 ASSIST-1 and ASSIST-2 trials (n=470). Hereby, it was detected that all patients who experienced an AE related to hypertension (n=13 in 12 patients) had also an above-average iclaprim exposure as expressed in AUC, Cmax or both.

The applicant reviewed all individual cases of hypertension and hypertension-related adverse events recorded in the ASSIST studies. The overall incidence of hypertension AEs during iclaprim IV treatment is very low (2.6%) and similar to the incidence seen with the comparator linezolid (2.2%).

All documented hypertension AEs were considered to be "not related" to iclaprim by the investigators.

However, in eight cases, where the AE occurred during iclaprim treatment and no alternative explanation could be found, an influence of iclaprim could not completely be ruled out.

There was no indication that drug-drug interactions or genetic polymorphisms of the hepatic cytochromes P450 2D6 and 2C19 could influence predisposition to AEs in general. None of the hypertension AEs was classified as serious or as severe in intensity.

Serious adverse events and deaths
In the Phase I-II studies no SAEs occurred with any dose of iclaprim given by the IV route.

In the Phase III studies SAEs occurred at similar rates in both treatment groups. Only 1 SAE was considered to be possibly drug-related (elevated ALT in 1 iclaprim-treated patient).

Six *deaths* were reported during the ASSIST-1 study: 5 in the iclaprim group and 1 in the linezolid group. Two deaths were recorded in ASSIST-2: 1 in the iclaprim group and 1 in the linezolid group. None of these deaths were considered by the investigator, the Sponsor, and the external safety officer to be related to study medication but related to serious underlying diseases. There was no indication that these deaths were concomitant with cardiovascular system-related AEs. 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, 4 of these deaths occurred well beyond 5 half-lives of the drug (3-12 days after the last dose of iclaprim). At this stage there is no reason to suspect that these deaths are associated with the iclaprim treatment, however, the CHMP requested further analysis of the deaths and their relation to the lower efficacy of iclaprim. The applicant reviewed observed numerically more death cases in the iclaprim group while the studies were ongoing. The clarification suggests that the cases were associated with patients' underlying conditions together with severe complicated infections (in one case, presence of Gram-negative pathogens resistant to Aztreonam).
No deaths occurred during any of the Phase 1 studies.

Adverse events by intrinsic factors
The safety profiles of both treatments showed similar patterns when analysed by ethnicity, age, and gender in the combined data base.

Adverse events by extrinsic factors
The safety profiles of both treatments showed similar patterns when analysed by geographical area (EU, US, ROW).

Laboratory findings
There were no clinically significant changes post-baseline in clinical laboratory values during the Phase I studies, including the drug-drug interaction studies, except the changes in liver function test results in 1 subject during the interaction study with digoxin (ICLA-18-DDI4).

In the Phase II study mean absolute values for all biochemistry parameters, with the exception of AST and ALT, were within the normal reference ranges. In each group, mean AST and ALT values were variable over the course of the study; however, median AST and ALT values were within the normal range.

In the two Phase III studies, no obvious differences were seen between the 2 treatments in the haematologic parameters either outside the normal range at each study visit or in shifts in values between BL and each study visit except for platelet count. Increase in platelet count during the

treatment period, linked to the inflammatory response, was somewhat more pronounced in the iclaprim arm, as compared to the linezolid arm. Overall, the increases in ALT and AST levels in the iclaprim group were similar to those observed with linezolid and were considered not to be of major clinical significance, since they were asymptomatic and without concomitant bilirubin increase.

