15 December 2016
EMA/CHMP/226929/2017
Committee for Medicinal Products for Human Use (CHMP)

# Assessment Report

## Solithromycin Triskel EU Services

International non-proprietary name: Solithromycin

Procedure No. EMEA/H/C/4179

Applicant: Triskel EU Services Ltd

## Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
**Telephone** +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
**Send a question via our website** www.ema.europa.eu/contact

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# List of abbreviations

%SEM percentage standard error of the mean
ALT alanine transaminase
AM alveolar macrophage
BAL bronchoalveolar lavage
BCRP breast cancer resistance protein
BLQ below the limit of quantitation
BMI body mass index
BSA body surface area
BSEP bile salt export pump
CABP community-acquired bacterial pneumonia
CE clinically evaluable
CFU colony-forming unit
CI confidence interval
CL/F clearance
CLd1, CLd2 distributional clearances
Cmax maximum plasma concentration
CrCL creatinine clearance
CSR clinical study report
CV% percent coefficient of variation
CYP human cytochrome P450
ECG electrocardiogram
ECR Early Clinical Response
eGFR estimated glomerular filtration rate
ELF epithelial lining fluid
EOT end of therapy
F absolute bioavailability
GI gastrointestinal
GMR geometric mean ratio
HMG CoA 3-hydroxy-3-methylglutaryl-coenzyme A
HPLC high performance liquid chromatography
HR heart rate
IC50 maximal inhibitory concentration
IIV inter-individual variability
Imax maximum inhibitory capacity
IV intravenous
Ka absorption rate constant
Ki concentration required for half-maximal inactivation
Kinact rate constant of maximal inactivation at saturation
LC-MS/MS liquid chromatography-tandem mass spectrometry
LLOQ lower limit of quantitation
LSM least squares mean
MDI metabolism-dependent inhibition
MDRD Modification of Diet in Renal Disease
ME microbiologically evaluable
OAT organic anion transporter
OATP organic anion transporter polypeptide
OCT organic cation transporter
PBPK population-based pharmacokinetics
PD pharmacodynamics
PICC peripherally inserted central catheter
PK pharmacokinetics
PPI proton pump inhibitor
QD once daily
Rac relative accumulation ratio
RAD radioactivity detection
SFU Short-term Follow-up
T1/2 terminal half-life
ULN upper limit of normal
V/F volume of distribution
Vc volume of distribution of the central compartment
Vss steady state volume of distribution
Vz volume of distribution associated with the terminal elimination phase
WTKG body weight

# 1. Recommendation

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for Solithromycin Triskel EU Services (solithromycin) in the treatment of community-acquired pneumonia (CAP), anthrax and tularaemia is not approvable since Major Objections have been identified, which preclude a recommendation for marketing authorisation at the present time.

The details of these Major Objections are provided in the preliminary list of questions. The Major Objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies in Quality and Clinical aspects:

***Quality***

**Drug substance**

- The starting material should be redefined to possibility of formation of impurity in the proposed starting materials that are carried to the drug substance and lack of details on impurity purge studies.

***Drug product –Powder for solution for injection***

- Formation of particulates during in-use stability studies for commercial scale batches was observed related to solubility of solithromycin. Further discussion is required on in-use shelf-life.
- Process validation data for proposed commercial scale batches should be provided for the injectable formulation as it is a non-standard manufacturing process.
- The test for sterility is not considered valid due to the absence of positive controls for gram positive bacteria during the validation of the sterility test.

***Clinical***

- There is a Major Objection to use of solithromycin to treat anthrax due to lack of confidence in the sufficiency of the CAP dose regimen to treat *B. anthracis* and lack of safety data to allow for an appropriate duration of therapy
- There is a Major Objection to use of solithromycin to treat tularaemia due to lack of confidence in the nonclinical efficacy model and sufficiency of the CAP dose regimen and lack of safety data to allow for an appropriate duration of therapy
- There is a Major Objection due to the hepatotoxicity of solithromycin, which impacts on the benefit-risk balance for all three proposed indications for use

***Proposal for questions to be posed to additional experts***

None at present

***Proposal for inspection***

**GMP inspection**

None required.

**GCP inspection**

The CHMP has asked for a routine GCP inspection to be carried out for study CE01-300, in accordance with Article 57 of Council Regulation (EC) No. 726/2004 and article 15 of Directive 2001/20/EC. One investigator site in Ecuador and one investigator site in Hungary as well as the sponsor in the US will be inspected. The inspection reports are expected to be available by 06/03/2017. The outcome of this inspection and the satisfactory responses to its findings are an integral part of this procedure and will be needed by Day 181.

***New active substance status***

Based on the review of the data the CHMP consider that the active substance solithromycin contained in the medicinal product Soloxera is to be qualified as a new active substance in itself.

# 2. Executive summary

## 2.1 Problem statement

Community-acquired pneumonia (CAP)

CAP refers to pneumonia of bacterial origin acquired outside of hospitals or extended-care facilities. In the European Union, approximately 3,370,000 cases of CAP occur annually, resulting in approximately 1 million hospitalisations. In adults, CAP occurs at an annual rate of approximately 1.2 per 1000 person-years and the rate increases with age to approximately 14 per 1000 person-years in adults aged ≥65 years. Most patients with CAP receive empiric antimicrobial therapy, as the microbial aetiology is typically not known at the time of presentation and commonly is never identified in routine clinical practice. *Streptococcus pneumoniae* remains the most common cause of CAP worldwide. Other common bacterial agents that cause CAP include *Haemophilus influenzae* (mostly non-type B), *Staphylococcus aureus* and *Moraxella catarrhalis*. Atypical pathogens such as *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae* and *Legionella pneumophila* also cause CAP.

CAP is a leading global cause of death due to communicable diseases. Rates exceeded those for tuberculosis and diarrhoeal diseases in 2013. Mortality among the elderly and very young from pneumococcal pneumonia remains high with current estimates ranging from 11 to ≥ 20% in immunocompetent patients admitted to the intensive care unit.

European guidelines for the treatment of CAP were developed by the European Respiratory Society (ERS) and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID). The current recommended empirical treatment for mild CAP is primarily directed toward *S. pneumoniae*. Oral amoxicillin (or Augmentin) or tetracycline are frequently the first-line treatments in EU countries. Macrolides are considered acceptable alternatives where macrolide resistance rates are low. A combination of a β-lactam and a macrolide is recommended for moderate or severe CAP or in cases of failure to respond to the first line treatment. The guidelines do not recommend empiric treatment for atypical pathogens (*L. pneumophila* and *M. pneumoniae*) for all patients with CAP, although this position remains a topic of intense debate.

The prevalence of penicillin-resistant *S. pneumoniae* (PRSP), macrolide-resistant *S. pneumoniae*, and multidrug resistant *S. pneumoniae* (MDRSP) varies by region, but is more prevalent in Southern European countries compared with Northern Europe. In one publication treatment failure rates for the macrolide class (clarithromycin, erythromycin, oxytetracycline and doxycycline) ranged from 15–20% in the 2008–2012 period and from 18–30% for commonly prescribed β-lactams (amoxicillin, cephalexin, cefaclor). In a recent review of studies conducted in Europe, erythromycin resistance in *S. pneumoniae* was observed in 15–17% of all *S. pneumoniae* isolates with rates approaching 50% for erythromycin in France, Italy, Greece and Hungary.

The use of oral fluoroquinolones (levofloxacin or moxifloxacin) as monotherapy in Europe is often recommended in CAP patients as a second line treatment, for cases when first line antimicrobial therapies are considered inappropriate or when these medicinal products have failed and when pneumonia is mild or moderate. For hospitalised patients, quinolones are now established treatment options. The EMA issued a

statement in 2008 advising that treatment with oral moxifloxacin for upper and lower respiratory tract infections should be limited to when other antibiotics cannot be used, or have failed.

Tularemia

Tularemia is a zoonotic disease caused by *Francisella tularensis*. This agent is one of the most infectious pathogenic bacteria known, requiring inoculation or inhalation of as few as 10 organisms to initiate human infection.

Two *F. tularensis* subspecies are virulent for humans: subsp. *tularensis* (type A), found mainly in North America, and subsp. *holarctica* (type B), found in Europe and throughout the northern hemisphere. Both subspecies are considered worldwide as potential weapons of bioterrorism.

Ulceroglandular tularemia is the most common form and is usually a consequence of a bite from an arthropod vector which has previously fed on an infected animal. The occasional naturally occurring cases of inhalation tularemia often arise from farming activities. The pneumonic form is the likely form of the disease should this bacterium be used as a bioterrorism agent. The case-mortality rate from natural infection is < 2%, but substantially greater (> 60%) with pneumonic tularaemia. According to the 2007 WHO guidelines, aminoglycosides are the first choice for severe tularaemia in adults and children. In less severe cases of tularaemia (type B), particularly in areas endemic for the less virulent type B tularaemia or in a mass casualty setting, oral ciprofloxacin or doxycycline (only in adults) is preferred. Currently in the EU, antibacterial agents approved for the treatment of tularaemia include doxycycline.

Anthrax

Anthrax is a zoonotic disease caused by *Bacillus anthracis*, an intracellular pathogen. Anthrax infection manifests depending of the route of exposure (cutaneous, inhalation and gastrointestinal). Each of these forms can progress to systemic disease, which may present clinically with signs of septicaemia with the subsequent development of meningoencephalitis. Inhalational anthrax, which has the highest mortality of all routes of infection, results in bacteraemia, disseminated systemic infection and meningoencephalitis in over 50% of infections. After being inhaled into the lungs, *B. anthracis* spores are transported by macrophages and other phagocytic cells to regional lymph nodes and germinate into toxin-producing bacteria. Treatments recommended for inhalation anthrax in the guidelines developed by the EMA for the treatment and prophylaxis of biological agents that might be used as weapons of bioterrorism and in the WHO guidelines are shown below.

**Recommended Treatments for Inhalation Anthrax**

| **Source of Recommendation (e.g.: Treatment Guideline)** | **Active Substance or INN** |
|---|---|
| Europe (CPMP/4048/01 rev. 6) | **Ciprofloxacin:** 1st line treatment and as alternative for oral follow-up<br>**Ofloxacin or levofloxacin:** alternative to ciprofloxacin in adults<br>**Doxycycline:** alternative 1st line treatment and follow-up when susceptibility is confirmed<br>**Penicillin G:** alternative 1st line treatment if susceptibility is confirmed<br>**Amoxicillin:** alternative 1st line treatment if confirmed susceptibility and as oral follow-up |
| (WHO 2008) | Penicillin has long been the antibiotic of choice<br>Alternative: ciprofloxacin or doxycycline<br>In severe life-threatening cases IV penicillin or another chosen primary antibiotic, i.e., ciprofloxacin, may be combined with another antibiotic, preferably one which also has good penetration into the central nervous system. Clarithromycin, clindamycin, vancomycin or rifampicin are suggested as supplementary antibiotics for inhalational anthrax |

Currently in the EU, ciprofloxacin, levofloxacin and penicillin VK are approved in some countries for treatment of anthrax.

## 2.2 About the product

Solithromycin is a fluoroketolide. *In vitro*, it shows activity against macrolide-resistant *S. pneumoniae* and *M. pneumoniae* and against some macrolide-resistant *S. aureus*. Replacement of the cladinose sugar on clarithromycin by a keto group at Carbon-3 of the macrolide core identifies solithromycin as a ketolide. Addition of fluorine at Carbon-2 changes the chemical behaviour of the keto group (preventing enolization), supporting its denotation as a fluoroketolide.

In addition to its antibacterial activity, solithromycin has demonstrated anti-inflammatory effects *in vitro* and in animal models.

The aryl alkyl side chain of solithromycin differs significantly from that of telithromycin. The telithromycin side chain terminal aromatic ring contains a pyridine moiety that has been demonstrated to antagonise nicotinic acetylcholine (nACh) receptors, offering a mechanistic explanation for the disorders of visual accommodation (blurred vision) and myasthenia gravis exacerbations observed with that drug, and potentially, for episodes of syncope. Importantly nACh receptor inhibition by telithromycin may disrupt autonomic reflex regulation of hepatic inflammation by antagonizing vagal efferent (acetylcholine) signalling to hepatic Kupffer cells.

Solithromycin has been developed for intravenous and oral administration. The indications proposed by the applicant for both presentations (200 mg capsule and 400 mg powder for solution for infusion) are:

{Invented name} is indicated for the treatment of the following bacterial infections in adults aged 18 years and older (see section 5.1):
- Community-acquired pneumonia (CAP)
- Treatment of inhalation anthrax following exposure to *Bacillus anthracis*
- Treatment of inhalation tularaemia following exposure to *Francisella tularensis*

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

The proposed posology section for the oral formulation SmPC is as follows:

Posology

Solithromycin hard capsules or powder for concentrate for solution for infusion may be used as initial therapy. Patients who commence treatment on the parenteral formulation may be switched to the oral formulation when clinically indicated.

*Recommended dose and duration*

The recommended oral dose regimen for {Invented name} is shown by infection type for patients with normal renal function (Table 1) and for patients with creatinine clearance < 30 ml/min (Table 2).

The safety and efficacy of solithromycin when administered for periods longer that 7 days have not been established in patients (see section 4.4).

**Table 1: Oral dose of {Invented name} by type of infection in patients with normal renal function**

| Indication | Dose Regimen | Duration of Treatment |
|---|---|---|
| **For patients receiving oral solithromycin treatment only** | | |
| *Community-acquired pneumonia* | 800 mg given as a single dose on the first day followed by 400 mg once daily on 4 subsequent days. | 5 days |
| *Inhalation anthrax* | 800 mg given as a single dose on the first day followed by 400 mg once daily on 6 subsequent days. | 7 days [A] (see section 4.4) |
| *Inhalation tularaemia* | 800 mg given as a single dose on the first day followed by 400 mg once daily on 6 subsequent days. | 7 days [A] (see section 4.4) |
| **For patients switching from intravenous to oral solithromycin therapy** | | |

| | | |
|---|---|---|
| *Community-acquired pneumonia* | 800 mg given as a single dose on the first day of oral dosing followed by 400 mg once daily for the remainder of the dosing period. | Total duration of IV and oral dosing: 7 days |
| *Inhalation anthrax* | 800 mg given as a single dose on the first day of oral dosing followed by 400 mg once daily for the remainder of the dosing period. | 7 days [A] (see section 4.4) |
| *Inhalation tularaemia* | 800 mg given as a single dose on the first day of oral dosing followed by 400 mg once daily for the remainder of the dosing period. | 7 days [A] (see section 4.4) |

[A] Guidelines recommend treatment for up to 60 days for inhalational anthrax, and for 14 days for inhalational tularaemia. Solithromycin efficacy for treatment of these diseases in macaque monkeys has been demonstrated for anthrax (21 days dosing) and tularaemia (up to 17 days dosing). Toxicology studies were conducted in rats and monkeys for 90 days. Safety has been established in humans for dosing up to 7 days only. Treatment with solithromycin beyond 7 days should be based on clinical assessment (see section 4.4).