However, increased ASAT/ALAT (as AEs) were almost 10-fold more frequent in ASSIST-2 study than in ASSIST-1 study in the iclaprim-arm and were more frequent in the iclaprim-arm than in the linezolid-arm only in ASSIST-2 study. In addition, the changes in the LFT values observed during iclaprim treatment did not disappear at completion of treatment and numerically more patients had marked increases in ALAT values at late follow-up visit than at the time of EOT. Of all treated patients, 14 in ASSIST-1 and 9 in the ASSIST-2 studies demonstrated elevated ALAT and/or ASAT levels at baseline (< 5 ULN). Of those, in 12 and 7, respectively, LFT values continued to rise during iclaprim treatment. Hence due to these findings after exposure to iclaprim and the rather limited clinical experience the possibility that iclaprim has a narrow hepatic safety margin cannot be dismissed. See below the response of the applicant to raised CHMP objection in this regard.

Safety in special populations
In Phase I Study ICLA-HKI-004, an open label, parallel, single dose study to investigate the pharmacokinetics of iclaprim in subjects with *hepatic* or *renal dysfunction* and in *obese* subjects, a total of 68 subjects were exposed with a single dose of 0.8 mg/kg iclaprim infused over 30 minutes. Systemic exposure to iclaprim (AUC) and maximum iclaprim concentrations (C_{max}) increased with increasing degree of obesity and hepatic impairment (with no effect of renal impairment, see PK data).

28 subjects experienced treatment-related AEs. No deaths or other serious AEs were reported and none of the AEs led to withdrawal of the subject from the study. No drug-related clinically relevant abnormalities were observed regarding clinical laboratory evaluation, vital signs and physical examination during this study. However, a transient QT and QTc interval prolongation was seen in all subject groups with maximal prolongation at C_{max}, at the end of the infusion period. No increases in QTc_F to >470 ms or >60 ms over baseline were observed in any of the subjects.

Pregnant or *lactating* patients were excluded from the studies and therefore, no data are available in pregnant or lactating women. Note iclaprim has shown teratogenic potential in rats. It is not known whether iclaprim is excreted in human milk. Excretion of iclaprim into the milk of lactating rats occurred at very low levels.

Overdose. No studies have been performed to determine a specific *antidote* to iclaprim. For dealing with potential liver damage following overdose, the administration of Leucovorin might have a beneficial effect.

Drug abuse information for iclaprim is not available.

Information on the effects of iclaprim on the *ability to drive or operate machinery* or impairment of mental ability is not available.

Safety related to drug-drug interactions and other interactions
Drug interaction, in particular with regard to CYP450, needs to be taken into consideration when using iclaprim with co-medication of other drugs, metabolised by the same CYP450 enzymes and Pgp., see PK assessment.

Ketoconazole, a standard inhibitor of CYP450 3A4, reduced the clearance of iclaprim (study ICLA-06-DDI1). 7 subjects exhibited maximal QTc increases after combination treatment. No absolute QTcB values beyond 450 ms and no absolute QTcF values beyond 480 ms were observed.

Similarly, omeprazole reduced slightly the clearance of iclaprim (study ICLA-19-DDI5) with no notable clinical AEs.

In the digoxin interaction study (ICLA-18-DDI4), increases in liver enzymes were observed after treatment B (digoxin during concomitant treatment with iclaprim). No concomitant increase of total bilirubin above 1.5 x ULN was observed in any of the 5 subjects. There were no serious treatment-emergent AEs.

Discontinuation due to AEs

The incidence of patients who discontinued because of drug related adverse reactions was low 1.2% of the patients in both treatment groups: 6 cases in the iclaprim group (2 infusion-related reaction, 2 prolonged QTc interval, 1 each of nausea, rash and face swelling); and 6 cases in the linezolid group were reported to have a total of 11 treatment-related AEs leading to discontinuation of study drug (including a case of prolonged QTc interval), with a single patient experiencing 6/11 AEs.

Post-marketing data

Iclaprim is not commercially available anywhere worldwide; therefore, post-marketing data are not available.

Overall safety conclusion

The limited safety database seems to indicate that the safety profile of iclaprim was similar to that of the comparator (linezolid) in tested selected patient populations. However, the present safety profile of iclaprim at the recommended dose level based on the limited experience in the target population raises concerns with regard to cardiac safety (QTc interval prolongation) and to a lesser extent with respect to liver safety.

- The phase I specific cardiac safety studies showed a dose dependent QTc interval prolongation after exposure of healthy subjects to single doses in the range of 0.4-3.2 mg/Kg. The recommended dosage of 0.8 mg/kg iclaprim is not totally void of clinically relevant QTc prolongation after single dose exposure.
An increase in the number of abnormal ECGs occurred after iclaprim administration, being most pronounced after infusion of the 3.2 mg/kg dose especially in the first study. Differences were less clear in the second study.
The spreading of the dose dependent effect over 2 studies and the relatively low numbers of subjects tested and absence of a positive control hampers the derivation of a more clear-cut conclusion with respect to the recommended 0.8 mg/kg iclaprim dose. Overall, these studies raise a concern that the safety margin of iclaprim is narrow with respect to QTc interval prolongation. Furthermore, data on the impact of eventually required more frequent dosing per day than the presently recommended BID regimen are not available (see also comment under dose response and PK/PD).

- With respect to QT prolongation the CHMP advised the applicant to adhere to ICH Guidance E14. The applicant believes that this advice was closely followed. Two formal ECG Phase I studies showed a propensity for QT prolongation; therefore, the applicant believes that according to ICH Guidance E14, no active-control QT study is needed but QT prolongation propensity has to be further evaluated in patients.
According to E14 the confidence in the ability of the study to detect QTc prolongation can be greatly enhanced by the use of a concurrent positive control group (pharmacological or non pharmacological) to establish assay sensitivity. Absence of a positive control should be justified and alternative methods to establish assay sensitivity provided. There is a concern that the absence of prospective moxifloxacin control data hampers the external validation of the effect size of the observed positive QTc interval prolongation effects of iclaprim in a fully controlled designed study for the evaluation of such effects.

- The applicant evaluated QTc in all patients in the Phase III studies at C_{max} (as suggested by the E14 guidance) on treatment days 1 and 4 using standardised equipment and a central laboratory for evaluation of the ECGs as an alternative justification for the absence of a positive control and based on the positive QTc prolongation findings in the formal placebo-controlled ECG Phase I studies. However, such studies were not specifically designed to assess the effect size of the QTc interval prolongation effects and as mentioned before patients at high risk patients including those patients with additional risk factors for QTc prolongation or TdP were generally limited in the two pivotal Phase III studies. Overall, although the incidence of QTc prolongation was similar in the iclaprim and

linezolid arm, there was a relationship between increased QTc and use of iclaprim when compared to linezolid. The mean increase in QTcF in the iclaprim group on Day 1 and Day 4±1 is about 8.9 ms (SD=12.069) and 11 ms (SD=18) resp. Of note, the independent data monitoring committee determined that the protocol should continue as originally written. Despite the amendment of the protocol to lift the exclusion of patients from the studies with a baseline QTc>470 ms, the maximum baseline value in the iclaprim group was 473 ms versus 525 ms in the linezolid group. Therefore, as such defined high risk patients were not really present in the cardiac safety assessment cohort of the pivotal studies. It is then not surprising those patients with QTc interval increases to QTc >500 ms were not observed.

The present rather limited data for patients at higher risk of developing QTc interval prolongation do not exclude the potential of iclaprim to increase the frequencies of clinically relevant outliers. This risk seems to be higher than for the used comparator (linezolid) in the pivotal studies.

- 2 healthy volunteers in Phase I studies discontinued the study drug due to severe increases in liver enzymes (study ICLA-18-DDI4, subject 106 with ALAT 20 ULN and subject 101 with ALAT 5 ULN). The applicant gave additional analyses as requested; the answer was not entirely satisfactory.