**Table 2: Oral dose of {Invented name} by type of infection in patients with creatinine clearance < 30 ml/min**

| Indication | Dose Regimen | Duration of Treatment |
|---|---|---|
| **For patients receiving oral solithromycin treatment only** | | |
| *Community-acquired pneumonia* | 800 mg given as a single dose on the first day followed by 200 mg once daily on 4 subsequent days. | 5 days |
| *Inhalation anthrax* | 800 mg given as a single dose on the first day followed by 200 mg once daily on 6 subsequent days. | 7 days [A] (see section 4.4) |
| *Inhalation tularaemia* | 800 mg given as a single dose on the first day followed by 200 mg once daily on 6 subsequent days. | 7 days [A] (see section 4.4) |
| **For patients switching from intravenous to oral solithromycin therapy** | | |
| *Community-acquired pneumonia* | 400 mg given as a single dose on the first day of oral dosing followed by 200 mg once daily for the remainder of the dosing period. | Total duration of IV and oral dosing: 7 days |
| *Inhalation anthrax* | 400 mg given as a single dose on the first day of oral dosing followed by 200 mg once daily for the remainder of the dosing period. | 7 days [A] (see section 4.4) |
| *Inhalation tularaemia* | 400 mg given as a single dose on the first day of oral dosing followed by 200 mg once daily for the remainder of the dosing period. | 7 days [A] (see section 4.4) |

[A] Guidelines recommend treatment for up to 60 days for inhalational anthrax, and for 14 days for inhalational tularaemia. Solithromycin efficacy for treatment of these diseases in macaque monkeys has been demonstrated for anthrax (21 days dosing) and tularaemia (up to 17 days dosing). Toxicology studies were conducted in rats and monkeys for 90 days. Safety has been established in humans for dosing up to 7 days only. Treatment with solithromycin beyond 7 days should be based on clinical assessment (see section 4.4).

*Missed dose*

If a dose is missed, it should be taken as soon as possible. Thereafter, daily dosing should be resumed, completing the prescribed treatment regimen.

Patients should not take a double dose to compensate for a missed dose.

*Elderly*

No dosage adjustment is required (see section 5.2).

*Renal impairment*

No dosage adjustment is necessary in patients with mild or moderate renal impairment. For patients with severe renal impairment (creatinine clearance <30 ml/min), the recommended dose of {Invented

name} is indicated in Table 2. The most appropriate dosing regimen for patients on haemodialysis has not been established (see section 5.2).

*Hepatic impairment*

No dosage adjustment is recommended for patients with mild, moderate, or severe hepatic impairment (see section 5.2).

*Paediatric population*
The safety and efficacy of {Invented name} in children and adolescents below 18 years of age have not yet been established.

Method of administration

{Invented name} capsules should be swallowed whole with a sufficient amount of water. The capsules may be taken with or without food.

The proposed posology section for the intravenous formulation SmPC differs only as follows:

**Table 1: Intravenous dose of {Invented name} by type of infection in patients with normal renal function**

| Indication | Dose Regimen | Total Duration of Treatment (including switch to oral therapy) |
|---|---|---|
| *Community-acquired pneumonia* | 400 mg infused over 60 minutes once daily until the patient is switched to oral dosing.<br>Patients who cannot be switched to oral therapy can remain on an intravenous regimen of 400 mg infused over 60 minutes once daily for 7 days. | 7 days |
| *Inhalation anthrax* | 400 mg infused over 60 minutes once daily until the patient is switched to oral dosing. | 7 days [A] (see section 4.4) |
| *Inhalation tularaemia* | 400 mg infused over 60 minutes once daily until the patient is switched to oral dosing. | 7 days [A] (see section 4.4) |

[A] Guidelines recommend treatment for up to 60 days for inhalational anthrax, and for 14 days for inhalational tularaemia. Solithromycin efficacy for treatment of these diseases in macaque monkeys has been demonstrated for anthrax (21 days dosing) and tularemia (up to 17 days dosing). Toxicology studies were conducted in rats and monkeys for 90 days. Safety has been established in humans for dosing up to 7 days only. Treatment with solithromycin beyond 7 days should be based on clinical assessment (see section 4.4).

**Table 2: Intravenous dose of {Invented name} by type of infection in patients with creatinine clearance < 30 ml/min**

| Indication | Dose Regimen | Total Duration of Treatment (including switch to oral therapy) |
|---|---|---|
| *Community-acquired pneumonia* | 400 mg infused over 60 minutes on first day followed by 200 mg infused over 60 minutes on subsequent days until the patient is switched to oral dosing.<br>Patients who cannot be switched to oral therapy can remain on an intravenous regimen of 200 mg infused over 60 minutes once daily for 7 days. | 7 days |
| *Inhalation anthrax* | 400 mg infused over 60 minutes on first day followed by 200 mg infused over 60 minutes on subsequent days until the patient is switched to oral dosing. | 7 days [A] (see section 4.4) |
| *Inhalation tularaemia* | 400 mg infused over 60 minutes on first day followed by 200 mg infused over 60 minutes on subsequent days until the patient is switched to oral dosing. | 7 days [A] (see section 4.4) |

[A] Guidelines recommend treatment for up to 60 days for inhalational anthrax, and for 14 days for inhalational tularaemia. Solithromycin efficacy for treatment of these diseases in macaque monkeys has been demonstrated for anthrax (21 days dosing) and tularemia (up to 17 days dosing). Toxicology studies were conducted in rats and monkeys for 90 days. Safety has been established in humans for dosing up to 7 days only. Treatment with solithromycin beyond 7 days should be based on clinical assessment (see section 4.4).

Method of administration

{Invented name} must be administered by intravenous infusion over a 60-minute period.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

For precautions to be taken before handling or administering the medicinal product, see section 6.2 for incompatibilities.

## *2.3 The development programme/compliance with CHMP guidance/scientific advice*

CHMP scientific advice was not sought. Several national agencies were consulted. The applicant followed existing and draft guidance available from CHMP regarding the clinical development of antibacterial agents.

### 2.4 General comments on compliance with GMP, GLP, GCP

**GMP**
Satisfactory GMP certificates are provided for drug product manufacturing sites.

**GLP**
All pivotal nonclinical toxicity studies (except the safety pharmacology) were conducted in accordance with International Conference on Harmonisation (ICH) nonclinical testing guidelines and in compliance with the Good Laboratory Practice (GLP) Regulations. The applicant has been asked to justify the lack of GLP compliance where applicable.

**GCP**
The Clinical Overview carries the following statement:
All studies submitted in this MAA were performed in full compliance with Good Clinical Practice (GCP) and are consistent with the International Conference on Harmonization (ICH) guidelines on drug development. All studies were closely monitored by the study sponsor's personnel or a contract research organization for compliance to the protocol and the procedures described in it. All clinical studies meet the ethical requirements of Directive 2001/20/EC.

### 2.5 Type of application and other comments on the submitted dossier

- **Legal basis**

The application has been filed in accordance with 2001/83/EC under Article 8(3) as a Centralised Procedure for a new active substance and using the optional scope Annex 3 (2) (a) of EC 726/2004.

- **Significance of paediatric studies**

In accordance with Regulation EC 1901/2006 a PIP (P/0180/2016) has been agreed for solithromycin.

The applicant has developed a suspension of solithromycin for paediatric use. The current application is confined to adults and concerns only the oral capsule and the powder for concentrate for solution for infusion, which provide 200 mg or 400 mg per dose unit, respectively.

- **CHMP guidelines/Scientific Advice**

CHMP scientific advice was not obtained. The clinical programme was conducted in line with existing CHMP guidance for antibacterial agents.

## 3. Scientific overview and discussion

### 3.1 Quality aspects

**Drug substance**

Solithromycin is a semisynthetic antibacterial in the fluoroketolide class. The synthetic process is satisfactorily described. The synthetic process involves three synthetic steps followed by two purification steps. CEM 275 is used as the regulatory starting material. The applicant has justified the use of CEM 275 as starting material based on the principles highlighted in ICH Q11. CEM is fully characterised and

obtained from two sources. The synthetic process of CEM 275 is fully described. The fate of impurities from CEM 275 to the API is fully described and supported by purge studies. However, the data is not sufficient and the starting material should be redefined to cover the possibility of formation of impurities in the proposed starting materials that are carried to the drug substance and lack of details on impurity purge studies.

Satisfactory structural characterisation of the drug substance has been provided. The drug substance specifications are adequate. Polymorphic form I of the drug substance is obtained in the synthetic process. However, in early clinical batches form II was also observed and hence a limit for form II is included in the specification. This is not acceptable and further data on analytical methods and justification of the limit of polymorphic form have been requested. All the specified impurities are fully identified and are controlled at adequate limits. The limits proposed are qualified based on the outcome of non-clinical studies and have been adequately justified. However, due to process improvement the proposed limits could be further tightened.

The drug substance is packed in a transparent low density polyethylene (LDPE) bag and sealed with a polypropylene strap seal. This inner bag (drug substance contact) is inserted into a secondary (outer) black LDPE bag and tied with another polypropylene strap seal. Stability data are provided for batches stored under long term and accelerated storage conditions. The stability data should be updated to support the proposed retest period.

**Drug product**

Capsules for oral use and a powder for concentrate for solution for intravenous infusion have been developed. The capsules contain 200 mg and the vials contain 400 mg of solithromycin.

***Capsules***

These are white, opaque, hard gelatin capsules. A satisfactory description of the formulation development has been provided. All the excipients proposed are commonly used for oral formulations and comply with *Ph. Eur* specifications. The formulation used in Phase 3 clinical studies was that proposed for commercial batches. A wet granulation process is used for manufacture of the capsules. Further information on the impact of polymorphic form on dissolution of the capsules should be provided. Further information on the development of the dissolution method development should be provided. The method should be shown to be discriminatory. The source of gelatin used for the capsule shell should be specified with regard to TSE/BSE declarations. The drug product controls are adequate and satisfactorily addressed. However, further changes are required to the acceptance limits for impurities, dissolution, assay and water content for limits proposed for release and shelf-life specifications.

The capsules are packaged into blister foil units, each comprised of 10 mil polyvinyl chloride (PVC)/2 mil / polychlorotrifluoroethene (PCTFE) Aclar®, sealed to 20 µm aluminum peel push lidding foil with a 7 $g/m^2$ heat seal coating comprised of copolymer vinylchloride, vinylacetate and polybutylmetacrylate. The PVC is pigmented white with titanium dioxide. The product contact materials are PVC and heat seal coating. Stability data are provided for Solithromycin capsules stored under long term and accelerated storage conditions showing no significant changes under long-term or accelerated conditions. However, the proposed shelf life in the submission is not acceptable as only 18 months' data for batches stored under long term storage conditions are provided. An update is requested on the on-going stability studies to support the proposed shelf-life.

***Powder for concentrate for solution for infusion***

The powder for concentrate for solution for infusion is a sterile, white to off-white lyophilized cake or powder. It is packed in a 50 mL (Type I) clear tubing glass vial, sealed with a grey fluropolymer coated

chlorobutyl rubber stopper and secured with aluminium over-seal with a blue flip-off seal. It is reconstituted with 20 mL sterile Water for Injections (WFI). A suitable target pH for the reconstituted formulation prior to dilution has been set. After reconstitution, 20 mL of the solution is withdrawn and added to 250 mL sterile 0.9% Sodium Chloride Injection for intravenous administration. During formulation development it was noted that there was precipitation and there was a high rate of pain at injection site reported in Phase 1 studies, which was associated with changes in pH during reconstitution. This has been addressed by using a buffering system with L-histidine, L-glutamic acid and L-aspartic acid (tri-amino acid buffer). The buffered formulation used in the Phase 3 clinical studies was the same as that proposed for commercial use.

As per in-use studies, formation of particulate matter was noted for some batches. An in-line 0.22µ filter was used during Phase 3 clinical studies. As per the information provided, the 'particulate matter' was due to air-bubbles detected by light obscuration method. The applicant has confirmed that no particles were seen on optical microscopy. However, there are limitations in the methods used for detecting particles and there is a tendency for solithromycin to precipitate due to change in pH as seen in Phase 1 studies. A detailed investigation should be conducted and results from batches near end-of-shelf life should be provided.

Satisfactory description of the manufacturing process has been provided. The manufacture involves sterile filtration followed by aseptic lyophilisation in vials. A design-space is claimed for lyophilisation but this is not appropriately supported by studies and hence the design-space is not acceptable. No process validation data are provided for the manufacturing process. The manufacturing process is considered non-standard due to use of substantial aseptic handling and hence process validation for full scale batches must be provided before the approval of the MA.

The drug product controls are adequate and in line with ICH Q6A and *Ph. Eur* general monograph for injectable products. However, changes to limits for impurities, assay, bacterial endotoxins and water content are recommended based on batch data and stability results. The analytical methods are fully validated. The *Ph. Eur* method is used for the test of sterility, however during the method validation the applicant failed to recover Gram-positive bacteria due to possible anti-bacterial action of solithromycin. Varying approaches for neutralisation of the microbial properties of solithromycin such as dilution, addition of polysorbate, use of different filters were tried without any success. Due to the risk of Gram-positive contamination not being detected, the method of sterility testing is considered as not validated. The applicant may use other alternative approaches such as enzymatic neutralisation of the solithromycin or using DNA detection based techniques along with a risk-assessment to demonstrate that possible contamination by Gram-positive bacteria has been fully evaluated.

Stability data are provided for Solithromycin for Injection stored under long term and accelerated storage conditions. Results demonstrate acceptable chemical and physical stability but they are presented up to 12 months only under long term storage conditions. The data presented are not sufficient to support the proposed shelf-life of 30 months; an update has been requested on the on-going studies.