The available Phase III clinical data suggest similar frequencies of elevated liver enzyme levels for iclaprim and linezolid. However, there are discrepancies in the incidences of increased LFTs values between ASSIST-1 and ASSIST-2: increased ASAT/ALAT (as AEs) were almost 10-fold more frequent in ASSIST-2 study than in ASSIST-1 study in the iclaprim-arm and were more frequent in the iclaprim-arm than in the linezolid-arm only in ASSIST-2 study. In addition, the changes in the LFT values observed during iclaprim treatment did not disappear at completion of treatment and numerically more patients had marked increases in ALAT values at late follow-up visit than at the time of EOT. For instance, 13 patients treated with iclaprim (2.6 %) presented increase in ALAT between 3 ULN and 10 ULN at the follow-up visit as compared to 3 (0.6 %) in the linezolid-arm.

Of all treated patients, 14 in ASSIST-1 and 9 in the ASSIST-2 studies demonstrated elevated ALAT and/or ASAT levels at baseline (< 5 ULN). Of those, in 12 and 7, respectively, LFT values continue to rise during iclaprim treatment. Hence due to these findings after exposure to iclaprim and the rather limited clinical experience the possibility that iclaprim has a narrow hepatic safety margin cannot be dismissed. The applicant's response to the CHMP's major objection gives insufficient assurance based on the limited available data that iclaprim is not hepatotoxic at the recommended dose level. It remains unclear why increase in ALT values develops long after stopping iclaprim despite the observation that in vitro mitochondrial toxicity data on human hepatocytes did not reveal adverse effects. Present limited patient database and analyses do not allow identification of patients (with normal or slightly increased LFT values at baseline) with increased risk for liver function test elevations in order to include targeted precautions in the SmPC for such patients. Although, in the light of present limited patient database a risk factor analysis (e.g. patients with underlying conditions, concomitant medications etc) is not expected to generate conclusive findings The applicant should conduct risk factor analysis with the available data collected in clinical programme in order to identify patients with increased risk for liver function test elevations.

- A case of clostridium colitis of mild nature possibly related to iclaprim was reported in ASSIST -1. A detailed narrative is not presented. The applicant was requested discuss this in more detail and put it in a broader perspective of the potential of iclaprim to cause *C. difficile* associated diarrhoea and pseudomembraneous colitis. The given answer of the applicant was sufficient; in the single reported case of *C. difficile* associated diarrhoea the likelihood that iclaprim is related to the occurrence of this AE was remote. The warning in the earlier SmPC paragraph in this regard is not changed.

- The extent of exposure to iclaprim is essentially limited to 14 days. Infections requiring $\geq$ 14 days therapy (which would often be the case for more severe complicated infections were generally excluded (as dictated by the protocol). There is a major concern that for the indication at large in general practice treatment for longer duration in severe complicated cases may be needed whereas the cardiac and liver safety of iclaprim in such cases is not studied.

At any rate, the relevant SmPC labelling needs further amendment. In addition, the contraindications should be expanded in similar fashion to that of moxifloxacin with "Both in preclinical investigations and in humans, changes in cardiac electrophysiology have been observed following exposure to iclaprim, in the form of QT prolongation. For reasons of drug safety, iclaprim is therefore contraindicated in patients with:

- Congenital or documented acquired QT prolongation
- Electrolyte disturbances, particularly in uncorrected hypokalaemia
- Clinically relevant bradycardia
- Clinically relevant heart failure with reduced left-ventricular ejection fraction
- Previous history of symptomatic arrhythmias

Iclaprim should not be used concurrently with other drugs that prolong the QT interval (see also section 4.5).

Since iclaprim is hepatically cleared and due to the lack of clinical data, iclaprim is also contraindicated in patients with impaired liver function (Child Pugh C) and in patients with transaminases increase > 5fold ULN.
The requested amendments of the SmPC were endorsed by the applicant.

Pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the applicant in principle fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The applicant has provided documents that set out a detailed description of the system of pharmacovigilance.
The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements, provided that the copy of the EudraVigilance registration of the QPPV is added to the DDPS.
The applicant has committed to implement the SOPs before marketing. All other PVS issues are resolved.

Risk Management Plan

The applicant submitted a Risk Management Plan as part of the marketing authorisation application.

During the clinical trial programme overall 798 subjects/patients have been exposed to single (n=204) or multiple (n=594) doses of intravenous (iv) iclaprim, in phase I, II, and III studies. A total of 562 patients has been exposed in phase II and III studies. The safety analysis of the applicant is primarily based on the 2 phase III studies ASSIST I and II.

The applicant did not provide total person times. The recommended dose of 0.8mg/kg body weight b.i.d., 8-14 days, until the infection is resolved was given to 530 patients.

In phase II and III studies, 500 patients were included. Multiple doses were defined as 'to 14 days' (approx. 60% 10 days; approx. 19% 14 days; none >15 days).

The following table with a summary of safety concerns and proposed activities was provided (table S4)

TABLE S4 ***Summary of safety concerns and proposed activities***

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Important Identified Risks		
Prolongation of ECG QT interval	Non-routine and routine pharmacovigilance activities	Warning in Section 4.4 of SmPC
Increase in liver enzyme levels	Non-routine and routine pharmacovigilance activities	Warning in Section 4.4 of SmPC
Increased plasma levels in obese individuals	Routine pharmacovigilance activities	Information on dose reduction in Section 5.2 of SmPC
Drug interactions: Inhibition of cytochrome enzymes (CYP 3A4 and CYP 2C19)	Non-routine and routine pharmacovigilance activities	Warning in Section 4.5 of SmPC
Development of antibiotic resistance	Non-routine and routine pharmacovigilance activities	Information in Section 4.1 of SmPC
Important Potential Risks		
Medication errors (e.g. increased plasma levels due to incorrect infusion times or dosing; incorrect preparation of final solution for infusion)	Non-routine and routine pharmacovigilance activities	Warning in Section 4.4 of SmPC; information in Sections 4.2, 4.9, and 6.6 of SmPC
Convulsions	Non-routine and routine pharmacovigilance activities	Warning in Section 4.4 of SmPC; information in Sections 4.2, 4.8, 4.9, and 6.6 of SmPC
C. difficile associated diarrhoea	Non-routine and routine pharmacovigilance activities	Warning in Section 4.4 of SmPC
Blood dyscrasia	Non-routine and routine pharmacovigilance activities	Warning in Section 4.4 of SmPC; information in Sections 4.2, 4.8, 4.9, 6.6 of SmPC
Important Missing Information		
Patients under 18 years of age	Routine pharmacovigilance activities	Information in Section 4.2 of SmPC
Pregnancy & lactation	Routine pharmacovigilance activities	No clinical data available in pregnant women or on the effects on fertility or on secretion in human breast milk. Warning in Section 4.6 of SmPC
Immunosuppressed patients	Routine pharmacovigilance activities	Warning in Section 4.4 of SmPC
Patients with severe renal impairment	Routine pharmacovigilance activities	Warning in Section 4.2, 4.4 of SmPC
Elderly patients	Routine pharmacovigilance activities	Warning in Section 4.2 4.4 of SmPC
Long-term use (>14 days)	Non-routine and routine pharmacovigilance activities	Warning in Section 4.4 of SmPC

The applicant has to provide a clear overview per study which populations have not been studied or have been studied to a limited degree.

On request of the CHMP, the applicant provided a discussion of the epidemiology of the risks and conditions in the target population for each identified or potential risk.

The epidemiology of the indications and important adverse events were detailed. (Additionally, the applicant is proposing a plan of active monitoring / non-routine pharmacovigilance to support the use of iclaprim in the post-marketing phase. A patient registry protocol is discussed and attached in the RMP document.
In the Template for EU Risk Management Plans, section 1.7.3 concerns: 'for each identified or potential risk, provide the epidemiology of the condition in the target population when unexposed to the product' (columns: identified or potential risks; incidence of condition; prevalence of condition; mortality of condition). So, the applicant also has to provide for all identified/potential risks epidemiological figures on incidence, prevalence and mortality in persons unexposed to the product.