***Conclusion on Quality aspects***

There are Major Objections regarding the Drug substance and Drug Product - Powder for solution for injection. These include issues relating to the redefinition of starting material, issues regarding formation of particulates during in-use studies, need for process validation data for proposed commercial scale batches as it is a non-standard manufacturing process and concerns that the test for sterility is not valid due to the absence of positive controls for Gram-positive bacteria. Other concerns include lack of data to support the applicant's proposed shelf-life for the capsule and the powder for concentrate for solution for infusion.

## *3.2 Non clinical aspects*

### 3.2.1 Pharmacology

Primary Pharmacology

The clinical section and assessment report provide an assessment of primary pharmacodynamics. Solithromycin has demonstrated activity *in vitro* and efficacy in animal infection models against pathogens known to cause CAP including strains resistant to β-lactams, fluoroquinolones and other macrolides and atypical CABP pathogens *M. pneumoniae*, *L. pneumophila* and *Chlamydophila pneumoniae*. Its activity is mediated by binding to 23S RNA of the 70S ribosome, interacting at multiple sites, and including ribosomes prepared from cells carrying *erm* methyltransferase, consistent with its activity against many *erm*-positive, macrolide-resistant bacteria.

Following the *B. anthracis* study (BBRC-3169) and *F. tularensis* study (FY14-020), the applicant concludes that the results demonstrate that solithromycin is efficacious in the cynomolgus macaque anthrax therapeutic model when administered by oral gavage once daily for 21 days, and is an effective treatment in cynomolgus macaques aerosol-challenged with a lethal exposure of *F. tularensis* SCHU S4. However, with there are Major Objections raised by the CHMP due to the fact that it remains unclear what the contribution from metabolites to the overall efficacy seen in both studies with NHPs is and therefore the relevance to humans, as in NHPs there is greater first pass metabolism leading to lower solithromycin but relatively higher exposure to *N*-Acetyl-CEM-101 and CEM-214 (see metabolism section below) *vs.* parent drug compared to that seen in humans following the CAP dosing regimen. Furthermore, the CHMP is of the view that the efficacy observed in the *F. tularenis* study is not sufficiently clear or convincing. In addition the systemic exposure levels associated with survival of *F. tularensis*-infected NHPs was ~1.4-fold higher than the target AUC values in humans when doses with the proposed regimen.

Secondary Pharmacology

Studies in mice exposed to cigarette smoke indicate that oral CEM-101 could have anti-inflammatory effects in chronic lung diseases, such as COPD, both by a direct anti-inflammatory effect on neutrophil recruitment and also by reversing corticosteroid resistance of macrophages, thus restoring the anti-inflammatory effects of inhaled corticosteroids. The anti-inflammatory effects of CEM-101 in lung disease were evaluated in a mouse model of bleomycin-induced pulmonary fibrosis (SR-MPP054-1309-6). Analysis of BAL samples collected showed a significant decrease in the number of white cells in the BAL fluid of the CEM-101 group vs. vehicle control group; specifically, the numbers of lymphocytes, neutrophils and eosinophils were significantly decreased in the CEM-101 group and numbers of macrophages were not significantly different. Furthermore, as CEM-101 significantly decreased monocyte chemotactic protein 1 (MCP-1) and MMP-9 mRNA expression levels in the lung (which are involved in the recruitment of inflammatory cells), it is proposed that CEM-101 may have the ability to limit disease progression of pulmonary fibrosis through reduced recruitment of inflammatory cells into pulmonary parenchyma and alveoli. In a model of airway inflammation and mucin production CEM-101 decreased inflammation-induced production of mucins MUC5A and MUC5B (overexpressed in chronic lung diseases such as cystic fibrosis).

Finally the applicant conducted several studies to evaluate if CEM-101 could have any therapeutic benefit in the treatment of non-alcoholic steatohepatitis (NASH), due to its significant anti-inflammatory properties – particularly as it has been demonstrated that CEM-101 accumulates and is metabolised in the liver, and hepatic inflammation plays a major role in the pathogenesis of NASH. The results from 3 studies in which NASH was induced in 2-day old C57BL/6J mice by streptozotocin injection and a high-fat diet (STAMTM model; Fujii 2013) demonstrated that CEM-101 significantly decreased blood glucose levels and non-alcoholic fatty liver disease (NAFLD) activity scores (a score $\geq$5 with steatosis and hepatocyte ballooning is generally considered diagnostic of NASH). It is theorised by the applicant that the apparent anti-diabetic, anti-NASH and anti-fibrosis effects may occur through inhibition of inflammation and hepatic gluconeogenesis.

Safety Pharmacology

Macrolides are known to have a torsadogenic potential and that this has been evaluated in detail for solithromycin (CEM-101). CEM-101 inhibited hERG current by (Mean ± SEM) 10.5 ± 0.9% at 2.19 μM (n = 4), 25.3 ± 1.2% at 8.0 μM (n = 3) and 51.6 ± 3.1% at 26.6 μM (n = 3) versus 0.1 ± 0.2% (n = 4) in control. HERG inhibition at all three concentration was statistically significant ($P<0.05$) when compared to vehicle control values. The applicant explains that since in humans, 80% of solithromycin present in plasma is bound to proteins (see clinical assessment report), this level of inhibition is considered of low biological significance – no discussion on clinical safety margins is presented.

No treatment-related effects were observed in cardiovascular parameters after oral doses of CEM-101 up to 320 mg/kg in conscious telemetered dogs. In addition to the specified cardiovascular safety pharmacology testing, there were no changes in ECG parameters in the monkey repeat-dose toxicity studies: up to 200 mg/kg/day in the 14-day oral study (1715-07146), up to 125 mg/kg/day in the 13-week oral study (1715-08278), or up to 25 mg/kg/day in the 28-day IV study (30339). A subsequent human thorough QT (TQT) study was negative (CE01-109).

As inhibition of hERG potassium current *in vivo* can be masked by concomitant block of L-type calcium (Ca) or sodium (Na) channel currents, the activity of CEM-101 was tested in Nav1.5 and Cav1.2 channel assays (130812.DRK). CEM-101 did not significantly inhibit Nav1.5 and Cav1.2 at the concentrations tested. The $IC_{50}$ values for the inhibitory effect of CEM-101 on Nav1.5 and Cav1.2 were not calculated due to only slight inhibition but were estimated to be greater than 27.8 μM and 30 μM, respectively.

Because CEM-101 produced moderate increases in heart rate in the Phase 1 TQT study in healthy subjects and in a Phase 1 drug-drug interaction study with ketoconazole a potential mechanism of a CEM-101 effect on heart rate was evaluated *in vitro* on the HCN4 channel (HCN4-1-20160108). CEM-101 at 20 μg/mL did not have any significant effect on human HCN4 channel currents expressed in Xenopus oocytes. To further explore the potential physiological mechanism of solithromycin exposure-related heart rate increases in healthy subjects, the ability of CEM-101 to inhibit binding of a panel of receptors with potential cardiovascular effects (adenosine (A1), adrenergic (α1A, α1B, β1, β2), endothelin (ETA, ETB), histamine (H2), muscarinic (M2), serotonin (5-HT4e) and the norepinephrine transporter) was evaluated. For both CEM-101 and clarithromycin, each of these binding assays demonstrated inhibition <20% and in most cases <10%. CEM-101 therefore was considered to have 'weak' inhibitory effects at a concentration of 1 μM.

The applicant should confirm which safety pharmacology studies were conducted in accordance with Good Laboratory Practise (GLP) and justify lack of compliance where appropriate and the potential impact on evaluation of the safety pharmacology endpoints should be explained.

The SmPC states the following: *Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.* Although it is indicated by the applicant there was no significant clinically relevant inhibition of receptors associated with potential cardiovascular effects a comparison of the maximum free therapeutic plasma concentrations obtained in patients and the in vitro effective concentrations on the hERG channels and other ion channels is not discussed and is requested. The SmPC should be updated accordingly.

In light of known torsadogenic potential of macrolides and reported solithromycin exposure-related heart rate increases in healthy subjects, the applicant should provide a more comprehensive statement in the SmPC including clinical safety margins regarding cardiac parameters observed *in vivo* in telemetered dogs treated with oral doses up to 320 mg/kg (the NOEL) and in repeat dose toxicology studies in monkeys (up to 200 mg/kg oral and up to 25 mg/kg IV).

The NOAEL for CEM-101 in the CNS rat safety study for the majority of toxicity findings (mortality, decreased body weight and body weight gain; decreased food consumption and food efficiency; decreased motor activity; correlative haematology, clinical chemistry and organ weight findings including distention of the gastrointestinal tract, biliary inflammation and small thymuses) in this study was 100 mg/kg/day.

However, the overall NOAEL in this study was considered to be 40 mg/kg/day based upon the presence of the following findings at 100 mg/kg/day CEM 101: phospholipidosis in the lung; lymphoid depletion in the thymus, lymph node and spleen (males only); vacuolar degeneration in the caecum (males only). There was no NOAEL in this study for the phospholipidosis in the lung for the females. In comparison oral administration by gavage of clarithromycin (1, 40, 100 and 250 mg/kg/day for 28 days) produced no findings related specifically to treatment with clarithromycin. Minimal changes in total movement in females administered telithromycin (250 mg/kg/day group) were resolved in recovery animals. Motor activity was decreased in these females but was again resolved in the recovery group. Clinical and gross necropsy findings were largely confined to anogenital staining in females. In light of the increased potential CNS toxicity (reported in study 22914) of CEM-101 in comparison with current marketed macrolides the applicant should provide further discussion of the clinical relevance of the findings reported and consider whether the SPC needs to be updated as proposed.

No treatment-related changes in respiratory parameters were observed after administration of doses up to 200 mg/kg/day in monkeys for 2 weeks. Under the conditions of this study, the NOAEL appeared to be 40 mg/kg/day in both sexes.

The potential for additional activities not known to be associated with the antimicrobial, anti-inflammatory or immunomodulatory activities of macrolides were evaluated, including effects on motilin receptor activation, phospholipidosis and inhibition of nACh receptors. No noteworthy effects are reported for the additional parameters evaluated. Activation of the motilin receptor induces gastric contraction and the initiation of the migratory motor complex (MMC), which is responsible for descending intestinal contractions. This activation was demonstrated for clarithromycin and erythromycin, but not CEM-101, in an in-vitro model. The formation of phospholipidosis is associated with many antibiotics, including macrolides, and was observed in some toxicology studies with CEM-101. The applicant references Das *et. al.* 2010, who demonstrated that like azithromycin, but unlike gentamicin, the phospholipid accumulation associated with CEM-101 is not associated with apoptosis. Telithromycin, clarithromycin, azithromycin and CEM-101 were tested against a variety of nicotinic acetylcholine receptors (nAChRs) to molecularly characterise a possible relationship between blockade of these receptors and the unusual adverse reaction (e.g. blurred vision, loss of consciousness) associated with telithromycin. The data from a series of studies support the hypothesis that the adverse reactions observed with telithromycin that were unusual and unexpected for macrolides can originate from the interaction of this compound and/or its metabolites with various types of nACh receptors. In contrast, CEM-101 displayed a spectrum of inhibition more like that of azithromycin and clarithromycin and therefore the applicant concludes it is unlikely to evoke these unusual adverse events.

No studies on the effects of CEM-101 on the renal system were reported in the non-clinical dossier. Reasons for this were not provided.

### 3.2.2 Pharmacokinetics

**Absorption:** In single dose oral and IV studies, at doses equivalent or close to the human equivalent dose (HED), the oral exposures were lower in animals than in humans. The repeat dose oral toxicokinetics (TK) of CEM-101 were assessed as part of general and reproductive toxicity studies in mice, rats, pregnant rats (GD 6-17), rabbits and monkeys. Following oral dosing CEM-101 is highly absorbed in rats and monkeys, but bioavailability is low (<20%) due to extensive metabolism as opposed to the much higher bioavailability reported in human. CEM-101 systemic exposure was dose-proportional in rats and greater than proportional in monkeys.

Following IV dosing in rats, no sex differences were reported at 5 mg/kg but absorption was higher in females at 15 mg/kg. A higher rate of metabolism to N-Acetyl-CEM-101 in male rats at this dose is the explanation given. Exposure was generally more than dose proportional at 5 and 15 mg/kg, especially in females.

In pregnant rats CEM-101 kinetics were predictable and followed a linear pattern, while higher doses of 200 and 300 mg/kg/day yielded plasma concentrations that were greater than dose proportional on GD17 suggesting substantial accumulation. In rabbits CEM-101 plasma concentrations were lower than observed in mice or rats. The PK was approximately dose proportional, with evidence of minor accumulation noted after 7 days of dosing.

Following repeat IV administration in dogs and monkey CEM-101 increases in systemic exposure (Cmax and AUC) were dose-proportional, with accumulation at higher doses in monkeys. The primary metabolite plasma levels were very low in dogs and hence it was concluded that the parent was not significantly metabolised. In monkeys, plasma concentrations of the primary metabolites, *N*-acetyl CEM-101 and CEM-214, were lower than CEM-101 concentrations, thus providing evidence that the metabolism of CEM-101 is limited following once daily intravenous administration of CEM-101 at doses up to 25 mg/kg/day for 28 days. The applicant states in the PK Written Summary that IV doses of 5, 15 or 45 mg/kg were administered in the Monkey 28-Day IV Infusion Study (# 30339). The study report states that doses were 5, 12.5 or 25 mg/kg. The applicant should update the report accordingly

**Distribution:** Following administration of a single IV or oral dose to the rat, the highest concentrations of radioactivity of the parent compound were present in the contents of the alimentary canal and bile in both sexes, suggesting the importance of biliary elimination which has been shown to be the major route of elimination of the parent compound. Intravenous dosing achieved Cmax tissue concentrations ~x2 of that achieved following oral dosing; except for liver, where Cmax was ~x3 higher in orally dosed animals than IV counterparts. Post Tmax time point tissue concentrations for both groups were reportedly similar. Variability noted in the IV dosed animals is attributed (as explained in the study report) to residual radioactive material in the dosing site (tail) of several rats. It is assumed by the applicant that these data do not alter the overall conclusions from this study.

The reporting of high concentration of CEM-101 relative to plasma in liver and lung tissue in toxicology species (rat and monkey) is theorised by the applicant to be likely due to lysosomal accumulation. This is a general characteristic of all macrolides, and is consistent with the observation of phospholipidosis in target organs, in particular the liver, in the repeat dose oral toxicity studies. Levels of the parent compound were either low or not detectable in the brains of both toxicology species (where examined). However, an increased potential for CNS toxicity was reported in study 22914 for CEM-101 in comparison with current marketed macrolides. No brain tissue was examined in this study for CEM-101 concentrations.

In the 13 week monkey repeat dose oral study the tissue concentrations had marked increases in comparison to increases in dose: 131- to 213-fold in liver, lung, salivary gland and heart when the dose was taken from 50 to 125 mg/kg; spleen, thymus, and bone marrow increased 37- to 86-fold; and mean concentrations in lymph node and eye increased 5- to 14-fold. The applicant is asked to discuss this finding in terms of the corresponding toxicokinetic profile and the clinical dosing regimen.

Solithromycin was shown to have a high volume of distribution; however the absence of solithromycin in the brain may be of concern for infections causing meningitis, as may occur with anthrax. The applicant is requested to discuss the clinical implications of absence of distribution to the brain in the clinical efficacy of solithromycin for brain infections and reflect the conclusions in the SmPC.

Placental transfer of CEM-101 has been observed in rats, rabbits, and sheep and the presence of CEM-101, N-Acetyl-CEM-101, and CEM-214 was confirmed in milk from lactating animals at higher concentrations (1 to 8-fold) than corresponding plasma concentrations observed at Cmax on GD 17 in the embryo-fetal developmental toxicity study in rats. The SPC states that the risk to human *'breast-feeding newborns/infants cannot be excluded'*. This is acceptable.

**Metabolism: *In vitro*:** A measurable consumption of solithromycin was observed with human hepatocytes incubated with 1 or 50 μM solithromycin (62% and 87% remaining at 2 hours, respectively). Multiple

metabolites were identified following incubation in human hepatocytes supporting both Phase I and Phase II metabolism pathways of solithromycin. A reaction phenotyping study showed that CYP3A4 is the most important CYP enzyme for solithromycin metabolism. It was shown that CEM-101 is a metabolism-dependent inhibitor of CYP3A4 – also known for other macrolides. Hence, the applicant conducted a comparative CYP3A4 inactivation study, comparing CEM-101 with telithromycin, clarithromycin, and erythromycin. Kinetic parameters allowed for the conclusion that CEM-101 should be designated as a more potent metabolism-dependent inhibitor of CYP3A4 in comparison to several well-known marketed macrolides (the reader is referred to the drug interaction section below).

***In vivo*:** Following oral dosing CEM-101 is extensively metabolised in rats and monkeys, mainly through side chain oxidation, dealkylation and acetylation, the N-acetylation being dominant in rats and side chain oxidation dominant in monkey. In humans the predominant circulating component is unchanged CEM-101. Two primary side chain metabolites, N-Acetyl-CEM-101 and CEM-214 (oxidative loss of triazolyl-phenylamino), demonstrate significant plasma exposure following oral administration in monkeys (both metabolites) and rats (mostly N-Acetyl-CEM-01), but exposure is generally low in mice and in humans. Dogs lack cytoplasmic N-acetyltransferase activity (due to the absence of N-acetyl transferase [Nat] genes in their genome - Trepanier 1997, Butcher 2002); hence negligible levels of N-Acetyl-CEM-101 were also detected in this species.

After oral administration, the Cmax and AUC of N-Acetyl-CEM-101 for rats and CEM-214 for monkeys were generally in the range observed for CEM-101. In contrast, concentrations of the metabolites were low in human plasma samples (each less than 10% of parent). Thus, while both metabolites significantly add to the total macrolide exposure in rat and monkey after oral administration, their concentrations are not significant in humans. Of note, in rats and monkeys as both metabolites retain the macrolide core and the desosamine sugar, they have antibacterial activity. The qualitative pattern of metabolism in monkey following IV administration is similar to that after oral dosing; however, the metabolites are present in much lower quantities, indicating that their formation is largely due to first-pass metabolism. Formation of the metabolites is also significantly reduced following IV dosing in rat and humans.

CEM-262, an oxidation product of CEM-214, is the major radioactive peak in human faecal samples, accounting for an average of 27% of the orally-administered dose [see clinical assessment report]. CEM-262 was present in the monkey plasma after oral administration of CEM-101. CEM-262 was the major radioactive component in faeces accounting for 20% and 4 % of the administered dose for male and female monkeys, respectively. Following IV administration of CEM-101, CEM 262 accounted for 52% and 43% of the administered dose in faeces, for male and female monkeys, respectively.

Overall, the applicant concludes that the metabolic profiles in nonclinical species were qualitatively similar to humans with adequate coverage for the main circulating human metabolites in at least one nonclinical species. However, quantitatively, CEM-101 exposure, after oral dosing at the human equivalent dose (across species), was lower than that achieved in the clinic. This quantitative difference imposes limits on the conclusions that can be drawn following the toxicology assessment of reported preclinical findings. Due to the low exposure multiples, the clinical significance of the toxicity profile in animals requires further justification; especially due to the reported risk of ALT elevation in the clinic - consistent with the known hepatotoxicity associated with other macrolides. Moreover, in the absence of long term clinical safety data, low exposure multiples do not allow for an adequate assessment of the contribution of the parent compound to the preclinical toxicity profile in order to support long-term human dosing.

**Excretion:** The primary route of excretion of CEM-101 and its metabolites in the rat is bile (67% for males, 71% for females) followed by faeces (19% for males, 17% for females). Excretion of CEM-101 was similar for male and female rats. Less than 10% was recovered in urine. The side chain metabolites were excreted in the urine, where they constituted a significant quantity of the radioactivity. In monkeys administered a single oral dose of [$^{14}$C]CEM-101 (50 mg/kg), the primary routes of excretion were bile

(30% for males, 39% for females) and faeces (39% for males, 31% for females) with less excretion in urine (7% for males, 9% for females). Following a single IV dosing (12.5 mg/kg), the primary route of excretion was faeces (73% for males, 58% for females) with less excretion in urine (2% for males and 6% for females).

In a bioavailability study in monkeys, up to 1.3% of administered CEM-101 was excreted in urine following administration of 100 mg/kg by oral capsule or nasogastric gavage or 20 mg/kg CEM-101 by IV administration.
These data support the view that metabolism is the major route of elimination following either oral or IV administration with the bile being the major route of excretion.

**Interactions:** In the in vitro drug interaction studies it was concluded that CEM-101 has the potential to inhibit its own metabolism, some inhibition was noted with OATP1B3, it was not significant inhibitor of BSEP or BCRP but both a substrate and inhibitor of P-gp in vitro.

### 3.2.3 Toxicology

**Single dose:** In the mouse single oral dose study the MTD could not be determined. In the equivalent monkey study the MTD was determined to be 400 mg/kg based on gastrointestinal clinical observations of emesis, diarrhoea, and soft faeces. Following IV dosing the MTD was 80 mg/kg in monkeys due to reported 'seizure-like' (ataxia, uncoordinated jerking of the trunk and limbs, lip smacking and hypersalivation, pale oral mucosa) symptoms in high-dose animals – of note the animal's heart and respiration rates were normal throughout these episodes. The MTD in dogs following IV infusion (3 hours) was 40 mg/kg based on the injection site masses noted at 80 and 120 mg/kg in the MTD phase of this study.

**Repeat dose: Rat oral:** repeat oral administration of CEM-101 for 28 days resulted in mortality at ≥250 mg/kg/day. Target organs/tissues of toxicity identified were liver, bone marrow, lymphoid tissues, testes, and skeletal muscle. Evidence of phospholipidosis was observed in lymphoid tissues, lungs, and cecum. Many adverse events were not reversible. The NOAEL was considered to be 40 mg/kg/day based on the findings of histiocytosis in the lymph nodes and lungs and vacuolar degeneration in the cecum. At this dose, the Day 29 CEM-101 plasma Cmax was 131 ng/mL for males and 133 ng/mL for females. The corresponding $AUC_{(0-24)}$ was 1060 ng•h/mL for males and 1330 ng•h/mL for females. These values correspond to a clinical safety margin at the intended human maintenance dose (400 mg) of <1. – see pharmacokinetics other concerns.

In the subsequent 13 week study, toxicities reported in the 28-day rat study did not appear to progress in severity or occur at lower doses with chronic dosing. The applicant suggests that there may be toxicological adaptation over time. Indeed Cmax at 100 mg/kg after 28 days of dosing was similar to that reported after 13 weeks of dosing at 125 mg/kg/day ((737 ng/g and 797 ng/g, respectively). The applicant explains that hepatic toxicity was less in the 13 week study even though liver concentrations were almost 8-fold higher (2920 ng/g at 100 mg/kg/day in the 28-day study *v* 22,500 ng/g at 125 mg/kg/day in the 13-week study). The clinical relevance of this is not discussed.

CEM-101 is extensively metabolised, mainly to 2 side chain metabolites, N-Acetyl-CEM-101 and CEM-214, both of which retain the macrolide core. In rats after oral administration the Cmax and AUC of N-Acetyl-CEM-101 was generally in the range observed for CEM-101. Of note concentrations of N-Acetyl-CEM-101 in the liver were ~2x (41 725 ng/g) that reported for the parent compound. It is therefore theorised by the applicant that this metabolite would carry some of the liability associated with the liver effects observed with CEM-101. The highest dose tested in this study was assigned the NOAEL with a corresponding Cmax of 593 ng/mL for males and 1000 ng/mL for females. The CEM-101 plasma $AUC_{0-T}$ was 6870 ng•h/mL for males and 8280 ng•h/mL for females. Due to the fact that in humans, N-Acetyl-CEM-101 is found only in small quantities and [parent] CEM-101 is the predominant AUC component it

is proposed that although the AUC of CEM-101 at the NOAEL in the 90-day oral rat study may be lower (AUC ratio of <0.7) than that likely to be achieved at the proposed human dosing regimen (loading dose of 800 mg on Day 1 followed by 400 mg on Days 2-5), a safety margin of 2.0 can be calculated based on the combined AUCs of CEM-101, N-Acetyl- CEM-101, and CEM-214.

Hepatobiliary inflammation was detected in the recovery animals of the 28-days study in rats, considered to be sequelae to biliary inflammation. In the 13-week study in rats the increased liver enzyme values (AST, ALKP, and/or ALT) were observed in all treated groups on Day 45. According to the applicant these increases were mild in severity, within the laboratory's historical control range (except for ALKP) and were generally absent or diminished by Day 92, were without any histopathological correlate, and therefore were not considered toxicologically significant. A mechanistic explanation for the different toxicological profile between 28-days study and 13-weeks study should be provided, along with a discussion on the relevance of these findings for human use. A comparison to data obtained with Cynomolgus monkey is also expected to rule out potential irreversible hepatotoxic damage to the liver in the expected clinical use, since available clinical data isn't reassuring of the lack of liver toxicity suggested by the non-clinical data. Although the presence of the 'active' metabolites may explain the liver toxicities reported in rats- as N-Acetyl-CEM-101 retains the macrolide core and the desosamine sugar, and possesses antibiotic activity (therefore is classified as a macrolide) – the relevance to the adverse effects on transaminases in humans where the level of these 'active metabolites' is much lower is unclear. Therefore the applicant is required to justify the clinical safety margins that take into account combined AUCs of CEM-101, N-Acetyl- CEM-101, and CEM-214 when these metabolites are not formed to the same extent in humans.

**Monkey oral:** following a DRF study, the 14 day oral toxicity study included four dose groups (0, 40, 100 and 200 mg/kg). Administration of CEM-101 caused emesis at ≥100 mg/kg/day during the treatment phase only. Reversible, very slight body weight loss and decreased body weight gain were observed in 200 mg/kg/day males and females, and 100 mg/kg/day males. Reversible increases in liver enzymes were noted at ≥100 mg/kg/day and resultant liver weight increases were reported – also associated with centrilobular hepatocellular vacuolation (high-dose). Thymic weights were decreased and correlated with thymic lymphoid atrophy that was reversible in high-dose females. CEM-101 at doses of ≥100 mg/kg/day resulted in histopathological lesions in the small intestine and liver, and in the mesenteric lymph nodes and thymus at all dose levels. The incidence of microscopic lesions was similar but of lower frequency at the end of the recovery period, suggesting reversibility of the CEM-101-related findings. There were no treatment-related changes in mortality, food consumption, ocular or ECG findings, haematology, coagulation, urinalysis, gross necropsy parameters, or respiratory function. The NOAEL for this study was 40 mg/kg/day. At this dose, the Day 14 CEM-101 plasma Cmax was 404 ng/mL for males and 813 ng/mL for females.

In the subsequent 13 week study, toxicologically significant findings noted (altered clinical pathology parameters, increased organ weights, macroscopic and microscopic findings) were confined to the high dose group (125 mg/kg/day) and consistent with the liver being the main target organ of toxicity. Indeed liver tissue concentrations of CEM-101 (Cmax on Day 91) were 1168-fold higher relative to plasma concentrations (spleen, 501-fold; lung; 465-fold; and salivary gland, 410-fold). In addition, histiocytosis was noted in several tissues, which is consistent with phospholipidosis. The CEM-101-related effects appeared to be reversible as all the clinical pathology alterations and many of the findings in the liver, lung, and spleen were reduced after the 12-week recovery period. Therefore, the NOAEL was determined to be 50 mg/kg/day. However, clinical pathology alterations that were reportedly reversible (objective) or showed a trend to reversibility (subjective) during the 12 week recovery period of the 13 week oral toxicology study (monkey) need to be clarified further given the concerns raised regarding liver toxicity. Of note, in the liver of high-dose animals, N-Acetyl-CEM-101 concentrations were 2,573,900 ng/g, slightly lower than the corresponding CEM-101 concentrations. No value for CEM-214 was determined but as this is the primary metabolite in the monkey it was assumed by the applicant that this concentration would also be high. As was the case in the rat the primary metabolites in the monkey are only found in

small amounts in the humans, and for the reasons given above, it could be assumed that the toxicities reported in the monkey may also be attributable to all macrolide-containing compounds. When the same rationale is applied to the monkey as was applied the rat and exposures from the macrolide-core containing metabolites are added, the clinical safety margin at the NOAEL of 50 mg/kg in the 90-day oral monkey study is increased from 0.8 to 2.1 (based on total macrolide exposure and on PK data from healthy subjects in Cohort A of CE01-115: Subjects received the oral CABP regimen of 800 mg of solithromycin on Day 1, followed by 400 mg for 4 additional days).

Pivotal studies were conducted in two non-rodent species due to the intolerance of oral dosing in dogs (intense nausea) and IV dosing (local tolerance) in rat tail veins.