In response to the question of the CHMP, the applicant provided a discussion on the possibility of off-label use, including off-label use in children. This discussion has to be added to the RMP.

Keeping in mind the circumstances of prescribing this medication, off-label use is not a potential risk at the moment. However, off-label use in children has to be regarded as potential risk, especially in the more severe conditions.
As a plan of active monitoring of interactions and development of antimicrobial resistance, the applicant proposed a study protocol concerning the establishment of a patient registry.
This proposed study is considered appropriate as additional pharmacovigilance of interactions and resistance. However, reports on interactions and resistance from other sources will have to be discussed in every PSUR as well.
On request of the CHMP, the applicant updated the RMP adequately regarding missing information on patients with severe cSSTI (in accordance with the sought indication), patients with renal impairment, elderly, long-term use (>14 days). However, the new information in sections 4.2 and 4.4 regarding severe renal impairment was not found. The applicant has to clarify this.
In response to the question of the CHMP, the applicant has proposed a text on cardiac monitoring to add to the SPC section 4.4. This text is agreed, but the last paragraph in section 4.4 has to be removed.

IV. ORPHAN MEDICINAL PRODUCTS

N/A

V. BENEFIT RISK ASSESSMENT

Regarding the Quality and Non-Clinical parts there are no major objections but some issues need to be addressed before these parts can be approved.

V.1 Benefits

Iclaprim is a diaminopyrimidine antibiotic that inhibits selectively DHFR and belongs to the same class of antibiotics as trimethoprim. It is predominantly active against Gram-positive microorganisms including *S. aureus* and MRSA. The good *in vitro* activity against MSSA and MRSA is especially encouraging since worldwide incidence of MRSA (hospital as well as community acquired) is steadily increasing while treatment options are still very limited. However, this interesting in vitro activity needs to be supported by adequate clinical data in the claimed indication in the treatment of cSSTI with the recommended dosing regimen.

The applicant has concluded non- inferiority of iclaprim versus comparator regimens based on the clinical cure rate at the TOC visit for patients in the pivotal Phase III studies ASSIST-1 and ASSIST-2. However, this conclusion cannot be accepted based on the review of these results:

The robustness of the efficacy data to support the sought indication in adult patients with cSSTI remains seriously questioned based on the provided (as requested) additional analyses using the cure definition by considering patients who showed full resolution of the clinical signs and symptoms and did not need further antibiotic therapy at the TOC and LFU visits in the "modified clinically evaluable" (MCE) population. The MCE population includes all patients in the clinically evaluable population (CE) who had an infecting Gram-positive pathogen at baseline (BL) and corrects for the identified marked imbalance between treatment groups in the use of prohibited antibiotics which made the PP population questionable for a correct efficacy assessment since these potential failures who received concomitant prohibited antibiotics are excluded from the PP population (per definition in the SAP). Hence it is acceptable to consider the MCE population as the pivotal analysis population to assess the clinical efficacy.
The provided analyses up to date confirm original conclusion of the CHMP that numerically and rather consistently lower cure rates were observed iclaprim treated groups especially in important subgroups with >38°C and >=2 additional SIRS criteria, with the leading diagnoses abscess and cellulites and those with *S. pyogenes* infection. This holds also for patients (with ≤8 BL symptoms with scores 2 or 3) due to MRSA constituting most MRSA infected patients. A similar pattern of efficacy results seem to emerge also in the corresponding analyses of available data for LFU

evaluations; difference between iclaprim and linezolid efficacy profiles seemed to be also more pronounced in favour of linezolid although the latter results should be interpreted with caution due to the noted deficiencies in the trial design with respect to the LFU efficacy evaluations. The latter results based on an important proportion of patients with useful LFT assessment remain of important clinical concern for the sought cSSTI indication at large.