**Dog:** in a non-pivotal IV 14 day study [60612] 40 mg/kg/day (high-dose) exceeded the MTD and 5 mg//kg/day was the NOAEL. High dose animals had to sacrificed early due to marked reduction in food consumption and subsequent weight loss (18% to 25% of pretest values by termination), leading to a moribund state. The kidney was identified as a target organ as evinced by mild bilateral multifocal hyperplasia/hypertrophy of renal cortical tubular epithelium, with minimal individual cell necrosis of cortical tubular epithelium. Adverse clinical signs in mid-dose animals included body weight loss, decreases in food consumption, increases in ALT and urea, as well as macroscopic findings at the infusion site. At 5 mg/kg/day CEM-101 was considered to be well tolerated.

In the pivotal 28 day study, doses of 5, 10 or 15 mg/kg/day were administered IV. Administration of CEM-101 at doses up to 10 mg/kg/day over a period of 90 minutes by IV infusion for 28 consecutive days to beagle dogs was generally well tolerated and resulted mainly in local lesions at the infusion sites primarily procedure-related (not dose related but exacerbated by test item). Premature euthanasia on 1 high-dose dog was reported due to poor clinical condition (poor food consumption/emaciation/no faecal output/decreased bodyweight, minor changes in haematology and urine output) therefore the NOAEL was 10 mg/kg/day for this study.

Dogs lack cytoplasmic N-acetyltransferase activity due to the absence of N-acetyl transferase (Nat) genes in their genome (Trepanier 1997, Butcher 2002) – hence negligible levels of N-Acetyl-CEM-101 and CEM- 214 were measured in this species. The Cmax and AUC values obtained at the NOAEL in the 28 dog IV study (Cmax was 2240 ng/mL for males and 1900 ng/mL for females. The $AUC_{(0-24)}$ was 14,300 ng•h/mL for males and 11,200 ng•h/mL for females) exceed that reported at the NOAEL in the oral 13 week monkey and rat studies.

**Monkey:** in the preliminary 7 day study 5 mg/kg/day was assigned the NOAEL. Subsequently doses of 5, 12.5 and 25 mg/kg were administered in the pivotal 28 day study. In this study based on the clinical signs and histopathological changes noted at the dosing sites in animals at 25 mg/kg/day, the NOAEL for CEM-101 for local effects at the dosing site was determined to be 12.5 mg/kg/day (Day 28 combined sex Cmax=2975 ng/mL; AUC=7455 ng•h/mL). For systemic toxicity, the NOAEL was determined to be 25 mg/kg/day as the only affected clinical parameters were reported increases in ALT and AST that were not toxicologically significant and within historical control values, respectively: (Day 28 combined sex Cmax=5860 ng/mL; AUC=20,300 ng•h/mL). Similarly to dogs, lesions at the injection sites were with increased incidence and severity with dose, suggesting that the lesions were procedure-related (as seen in control animals) but exacerbated by the administration of solithromycin.

No evidence of hepatic phospholipidosis was observed in dogs or monkeys following IV administration up to 28 days. Conversely, phospholipidosis or histiocytosis consistent with phospholipidosis was observed in multiple tissues in rats and monkeys after orally administered CEM-101. The toxicological meaning of this observation should be further discussed and contextualized with the proposed clinical use of solithromycin with reference to potential implications for humans.

In conclusion the major target organs and observations of toxicity with CEM-101 (liver, gastrointestional, histiocytosis/phospholipidosis) appeared to be related to the class of macrolides. While IV dosing did not exceed 28 days and maximum administered doses were lower, effects were less apparent following IV than oral administration. The applicant considers that these findings suggest that metabolites generated from the first-pass effect of CEM-101 contribute to the toxicological effects of solithromycin in the toxicology species. However, at the time of this assessment it remains unclear what the clinical relevance of the findings in animals is as exposure levels to CEM-101 and 'active' metabolites are lower and higher than that seen in clinic, respectively.

The NOAEL for the IV repeat-dose toxicity dog study was based primarily on inappetence and its sequelae and not on macroscopic or microscopic findings of toxicity, and for the monkey study was based on effects associated with the infusion rather than systemic effects. Based on these NOAELs, the 28-day IV dog and monkey studies provide exposure margins of 1.0 and 0.6, respectively, based on solithromycin exposure and on PK data from Cohort 1 of **CE01-121:** Healthy adult subjects received 400 mg over 60 minutes for 7 days.

The reported clinical safety margin at the NOAELs of 50 and 40 mg/kg in the 90-day oral monkey and rat studies was increased from 0.8 to 2.1 and <0.7 to 2.0 (based on total macrolide exposure and on PK data from healthy subjects in Cohort A of CE01-115: Subjects received the oral CABP regimen of 800 mg of solithromycin on Day 1, followed by 400 mg for 4 additional days). The applicant has been asked to justify the use of combined AUCs of CEM-101, N-Acetyl- CEM-101, and CEM-214 to calculate clinical safety margins when these metabolites are not formed to the same extent in humans.

**Genotoxicity:** An adequate battery of tests was conducted for the evaluation of the genotoxic potential of CEM-101. The genotoxic potential of CEM-101 (tested individually) was assessed in multiple in vitro and in vivo studies, and the test-item did not display any mutagenic or clastogenic potential.

**Carcinogenicity**: Carcinogenicity studies have not been conducted with CEM-101. The applicant explains that the mechanism of action of CEM-101 would not implicate it in carcinogenesis or tumour promotion. CEM-101 disrupts protein synthesis in bacteria by binding to multiple sites on the 23S component of the 50S ribosomal subunit. It shows no effect on eukaryotic translation, demonstrating selectivity for bacterial ribosomes. As anticipated based on prescribing information for other macrolide antibiotics, CEM-101 was not genotoxic in 4 studies that evaluated genetic toxicity potential. Studies up to 13 weeks in duration in rats and monkeys did not show any evidence of preneoplastic lesions. Given that there are no carcinogenicity data or longer term clinical exposure data, and that the safety of solithromycin has only been evaluated for up to 90 days via oral administration and 28 days via IV administration in toxicology species, there are no data on which a benefit-risk balance can be made for long term treatment. Therefore the SPC should be updated accordingly.

**Reproductive toxicology:** following completion of reproductive and developmental toxicity programme in accordance with ICH S5 (R2) guideline, it was concluded by the applicant that CEM-101 showed no evidence of reproductive toxicity. The reproductive parameters in the male and female animals were examined and considered to be unaffected by treatment with CEM-101 and a NOAEL of 220 mg/kg/day (the highest dose level tested) assigned for reproductive toxicity – no TK analysis was conducted in this study although clinical signs indicate exposure to the test item.

Maternal toxicity was reported in the rat and rabbit EFD studies (clinical signs, reduction in body weight, food consumption); and in rabbits decreases in viable fetuses and litter size, and increases in postimplantation loss and resorptions, were noted at 200 mg/kg/day and hence the NOAEL for developmental toxicity was concluded to be 110 mg/kg/day in this species. At this dose, the GD 18 CEM-101 plasma Cmax was 467 ng/mL and the $AUC_{(0-24)}$ was 2020 ng•h/mL. In the rat the NOAEL developmental toxicity was determined to be 220 mg/kg/day, the highest dose level tested. At this dose, the GD 17 CEM-101 plasma Cmax was 1570 ng/mL and the AUCτ was 18,300 ng•h/mL.

No CEM-101-related changes were seen in fetal body weight or identified following fetal external, visceral, and skeletal examinations in the treated rabbits or rats as compared to controls. However, at GD 19 fetal rabbit CEM-101 plasma concentrations were detectable only at the 200 mg/kg/day dose, and were approximately 40-fold less than the maternal CEM-101 plasma concentrations. Metabolites could not be detected in rabbit's fetal plasma at any administered dose. In the rat fetal plasma concentrations of CEM-101 were approximately 15-fold lower than the maternal concentrations for doses of 100 to 220 mg/kg/day CEM-101; and ranged from 3.4- to 8.9-fold lower for N-Acetyl-CEM-101 and from 1.4- to 2.8-fold lower for CEM-214 compared to maternal concentrations.

The applicant should update the text of section 5.3 to reflect the fact that clinical exposure margins were low/negligible in these studies. The inability to obtain adequate exposure in toxicology species relative to what could be anticipated in the clinic may be a more accurate reflection of the test items ability to impact on reproduction and development in these animal studies.

In the pre- and post-natal development rat study CEM-101 was excreted in rat milk and concentrations were higher than those observed in maternal rat plasma in a separate study with a similar dosing regimen. The NOAEL for general maternal toxicity in F0 females was considered to be 100 mg/kg/day, based on the body weight and food consumption effects noted at 200 mg/kg/day. The NOAEL for F1 developmental toxicity was considered to be 100 mg/kg/day, based on the decreased pup weight relative to controls noted early in the preweaning period.

**Juvenile toxicology:** the applicant states that studies in juvenile animals have not been conducted with CEM-101, in accordance with the agreed initial paediatric study plan of 30 January 2014 in the US and the agreed paediatric investigational plan of 30 September 2014 in the European Union.
.
**Local tolerance:** In the non-GLP rabbit local tolerance study with the equivalent of the clinical formulation utilised in study **CE1-104** signs of pain were noted during dosing and erythema was noted to be primarily very slight. In addition histopathological findings of subcutaneous and perivascular inflammation or oedema were noted. The results support the assessment of the injection sites performed during the pivotal repeat dose toxicity IV studies in dogs and monkeys, performed with CEM-101. Here perivascular inflammation, perivascular necrosis, intimal hyperplasia, chronic organizing thrombosis, and/or epidermal crust were reported at the injection site. Overall, it was concluded that IV administration of CEM-101 results in exacerbation of the procedure-related local reaction to the injection (as seen in control groups), which is generally reversible. Of note poor tolerability was also noted in the clinical compared to IV moxifloxacin.

No effects on accidental ocular exposure are discussed; however, no treatment-related ocular toxicity was noted in any of the pivotal toxicology studies.

**Immunotoxicology:** The immunomodulatory effects of solithromycin observed in animal models are not considered, by the applicant, to suggest immunotoxicity and no additional tests were deemed necessary. Following scientific advice given by the MHRA in 2015 the applicant writes in the meeting minutes that 'immunotoxicity assessment will be included in the MAA, based on the ICHS8 guideline'. The applicant has evaluated the findings in the pivotal standard toxicology studies to identify any findings potentially related to the immunotoxicity of CEM-101. Changes were identified in the lymphoid system in all species and routes tested (increased neutrophils, decreased lymphocytes , reduced thymus weight, thymic atrophy, increased spleen weight, lymphoid depletion in thymus, and lymphoid depletion in spleen and lymph nodes). In addition in high dose rats orally dosed, adrenal weight was increased relative to body weight and to brain weight. The applicant concludes in accordance with Appendix 1, Section 1.4 of the ICH S8 guideline, the changes noted in the lymphoid organs of the animals tested are considered related to stress. However, the guideline states that these findings alone should not be considered sufficient evidence of stress-related immunotoxicity. In order to justify the absence of specific immunotoxicology studies, the

applicant should discuss how the evidence presented allows for determination of which changes are secondary effects of stress as opposed to primary test article effects.

**Phototoxicity:** Since the absorption is outside the accepted UVa / UVb / visible light range associated with the potential for phototoxicity and the distribution of solithromycin is low in eyes and in the skin, its potential to induce phototoxicity is expected to be low, and therefore no phototoxicity testing was conducted. This is accepted.

**Metabolites:** Separate studies were not conduced with metabolites as no human metabolites exceed 10% of parent exposure in plasma, and metabolite exposure was not disproportionally higher in humans than in the toxicity species. This is accepted.

**Impurities:** Impurities in the drug substance were adequately qualified in accordance with ICH Q3A(R2).

**Excipients:** Separate toxicity studies were not conducted for excipients in the drug products, all of which are compendial, consistent with USP, NF, and Ph.Eur., and present in other approved products – see the Quality assessment report.

### 3.2.4 Ecotoxicity/environmental risk assessment

Solithromycin PECsurfacewater value is above the action limit of 0.01 µg/L but is not a PBT substance as log D does not exceed 4.5. The applicant is asked to refine the Fpen submitting a well-documented worst-case for the prevalence data for the sought indications. The provided risk assessment should be recalculated if a new PECsurfacewater has been assessed.
The Log Koc of solithromycin is below 4.0 and it is therefore not expected to amass significantly in the soil compartment. A terrestrial assessment is, therefore, not required. It is not readily biodegradable; however the applicant has not submitted the final study report for the aquatic sediment transformation test. It is stated in the ERA that the fate of solithromycin in water/sediment systems is being evaluated in a GLP-compliant, transformation in aquatic sediment systems study, following OECD Test Guideline 308. The study results and report are expected in 2017. If greater than 10% of the dosed solithromycin partitions and remains in the sediment after 14 days, a sediment effects assessment (OECD 218) will be triggered.

In the environmental effect studies, results indicate that solithromycin will pose a significant risk to the environment, however, a definitive conclusion on the potential risk of solithromycin to the environment cannot be finalised at the time of this assessment.
This is because an aquatic sediment systems study, following OECD Test Guideline 308, was triggered (because solithromycin is not readily biodegradable), and is ongoing. The results of the OECD 308 test may trigger a sediment toxicity test (OECD 218). An updated environmental assessment for solithromycin, including additional study reports, will have to be submitted for evaluation

### 3.2.5 Discussion on non-clinical aspects

The primary pharmacodynamic studies demonstrated in-vitro activity and efficacy in animal infection models against pathogens known to cause CAP, including strains resistant to other macrolides and atypical CABP pathogens *[M. pneumoniae, L. pneumophila, and Chlamydophila pneumoniae]*. The activity of solithromycin is mediated by binding to 23S RNA of the 70S ribosome.

In secondary pharmacodynamic studies it was demonstrated that, similar to other macrolides, solithromycin exhibits anti-inflammatory and immunomodulatory properties but is significantly more effective than older macrolides.

Macrolides are known to have a torsadogenic potential. Subsequently it was demonstrated that solithromycin inhibits the hERG current. The level of inhibition reported is considered by the applicant to be of low biological significance since 80% of solithromycin present in human plasma is bound to proteins but no discussion on clinical safety margins is presented. Furthermore, in light of the known torsadogenic potential of macrolides and the solithromycin exposure-related heart rate increases in healthy subjects, the applicant is requested to update the SmPC with clinical safety margins regarding cardiac parameters observed *in vivo* in telemetered dogs treated with oral doses up to 320 mg/kg (the NOEL) and in repeat dose toxicology studies in monkeys (up to 200 mg/kg oral and up to 25 mg/kg IV).