The applicant's reliance on the statistical non-inferiority- with observed non-inferiority margin within -10% for clinical cure as defined by the protocol at TOC for both studies and combined dataset- in the MCE population becomes less relevant in the light of above described results. Even then numerically iclaprim global cure rates were lower than for linezolid. Furthermore, in the analysis of therapeutic success in the microbiologically evaluable MCE population which is acknowledged to be an important indicator of clinical efficacy, iclaprim showed consistently less favourable results than linezolid across all analysis sets and in both studies. The lower non-inferiority margin exceeded the -12.5% value per study and the -10% for the combined data in favour of linezolid. Overall, in the combined dataset results from these pivotal studies, clinical cure rates as defined in the SAP at TOC in patients in MITT population as well as MCE populations for the leading diagnosis seem to favour linezolid. This is also reflected in the bacteriological eradication and persistence results for the predominant pathogens *S. aureus* (both MSSA and MRSA) and *S. Pyogenes* of severe infection based on the given SIRS definition. Similarly, despite the given detailing of the applicant cure rates in patients from the linezolid arm were higher than those in the iclaprim arm (97.0% versus 63.0%) in the small group (approx. 41-50 patients per group) of patients with 2 or more Gram-positive pathogens identified at baseline.

The applicant's answers to the major efficacy objections and other concerns in relation to the efficacy results from the two pivotal ASSIST studies do not provide convincing clinical evidence in support of the non-inferiority of iclaprim to linezolid in the sought indication at large. Consequently, there is insufficient evidence to support a favourable efficacy conclusion for the use of iclaprim in the treatment of adult patients with cSSTI at the recommended dosage of 0.8 mg/kg twice daily (with a maximum of 100 mg per dose) up to 14 days.
The dosage regimen is not adequately supported by the rather limited clinical data especially in severe cSSTI nor the pharmacokinetic profile and experimental findings concerning T/>MIC; the major objection in relation to pharmacodynamics is not resolved whereas the assessment of the susceptibility table in section 5.1 of the SPC cannot be finalised.

V.2 Risks

The present safety profile of iclaprim at the recommended dose level based on the limited experience in the target population raises major concerns with regard to cardiac safety followed by the liver safety.

With regard to cardiac safety, the phase I specific cardiac safety studies showed a dose dependent QTc interval prolongation after exposure of healthy subjects to single doses; the recommended dosage of 0.8 mg/kg iclaprim was not totally void of clinically relevant QTc prolongation. In the pivotal clinical studies, this risk seems to be higher than for the used comparator (linezolid) based on the evaluated QTc in all patients at C_{max} (as suggested by the E14 guidance) on treatment days 1 and 4 although such studies were not specifically designed to assess the effect size of the QTc interval prolongation effects. The maximum QTc baseline value in the iclaprim group was 473 ms. Therefore, high risk patients with QTc>473 ms were not really present in the cardiac safety assessment cohort of the pivotal studies. The present rather limited data do not exclude the potential of iclaprim to increase the frequencies of clinically relevant outliers. The applicant acknowledges that high risk patients with QTc>473 ms were not really present in the cardiac safety assessment cohort of the pivotal (ASSIST) studies. Furthermore, the risk of increases QTc values in the iclaprim treated patients is higher than for the used comparator (linezolid). Iclaprim has demonstrated propensity to induce a dose dependent QTc interval prolongation in healthy subjects. The present limited clinical data do not exclude the potential of iclaprim to increase the frequencies of clinically relevant outliers.

2 healthy volunteers in Phase I studies discontinued the study drug due to severe increases in liver enzymes. The available Phase III clinical data suggest similar frequencies of elevated liver enzyme levels for iclaprim and linezolid. However, there are discrepancies in the incidences of increased LFTs values between ASSIST-1 and ASSIST-2. In addition, the changes in the LFT values observed during iclaprim treatment did not disappear at completion of treatment and numerically more patients had marked increases in ALAT values at late follow-up visit than at the time of EOT.

Of all treated patients, 14 in ASSIST-1 and 9 in the ASSIST-2 studies demonstrated elevated ALAT and/or ASAT levels at baseline (< 5 ULN). Of those, in 12 and 7, respectively, LFT values continue to rise during iclaprim treatment. Hence, due to these findings after exposure to iclaprim and the rather limited clinical experience the possibility that iclaprim has a narrow hepatic safety margin cannot be dismissed.

The applicant's answers to CHMP major and other concerns in relation to hepatic safety give insufficient assurance that iclaprim is not hepatotoxic at the recommended dose level. It remains unclear why increase in ALT values develops long after stopping iclaprim despite the observation that in vitro mitochondrial toxicity data on human hepatocytes did not reveal adverse effects. Present limited patient database and analyses do not allow identification of patients (with normal or slightly increased LFT values at baseline) with increased risk for liver function test elevations in order to include targeted precautions in the SmPC for such patients. Although, in the light of present limited patient database a risk factor analysis (e.g. patients with underlying conditions, concomitant medications etc) is not expected to generate conclusive findings the applicant should conduct risk factor analysis with the available data collected in clinical programme in order to identify patients with increased risk for liver function test elevations.
The applicant's endorsement of the CHMP proposed relevant contraindications and warnings for section 4.3 and 4.4 respectively are only relevant in case of a positive benefit-risk conclusion for at least a second line indication. However, on the basis of available data, the outstanding major cardiac and hepatic concerns outweigh the questioned benefit whereas there is no sufficient clinical evidence provided that Mersarex is beneficial in the treatment (second-line) of special patient groups failing other antibiotics or intolerant to standard antibiotics used in the treatment of cSSTI.

The potential for the emergence of resistance after clinical use of iclaprim cannot be denied. The present clinical database rather limited. Analysis of all isolates in of *S. aureus* and *S. pyogenes* revealed increase in iclaprim MIC >2-fold in five patients: 2 cases 0.25→ >16 µg/ml; 2 cases 0.06 →>16 µg/mlµand 1 case 0.12 →>16 µg/ml. Most cases were associated with *superinfection* by an unrelated resistant strain of *S. aureus* (resulting from selection pressure). From the clinical point of view presence at baseline and emergence of strains of *S. aureus* and MRSA strains with (≥0.25 µg/ml; and noted >16 µg/ml in several clusters from Latvia, Romania and Russia) during and after exposure to iclaprim are of concern which impacts on the clinical efficacy profile of iclaprim at the recommended dose level. The number of baseline isolates with elevated MIC values for *S. aureus* and MRSA (≥0.25 µg/ml) and for *S. pyogenes (>0.06 µg/ml),* was very small yet numerically more failures were observed in the latter category of isolates. This conclusion is relevant for the benefit-risk assessment.

The extent of exposure to iclaprim is essentially limited to 14 days. Infections requiring ≥ 14 days therapy (which would often be the case for more severe complicated infections were generally excluded (as dictated by the protocol). There is a major concern that for the indication at large in general practice treatment for longer duration in severe complicated cases may be needed whereas the cardiac and liver safety of iclaprim in such cases is not studied.

In conclusion, the applicant's answers to the major objection and other concerns in relation to cardiac and hepatic safety do not provide adequate new insight to change the conclusion of the CHMP that the present safety profile of iclaprim at the recommended dose level based on the limited experience in the target population remains a major concern with regard to cardiac safety, it has a narrow safety margin.

V.3 Balance

On the basis of present data, the major cardiac and hepatic concerns outweigh the questioned benefit whereas there is no clinical evidence provided that Mersarex is beneficial in special patient groups failing other antibiotics or intolerant to standard antibiotics used in the treatment of cSSTI.

Overall, the present database does not allow a positive benefit risk conclusion for iclaprim.

V.4 Conclusions

The overall B/R ratio of **Mersarex** can be considered negative for the sought (slightly adjusted) indication in the treatment of adult patients with cSSTI (due to Gram+ pathogens as reflected in section 5.1 of the SPC).

The SPC needs to be amended.