In a rat safety study, it was clear that an increased potential for CNS toxicity was applicable to the proposed product in relation to previously approved macrolides and hence the applicant needs to provide further discussions and update the SmPC accordingly.

Following oral dosing solithromycin is highly absorbed in rats and monkeys, but bioavailability is low (<20%) due to extensive metabolism as opposed to the much higher bioavailability reported in human. Metabolism is the major route of elimination following either oral or IV administration with the bile being the major route of excretion. In metabolism studies it was revealed that the metabolic profiles in nonclinical species were qualitatively similar to humans with adequate coverage for the main circulating human metabolites in at least one nonclinical species. However, solithromycin exposure after oral dosing at the human equivalent dose (across species) was lower than that achieved in clinical studies. This quantitative difference imposes limits on the conclusions that can be drawn following the toxicology assessment of reported nonclinical findings. Due to the low exposure multiples, the clinical significance of the toxicity profile in animals requires further justification, especially due to the reported risk of ALT elevation in patients, which is consistent with the hepatotoxicity known to be associated with other macrolides. Moreover, in the absence of long-term clinical safety data, low exposure multiples do not allow for an adequate assessment of the contribution of the parent compound to the nonclinical toxicity profile in order to support long-term human dosing. Furthermore a mechanistic explanation for the different toxicological profile between 28-day rat study and 13-weeks study should be provided, along with a discussion on the relevance of these findings for human use.

The major target organs and observations of toxicity with solithromycin (liver, gastrointestinal, histiocytosis/phospholipidosis) appeared to be related to the class of macrolides. While IV dosing did not exceed 28 days and maximum administered doses were lower, effects were less apparent following IV than oral administration. The applicant suggests that metabolites generated from the first-pass effect of solithromycin contribute to the toxicological effects of solithromycin in the nonclinical studies. However it remains unclear what the clinical relevance of the findings in animals is as exposure to solithromycin is lower and exposure to 'active' metabolites is higher compared to the clinical findings.

The NOAEL for the IV repeat-dose toxicity dog study was based primarily on inappetence and its sequelae and not on macroscopic or microscopic findings of toxicity. In the monkey study the NOAEL was based on effects associated with the infusion rather than systemic effects.
Based on these NOAELs, the 28-day IV dog and monkey studies provide exposure margins of 1.0 and 0.6, respectively, based on solithromycin exposure compared to Cohort 1 of study CE01-121, in which healthy adult subjects received 400 mg IV over 60 minutes once daily for 7 days.

The reported clinical safety margin at the NOAELs of 50 and 40 mg/kg in the 90-day oral monkey and rat studies was increased from 0.8 to 2.1 and <0.7 to 2.0 (based on total macrolide exposure and on PK data from healthy subjects in Cohort A of CE01-115, in which subjects received the oral CABP regimen of 800 mg of solithromycin on Day 1, followed by 400 mg for 4 additional days. The applicant has been asked to justify the use of combined AUCs of CEM-101, N-Acetyl- CEM-101, and CEM-214 to calculate clinical safety margins when these metabolites are not formed to the same extent in humans.

No genotoxic potential was evident following a complete assessment in accordance with ICH guidelines. No carcinogenicity studies were conducted. There are no data on which a benefit-risk balance can be made for long term treatment. Therefore the SmPC should be updated accordingly. Although no reproductive toxicity was evident following solithromycin administration in toxicology species, the inability to obtain adequate exposure in these species relative to what could be anticipated in humans should be reflected in the SmPC.

Studies in animals support the clinical view that the proposed product is not well-tolerated locally. Intravenous infusion of solithromycin resulted in exacerbation of the procedure-related local reaction to the injection (as seen in control groups) and included signs of pain, subcutaneous and perivascular inflammation or oedema.

No further toxicology studies were conducted. The immunomodulatory effects of solithromycin observed in animal models are not considered by the applicant to suggest immunotoxicity and no additional tests were deemed necessary. The applicant concludes that changes noted in the lymphoid organs of the animals tested are considered related to stress. Further justification is required to substantiate this view.

Finally, a definitive conclusion on the potential risk of solithromycin to the environment cannot be given at the time of this assessment due to outstanding study data.

### 3.2.6 Conclusion on non-clinical aspects

There are no major objections from a non-clinical perspective but there are several other concerns.

## *3.3 Clinical aspects*

### 3.3.1 Pharmacokinetics

The clinical development of solithromycin (CEM-101) commenced in 2008 with oral and then intravenous formulations. The hard gelatine oral capsule formulation (200 mg solithromycin) did not change throughout clinical development. The planned commercial formulation for intravenous administration was used in later Phase 1 studies and in the Phase 3 IV to-oral CAP study (301). The excipients L-histidine, L-glutamic acid and L-aspartic acid serve as a tri-amino acid buffer. The lyophilisate is reconstituted with 20 mL water and added to a 250 mL bag of NaCl 0.9% or other compatible infusion solution.

**Absorption**

In study 104 5 fasted subjects received 400 mg IV and 400 mg oral doses 14 days apart. Mean absolute bioavailability (F) was 62% with a CV% of 21% and a range was 46%-80%.

In oral single dose (101) and multiple dose (102) studies in fasting subjects mean $C_{max}$ for solithromycin increased in a greater than dose-proportional manner up to single 1200 mg doses and mean $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ increased in a greater than dose-proportional manner up to single 1600 mg doses.

**Table 8 Mean Pharmacokinetic Parameters for CEM-101 Following Single Dose Administration**

| Parameter | Dose Cohort | | | | | | |
|---|---|---|---|---|---|---|---|
| | 50 mg (n=3[a]) | 100 mg (n=5) | 200 mg (n=5) | 400 mg (n=5) | 800 mg (n=5) | 1200 mg (n=5) | 1600 mg (n=5) |
| $C_{max}$ (ng/mL)[b] | 22.30 (20.99) | 68.26 (56.01) | 254.80 (24.30) | 784.40 (33.15) | 1324.40 (69.38) | 1964.00 (14.19) | 1781.60 (67.51) |
| $t_{max}$ (hr)[c] | 1.50 (1.0-1.5) | 2.00 (1.5-2.5) | 3.00 (2.0-4.0) | 4.00 (3.0-4.0) | 3.50 (2.5-6.0) | 6.00 (3.5-6.0) | 6.00 (4.0-6.0) |
| $AUC_{0\text{-last}}$ (ng*hr/mL)[b] | 40.24 (44.99) | 394.38 (84.95) | 1730.43 (30.30) | 6940.81 (41.14) | 13664.99 (69.98) | 26757.62 (24.09) | 28599.21 (79.31) |
| $AUC_{0\text{-inf}}$ (ng*hr/mL)[b] | ND | 624.48[d] (55.79) | 1859.05 (29.69) | 7128.69 (40.36) | 13836.55 (69.44) | 26957.02 (23.90) | 28861.93 (78.53) |

After multiple dosing there was high variability in plasma concentrations (CV up to 84%) over the dose range studied. Mean plasma $C_{min}$ values appeared to be comparable during Days 4 to 7, suggesting that steady state was attained. The mean accumulation index (AI) values were ~3, 2.5 and 2-fold for the 200, 400 and 600 mg doses, respectively, after excluding outlying low values.

**Table 8 Summary of PK Multiple-Dose Results for CEM-101 in Plasma on Day 7**

| Pharmacokinetic Parameters | Treatment A (200 mg) | Treatment B (400 mg) | Treatment C (600 mg) |
|---|---|---|---|
| | Arithmetic Mean ±SD | Arithmetic Mean ±SD | Arithmetic Mean ±SD |
| $AUC_{\tau}$ (µg*hr/mL) | 2.309 ±0.7730 (n=5) | 13.27 ±7.356 (n=10)<br>14.68 ±6.200 (n=9) | 18.41 ±5.555 (n=10) |
| $C_{max,ss}$ (µg/mL) | 0.248 ±0.0839 (n=5) | 1.09 ±0.521 (n=10)<br>1.20 ±0.399 (n=9) | 1.50 ±0.404 (n=10) |
| $C_{min,ss}$ (µg/mL) | 0.0195 ±0.00624 (n=5) | 0.225 ±0.151 (n=9)<br>0.225 ±0.151 (n=9) | 0.303 ±0.135 (n=10) |
| $C_{ssav}$ (µg/mL) | 0.0962 ±0.0322 (n=5) | 0.553 ±0.306 (n=10)<br>0.612 ±0.258 (n=9) | 0.767 ±0.231 (n=10) |
| Flux (%) | 238 ±25.5 (n=5) | 173 ±37.9 (n=9)<br>173 ±37.9 (n=9) | 159 ±28.2 (n=10) |
| $T_{max,ss}$ (hr) | 3.50 (2.50, 3.50) (n=5) | 4.00 (2.50, 6.00) (n=10)<br>4.00 (2.50, 6.00) (n=9) | 3.50 (2.50, 6.02) (n=10) |

Single and multiple IV doses

Study 121 evaluated 400 mg lyophilised solithromycin made into solution.

Overall, 7/20 who received 400 mg solithromycin QD via a peripheral vein discontinued due to AEs (4 at 60 minute and 3 at 30 minute infusions). Mean $C_{max}$ (end of infusion) was ~1.5-fold higher for 30 vs. 60 minute infusions. $AUC_{0\text{-}24}$ values were ~2-fold higher on Day 7 vs. Day 1 and mean AIs were just over 2-fold. The 800 mg dose gave a mean $C_{max}$ value of 6.2 µg/mL, which was 2.2-fold higher than the mean observed after 400 mg doses given over 60 minutes on day 7.

**Table 17 PK Parameters for Solithromycin in Plasma after Multiple 400 mg Doses**

| Dose (mg) | 400 | 400 | 400 |
|---|---|---|---|
| Infusion Volume and Time | 250 mL over 60 minutes | 250 mL over 30 minutes | 250 mL over 60 minutes |
| Venous Administration | Peripheral | Peripheral | Central (PICC) |
| **Cohort** | **1** | **2** | **3** |
| **Day 1** | | | |
| N | 10 | 10 | 5 |
| Mean $C_{max}$, µg/mL (CV%) | 2.170 (20.3) | 3.200 (40.3) | 2.400 (27.6) |
| Mean $T_{max}$, h (CV%) | 0.90 (23.4) | 0.48 (29.9) | 1.00 (0) |
| Median $t_{1/2}$, h | ND | ND | ND |
| Mean $AUC_{0-24}$, µg•h/mL (CV%) | 5.340 (17.8) | 5.930 (31.6) | 6.540 (20.7) |
| **Day 7** | | | |
| N | 6 | 7 | 5 |
| Mean $C_{max}$, µg/mL (CV%) | 2.850 (18.9) | 4.200 (11.4) | 3.310 (23.8) |
| Mean $T_{max}$, h (CV%) | 1.00 (0) | 0.43 (28.5) | 0.80 (34.2) |
| Median $t_{1/2}$, h | 8.64 | 8.04 | 8.23 |
| Mean $AUC_{0-24}$, µg•h/mL (CV%) | 12.600 (34.7) | 13.600 (27.9) | 14.600 (32.1) |
| Mean $CL_{ss}$, L/h ($SD_v$) | 36.2 (16.7) | 32.0 (10.8) | 29.5 (8.7) |
| Mean $V_{ss}$, L (CV%) | 346 (21.5) | 303 (26.3) | 275 (21.5) |
| Mean accumulation ratio | 2.26 | 2.08 | 2.14 |

IV to PO studies

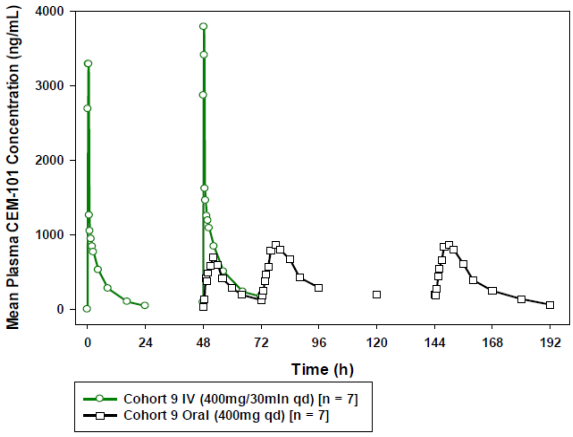
In study 116 after single IV doses of 400, 600 or 800 mg, mean $AUC_{inf}$ values increased more than dose proportionally (8.40 µg•h/mL at 400 mg to 23.85 µg•h/mL at 800 mg). With multiple doses, mean Cmax values on Day 7 were slightly higher vs. Day 1 and ~2-fold accumulation was observed at this dose based on Day7 vs. Day 1 AUCs. There was a trend for lower clearance as dose increased.

**Table 18 Mean PK Parameters for Solithromycin in Plasma, Multiple Doses in Tribuffer #1**

| | Dose Levels, mg (Infusion Time, min) | | |
|---|---|---|---|
| **Mean Parameter** | **200 (30 min)** | **400 (30 min)** | **800 (60 min)** |
| **Day 1** | **N=5** | **N=5** | **N=5** |
| $C_{max}$ (µg/mL) | 1.74 | 4.05 | 5.50 |
| $T_{max}$ (h) (median) | 0.48 | 0.47 | 0.98 |
| $t_{1/2}$ (h) | 3.8 | 5.27 | 6.83 |
| $AUC_{0-24}$ (µg•h/mL) | 2.54 | 7.74 | 25.70 |
| $AUC_{0-t}$ (µg•h/mL) | 2.49 | 7.74 | 25.70 |
| $AUC_{inf}$ (µg•h/mL) | 2.59 | 8.24 | 28.40 |
| CL (L/h) | 77.4 | 53.3 | 28.2 |
| Vz (L) | 424 | 395 | 269 |
| **Day 7** | **N=5** | **N=4** | |
| $C_{max}$ (µg/mL) | 2.07 | 4.39 | n/a |
| $T_{max}$ (h) (median) | 0.33 | 0.42 | n/a |
| $t_{1/2}$ (h) | 5 | 8.38 | n/a |
| $AUC_{0-24}$ (µg•h/mL) | 4.36 | 15.90 | n/a |
| $AUC_{0-t}$ (µg•h/mL) | 4.36 | 17.90 | n/a |
| $AUC_{inf}$ (µg•h/mL) | 4.58 | 18.30 | n/a |
| CL (L/h) | 45 | 23.4 | n/a |
| Vz (L) | 326 | 278 | n/a |

The IV to PO cohort (N=7) finally received 400 mg IV for 3 days followed by 400 mg PO as capsules for 4 days in an open-label fashion. Cmax was higher after IV infusions vs. oral dosing but $AUC_{0-24}$ was similar on Day 3 (IV; 13.00 µg•h/mL) and on Day 4 or Day 7 (oral; 11.4 and 10.9 µg•h/mL, respectively).

Figure 5 Mean Solithromycin Plasma Concentration vs Time Plots, IV to Oral Cohort




In Study 118 Cohort 3 received 400 mg IV on Days 1 to 3, 800 mg orally on Day 4 and 400 mg orally on Days 5 to 7. Cmax on IV dosing was slightly under-estimated due to sampling after rather than at the end of the infusion. Oral dosing was in the fasted state. There was ~2-fold accumulation of solithromycin on Day 3. Following the 800 mg oral dose on Day 4, mean (CV%) Cmax and $AUC_{0-24}$ values were 1701 (27%) ng/mL and 19946 (42%) h·ng/mL, respectively. When the dose was reduced to 400 mg QD on Day 5 onwards, mean (CV%) Cmax, $AUC_{0-24}$ and $t_{1/2}$ values on Day 7 were 1066 (50%) ng/mL, 11874 (59%) h·ng/mL and 7.25 (12%) hours, respectively. The post-steady-state $t_{1/2}$ value was prolonged compared with the value determined on Day 1.

Table 14. IV to Oral Step-down Cohort: Descriptive Statistics of Plasma Solithromycin Pharmacokinetic Parameters (PK Completion Population)

| | IV to Oral Step-down Cohort | | | |
|---|---|---|---|---|
| PK Parameter (unit) | Day 1/400mg IV | Day 3/400mg/IV | Day 4/800mg PO | Day 7/400mg PO |
| $C_{max}$ (ng/mL) | | | | |
| n | 7 | 7 | 7 | 7 |
| Mean (%CV) | 1431 (20%) | 2650 (41%) | 1701 (27%) | 1066 (50%) |
| Median | 1390 | 2690 | 1680 | 798 |
| Min, Max | 1010,1860 | 1370,4490 | 1160,2320 | 676,2060 |
| Geo Mean | 1407 | 2457 | 1650 | 975 |
| $AUC_{24}$ (h·ng/mL) | | | | |
| n | 7 | 7 | 7 | 7 |
| Mean (%CV) | 5736 (21%) | 10822 (23%) | 19946 (42%) | 11874 (59%) |
| Median | 5470 | 10322 | 16659 | 8655 |
| Min, Max | 4641,8261 | 8444,15130 | 11521,35035 | 6376,25696 |

Influence of food

Study 103 compared 400 mg (2×200 mg capsules) oral doses administered under fasted conditions and at 30 min after the start of a meal of ~900 calories (~150/250/500 calories from protein/carbohydrate/fat, respectively). Food had no effect on the plasma profile of solithromycin.

Table 8 Summary of Results for CEM-101 in Plasma

| Pharmacokinetic Parameters | Treatment A (Fasted) Mean ± SD | Treatment B (Fed) Mean ± SD | B/A (Fed vs. Fasted) % MR (90% CI)* |
|---|---|---|---|
| $C_{max}$ (µg/mL) | 0.609 ± 0.235 | 0.633 ± 0.201 | 106.81 (97.56, 116.93) |
| $AUC_{0-t}$ (µg*hr/mL) | 5.470 ± 2.292 | 5.083 ± 1.761 | 97.08 (86.86, 108.50) |
| $AUC_{inf}$ (µg*hr/mL) | 5.614 ± 2.284 | 5.267 ± 1.771 | 97.81 (87.89, 108.85) |
| $AUC_{\%extrap}$ (%) | 3.048 ± 1.571 | 3.770 ± 1.437 | N/A |
| $T_{max}$ (hr) | 3.50 (2.50, 6.00) | 3.50 (2.50, 6.01) | N/A |
| $t_{1/2}$ (hr) | 5.46 ± 0.764 | 5.10 ± 0.668 | N/A |
| $k_{el}$ (1/hr) | 0.129 ± 0.0164 | 0.138 ± 0.0166 | N/A |
| Vd/F (L) | 676.0 ± 356.9 | 610.5 ± 187.4 | N/A |
| CL/F (L/hr) | 88.03 ± 48.94 | 84.35 ± 27.70 | N/A |

## Distribution

After 7 days QD oral dosing (102) mean Vz/F was 1497, 558 and 530 L for 200, 400 and 600 mg doses, respectively. After 400 mg QD IV dosing (121) $V_{ss}$ values were 346 and 303 L with 60 and 30-minute peripheral infusions compared to 275 L when dosing via a PICC. Protein binding of solithromycin has been evaluated in human plasma (81% bound), human serum albumin (46% bound), and α1-acid glycoprotein (8.4% bound) by equilibrium dialysis.

In the ELF study (114), fasting healthy subjects received 400 mg solithromycin (2 × 200 mg capsules) orally once daily for 5 days and were assigned to bronchoscopy at intervals after the last dose. Plasma and BAL urea concentrations were used to determine the ELF volume. The highest estimated ELF and alveolar macrophage (AM) concentrations of solithromycin occurred at 3 and 6 h and were substantially higher than for plasma. AM concentrations were also higher than ELF concentrations.

Table 11 CEM-101 Concentrations in Plasma, ELF, and AM

| Sampling Time | N | Plasma (mg/L) Mean (SD) | ELF (mg/L) Mean (SD) | AM (mg/L) Mean (SD) |
|---|---|---|---|---|
| 3-hours | 6 | 0.730 (0.692) | 7.58 (6.69) | 99.4 (140.8) |
| 6-hours | 6 | 0.595 (0.325) | 6.50 (2.73) | 101.7 (52.6) |
| 9-hours | 6 | 0.301 (0.185) | 3.78 (4.32) | 64.1 (17.2) |
| 12-hours | 6 | 0.300 (0.171) | 2.54 (2.55) | 67.8 (24.6) |
| 24-hours | 6 | 0.086 (0.070) | 1.02 (0.83) | 25.9 (20.3) |

The mean ratios of ELF and AM to simultaneous plasma concentration for CEM-101 during the 24-hour period after drug administration ranged from 8.8 to 14.0 and 132 to 345, respectively. The $AUC_{(0-24)}$ values based on mean and median ELF concentrations were 80.3 and 63.2 mg•h/L, respectively. The ratios of ELF to plasma based on the mean and median $AUC_{(0-24)}$ values were 10.3 and 10.0, respectively. The $AUC_{(0-24)}$ values based on mean and median concentrations in AM and plasma were 1498 and 1282 mg•h/L, respectively. The ratios of AM to plasma based on the mean and median $AUC_{(0-24)}$ values were 193 and 202, respectively.

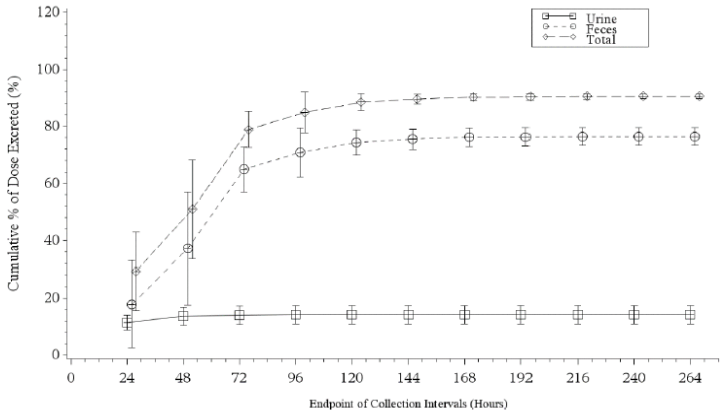
In contrast, concentrations in saliva (microbiological method) were below those in plasma at each time point and reached a maximum of 0.24 mg/L at the 6-hour time point.

In the ADME study (108) the whole blood total radioactivity at the 4, 8 and 24-hour time points was approximately 75% of plasma total radioactivity.

## Excretion

In study 108 subjects received 800 mg (~100 µCi) of $^{[14C]}$-solithromycin. Blood, urine and faecal samples were collected for ≥ 168 hours post-dose. The percent total radioactivity recovered ranged from 89.3 to 91.8%. Overall, 90.6% of the radioactive dose was recovered in urine and faeces, with 76.5% in faeces and 14.1% in urine.

Mean (SD) Cumulative Percent of Dose Excreted in Urine, Feces, and Total, Linear Scale (N = 7)




Note: The curves for cumulative % of dose excreted in feces and total are shifted to the right for ease of reading.
Subject 4 was excluded due to noncompliance.

**Total Radioactivity Excreted and Mass Balance After a Single Oral Administration of 800 mg (~100 µCi) of [$^{14}$C]-Solithromycin Solution (N = 7)**

| | Total Radioactivity in Urine | Total Radioactivity in Feces | Total Radioactivity Recovered |
|---|---|---|---|
| **Pharmacokinetic Parameters** | **Mean ± SD (Median)** | **Mean ± SD (Median)** | **Mean ± SD (Median)** |
| Cum Ae (mg eq) | 110 ± 25.9 (106) | 598 ± 24.7 (603) | 708 ± 6.59 (706) |
| Cum % Dose (%) | 14.1 ± 3.31 (13.6) | 76.5 ± 3.14 (76.5) | 90.6 ± 0.879 (90.7) |

Note: Actual doses in mg eq for each subject were used in the calculation of Cum % Dose.
Subject 4 was excluded due to noncompliance.

## Metabolism

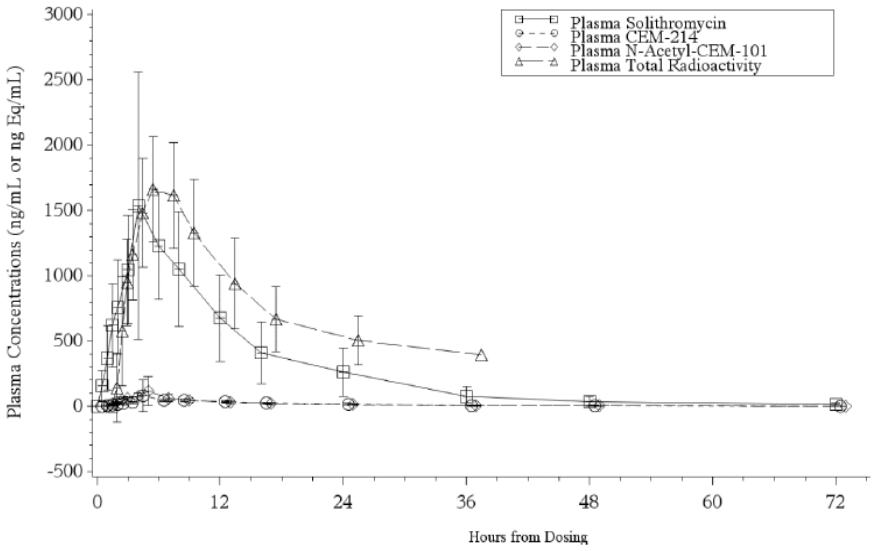
In-vitro studies

Solithromycin at 0.4 and 4 µg/mL was metabolised by approximately 54.6% and 11.5%, respectively, by CYP450 in human microsomes after incubation for 60 minutes. Analysis of metabolism by reaction phenotyping using both chemical inhibitor and recombinant CYP450 approaches indicated that CYP3A4 is likely the major CYP450 enzyme governing the metabolism of solithromycin in humans. In dog, monkey and human hepatocytes there were two potential hydroxylated metabolites of solithromycin detected which increased with time. Aniline was not detected in any of the incubation samples.

In-vivo study (108)

Plasma concentrations of *N*-acetyl-solithromycin and CEM-214 were much lower than those of solithromycin (5.3 and 4.8% of parent drug, respectively, based on $AUC_{0\text{-inf}}$). The plasma half-life of solithromycin and the side chain metabolites was approximately 7.5 hours. The shapes of mean plasma concentration-time plots for solithromycin, *N*-acetyl-solithromycin and CEM-214 and those of plasma total radioactivity were similar through 36 hours post-dose.

**Mean (SD) Plasma Concentrations of Solithromycin, CEM-214 and *N*-Acetyl-CEM-101 and Plasma Total Radioactivity Concentration Equivalents Versus Time, Linear Scale (N = 8)**




**Pharmacokinetic Parameters of Plasma Total Radioactivity**

| | Plasma Total Radioactivity Pharmacokinetic Parameters | | | |
|---|---|---|---|---|
| **Pharmacokinetic Parameters** | **N** | **Mean** | **SD** | **Median** |
| $C_{max}$ (µg equivalents/mL) | 8 | 1.731 | 0.392 | 1.710 |
| $AUC_{0-t}$ (µg equivalents*hr/mL) | 8 | 22.250 | 9.824 | 20.597 |
| $AUC_{0-24}$ (µg equivalents*hr/mL) | 6 | 24.893 | 5.685 | 24.408 |
| $T_{max}$ (hr) | 8 | 4.38 | 1.50 | 4.02 |

**Pharmacokinetic Parameters of Plasma Solithromycin, CEM-214, and *N*-Acetyl-CEM-101**

| | Plasma Solithromycin | | | | Plasma CEM-214 | | | | Plasma *N*-Acetyl-CEM-101 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Pharmacokinetic Parameters** | **N** | **Mean** | **SD** | **Median** | **N** | **Mean** | **SD** | **Median** | **N** | **Mean** | **SD** | **Median** |
| $C_{max}$ (µg/mL) | 8 | 1.665 | 0.959 | 1.570 | 8 | 0.087 | 0.118 | 0.046 | 8 | 0.117 | 0.109 | 0.071 |
| $AUC_{0-t}$ (µg*hr/mL) | 8 | 19.291 | 9.258 | 18.863 | 8 | 0.913 | 0.323 | 0.912 | 8 | 1.012 | 0.410 | 0.966 |
| $AUC_{0-24}$ (µg*hr/mL) | 8 | 16.308 | 6.778 | 17.021 | 8 | 0.740 | 0.236 | 0.698 | 8 | 0.882 | 0.329 | 0.879 |
| $AUC_{0-inf}$ (µg*hr/mL) | 8 | 19.492 | 9.299 | 19.067 | 8 | 0.939 | 0.324 | 0.947 | 8 | 1.032 | 0.415 | 0.980 |
| $T_{max}$ (hr) | 8 | 4.45 | 1.53 | 4.01 | 8 | 6.75 | 1.83 | 8.00 | 8 | 3.38 | 1.06 | 4.00 |
| $T_{1/2}$ (hr) | 8 | 7.82 | 1.30 | 7.26 | 8 | 7.46 | 2.37 | 6.65 | 8 | 7.83 | 1.93 | 7.45 |
| $\lambda_z$ (1/hr) | 8 | 0.0904 | 0.0125 | 0.0954 | 8 | 0.0999 | 0.0257 | 0.104 | 8 | 0.0923 | 0.0179 | 0.0932 |
| $C_{max}$ Ratio[a] | 8 | 98.9 | 66.6 | 78.1 | | | | | | | | |
| $AUC_{0-24}$ Ratio[a] | 6 | 77.2 | 10.3 | 76.4 | | | | | | | | |

Single oral dose of 800 mg (~100 µCi) of [$^{14}$C]-solithromycin solution.
[a]Ratio of solithromycin in plasma to total plasma radioactivity over a 24-hour interval.

- Solithromycin accounted for 60 to 94% (mean 77%) of total radioactivity in plasma through 24 hours post-dose, while *N*-acetyl-solithromycin accounted for 3 to 7% and CEM-214 accounted for 2 to 6%. In addition, carboxyl destriazolyl-phenylamino solithromycin (CEM-262) was present at low levels. No additional major metabolites of solithromycin were present in the plasma samples that would contribute to the total radioactivity AUC.
- Metabolite profiling of urine showed that a peak containing solithromycin and *N*-acetyl-solithromycin was the major radioactive component, accounting for an average of 9.84% of the administered dose and with solithromycin as the major component of this peak. A radioactive metabolite peak with a retention time 26.8 minutes, identified as desmethyl solithromycin, accounted for an average of 0.49% of the administered dose.

- Metabolite profiling of faeces showed that CEM-262 was the major radioactive peak, accounting for an average of 27.36% of the administered dose. A peak containing *N*-formyl solithromycin, parent drug and *N*-acetyl-solithromycin accounted for an average of 19.80% of the administered dose.
- Solithromycin was the major component in this peak. A peak identified as solithromycin *N*-oxide accounted for an average of 7.00% of the administered dose.

**Dose proportionality and time dependency**

In Phase 1 studies solithromycin exposure generally increased in a greater than dose-proportional manner up to a dose of 400 mg and in a dose-proportional manner above 400 mg. After oral dosing (200-600 mg QD) for 7 days, the slope estimates for AUC and $C_{max}$ ranged from 1.60 to 2.25 on Days 1 and 7, suggesting that the PK parameters increased in a more than dose proportional manner. The ratio of $AUC_{\tau}$ on Day 7 vs. $AUC_{inf}$ on Day 1 was 254% (214% after excluding outlying low values), suggesting non-linear kinetics of solithromycin over time for the dose range studied.

**Intra- and inter-individual variability**

The final POPPK model indicated that the inter-individual variability in intrinsic clearance is 44%. Solithromycin exposure is dependent not only on intrinsic clearance but also on PK parameters that define instantaneous clearance as solithromycin concentrations change (i.e. $IC_{50}$, $K_{out}$ and $I_{max}$). The resultant variability in solithromycin PK is relatively high (70 to 80%) in patients with CAP in study 300.

**Pharmacokinetics in target population**

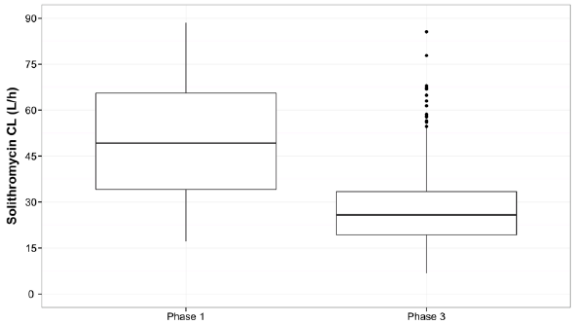
POPPK

Data from 5 Phase 1 studies were pooled with data from the Phase 3 studies in CAP (300 and 301). In the oral CAP Phase 3 study (300) all patients had 4 blood samples collected on Day 4 (pre-dose and at 1, 2 and 4 hours post-dose) and a subset of 40 patients had up to 5 additional samples collected on Day 1 and Day 2. In the IV to PO Phase 3 CAP study (301) all patients had blood samples collected on Day 1 (end-of-infusion, 1 and 4 hours post-infusion) and on the day of oral switch (pre-dose and 1, 2 and 4 hour post-dose) while 45 patients contributed additional samples.

The most robust fit to the data was obtained using a three-compartment model with auto-inhibition of clearance via a hypothetical inhibitory metabolite, and either zero-order drug delivery (IV administration) or a delayed absorption process occurring through multiple transit compartments coupled with an absolute bioavailability term (oral administration). The intra-individual (residual) variability was estimated at less than 0.1 SD of solithromycin concentrations, which indicates a low extent of unexplained variability in the model fit. Three statistically significant relationships were identified between IIV in solithromycin intrinsic clearance and body weight, CrCL and study phase. There were minimal differences in the maximum estimated $AUC_{0\text{-}24}$ across the range of observed body weights and across the CrCL categories, suggesting no requirement for dose adjustment based on these characteristics. However, there were very few patients in the database with CrCL <30 mL/min/1.73 $m^2$ due to the exclusion criteria.

Healthy subjects were predicted to have ~2-fold higher clearance than patients with CAP. While this is a large difference, there was some overlap in the distributions of Bayesian *post hoc* estimates of clearance.

**Figure 17** **Box-and-whisker Plots Showing Distributions of Solithromycin Intrinsic Clearance, Stratified by Study Phase**




The comparison of plasma solithromycin using the final recommended dose regimen is compared between healthy subjects (actual data) and patients with CAP (POPPK estimates) below.

**Table 44** **Geometric Mean (CV%) Solithromycin PK Parameters**

| Study | Dose (mg)/ Route/ Day(s) | $C_{max}$ (µg/mL) | $AUC_{0-24}$ (µg•h/mL) | $T_{1/2}$ [a] (h) | CL (L/h) | $V_{ss}$ (L) |
|---|---|---|---|---|---|---|
| CE01-115 [a] | 800 / Oral / 1 | 0.897 (65.9) | 9.990 (59.4) | NC | NC | NC |
| | 400 / Oral / 5 | 0.857 (54.8) | 9.850 (65.5) | 8.98 (8.76) | 33.4 (85.3) | 433 (81) |
| CE01-118 [a, d] | 400 / IV / 1 | 1.43 (20.0) | 5.74 (20.9) | 4.54 (9.17) | 69.7 (17.3) | 454 (16.8) |
| | 800 / Oral / 4 | 1.70 (26.9) | 19.9 (41.7) | NC | NC | NC |
| | 400 / Oral / 7 | 1.07 (49.9) | 11.9 (59.1) | 7.25 (12.0) | NC | NC |
| CE01-121 [a, c] | 400 / IV / 1 | 3.200 (40.3) | 5.930 (31.6) | ND | NC | NC |
| | 400 / IV / 7 | 4.200 (11.4) | 13.600 (27.9) | 8.04 | 32.0 (10.8) | 303 (26.3) |
| CE01-300 [a, e, f] | 800 / Oral / 1 | 1.54 (70.2) | 18.9 (71.8) | 9.58 (28.4) | 41.8 (76.6) | 388 (63.7) |
| | 400 / Oral / 4 | 1.05 (73.6) | 12.6 (80.5) | 10.5 (32.9) | 31.7 (80.0) | 387 (64.2) |
| CE01-301 [a, f, g] | 400 / IV / 1 | 3.08 (35.1) | 21.5 (43.8) | 10.1 (27.0) | 22.8 (47.8) | 215 (24.1) |
| | 800 / Oral / 2-7 [h] | 2.20 (54.0) | 26.9 (62.4) | 10.2 (32.2) | 30.1 (61.7) | 349 (48.2) |

a PK parameters for CE01-115, CE01-118, and CE01-121 derived using noncompartmental methods; values for CE01-300 and CE01-301 are derived from the fit of the pooled population PK model.
b $V_z$ CE01-118, $V_{ss}$ for CE01-115, CE01-121, CE01-300, and CE01-301
c CE01-121, Cohort 2 (n=10): 400 mg IV over 30 min QD for 7 days
d CE01-118, Cohort 3 (PK Completion Cohort, n=7): 400 mg IV over 30 min QD for 3 days followed by 800 mg oral on Day 4 and 400 mg oral QD on Days 5-7
e CE01-300 (n=386 and 368 on Days 1 and 4, respectively): 800 mg oral on Day 1 followed by 400 mg oral QD on Days 2 - 5; most patients received more than 1 dose in the first 24-hour period.
f CL and $T_{1/2}$ derived using noncompartmental methods applied to the fitted solithromycin concentration-time profile for each patient. $V_{ss}$ derived as $V_c + V_{p1} + V_{p2}$. CL and $V_{ss}$ are conditioned on F for the values reported while on oral solithromycin.
g CE01-301 (n=405 and 280 following IV and oral , respectively): 400 mg IV over 30 min QD followed by 800 mg oral ×1 and 400 mg oral QD for the remainder of the 7-day treatment regimen.; most patients received more than 1 dose in the first 24-hour period.
h Parameters derived from the first day of oral dosing (Days 2 - 7) in subjects who received at least 1 oral dose.

Using the POPPK-predicted values the absolute bioavailability was estimated in 280 CAP patients in the IV to PO switch study (301; 400 mg IV until oral switch to 800 mg and then 400 mg QD). The mean (CV%) estimate of absolute bioavailability was 66.3% (32.7% CV), which is consistent with that observed in study 104 in healthy subjects.

**Table 39 Summary Statistics for Individual, Model-derived Solithromycin Plasma Exposure and Secondary PK Parameters (CE01-301)**

| Parameter | Geometric Mean (CV%) | |
|---|---|---|
| | Solithromycin 400 mg IV (n=405) [a] | Solithromycin 800 mg first oral dose (n=280) [b] |
| Absolute bioavailability [c] | - | 0.663 (32.7) |
| $AUC_{0-24}$ µg•h/mL | 21.5 (43.8) | 26.9 (62.4) |
| $C_{max}$ (µg/mL) | 3.08 (35.1) | 2.20 (54.0) |
| $T_{max}$ (h) [d] | 1 (1 - 2) | 3.58 (1.17 - 8.25) |
| CLav (L/h) [e] | 22.8 (47.8) | 30.1 (61.7) |
| $V_{ss}$ (L) [e] | 215 (24.1) | 349 (48.2) |
| $T_{1/2}$ (h) [e] | 10.1 (27.0) | 10.2 (32.2) |

Source: ICPD 00379-2 Table 7

a. Parameters derived from data collected on Day 1 of the study.
b. Parameters derived from the first day of oral dosing (Days 2 - 7) in subjects who received at least 1 oral dose.
c. Absolute bioavailability derived from the population PK model and summarized as arithmetic mean (CV%) as the individual estimates do not conform to a log-normal distribution.
d. $T_{max}$ is summarized using median (min. - max.).
e. CLav and $T_{1/2}$ derived using non-compartmental methods applied to the fitted solithromycin concentration-time profile for each patient. $V_{ss}$ is derived from the population PK model as the sum of the 3 volumes of distribution ($V_c + V_{p1} + V_{p2}$). CLav and $V_{ss}$ are conditioned on F for the values reported while on oral solithromycin.

In the oral Phase 3 CAP study, 2 batches of solithromycin capsules were utilized, with each batch produced by a different manufacturer. Estimates of predicted PK parameters on Days 1 and 4 for the PK population are shown below.

**Table 38 Summary Statistics for Individual, Model-derived Solithromycin Plasma Exposure and Secondary PK Parameters on Days 1 and 4 for Patients from CE01-300 Included in the PK Population**

| Parameter | Geometric Mean (CV%) or Median (min. - max.) | |
|---|---|---|
| | Day 1 (800 mg) (n=386) | Day 4 (400 mg) (n=368) [a] |
| $AUC_{0-24}$ (µg•h/mL) | 18.9 (71.8) | 12.6 (80.5) |
| $C_{max}$ (µg/mL) | 1.54 (70.2) | 1.05 (73.6) |
| $T_{max}$ (h) [b] | 3.5 (1 - 14.5) | 3.5 (1.17 - 7.5) |
| CLav (L/h) [c] | 41.8 (76.6) | 31.7 (80) |
| $V_{ss}$ (L) [c] | 388 (63.7) | 387 (64.2) |
| $T_{1/2}$ (h) [c] | 9.58 (28.4) | 10.5 (32.9) |

Source: ICPD 00379-2 Table 6

a. 18 patients did not receive solithromycin dose on Day 4, and these 18 patients were excluded for solithromycin Day 4 exposure and secondary PK parameters calculation.
b. $T_{max}$ is summarized using median (min. – max.).
c. CLav and $T_{1/2}$ derived using non-compartmental methods applied to the fitted solithromycin concentration-time profile for each patient. $V_{ss}$ is derived from the population PK model as the sum of the 3 volumes of distribution ($V_c + V_{p1} + V_{p2}$). CLav and $V_{ss}$ are conditioned on F for the values reported while on oral solithromycin.

The dataset of 386 patients who received 800 mg on Day 1 included 56 who received capsules from one batch and 330 who received capsules from another batch. Mean Cmax and $AUC_{0-24}$ were similar after dosing with each of the 2 batches utilized in the study. The CV% of solithromycin Cmax and $AUC_{0-24}$ on Day 1 were > 40% for both batches. The LSM GMRs for these parameters were close to 1.0.

**Impaired renal function**

Study 115 evaluated the PK and protein binding of solithromycin after oral administration of 800 mg on Day 1 followed by 400 mg on Days 2 to 5 in:
**Group A:** eGFRMDRD ≥90 mL/minute/1.73m$^2$ approximately matched to renally impaired subjects for ±20 years of age, ±20% weight, race and gender.
**Group B**: eGFRMDRD <30 mL/minute/1.73m$^2$ and not on dialysis
**Group C**: eGFRMDRD 30-59 mL/minute/1.73m$^2$

The solithromycin GM Cmax following an 800 mg dose on Day 1 was 1.8-fold higher in subjects with severe renal impairment (B) vs. controls, with a similar ratio on Day 5 following a 400 mg dose. The GM $AUC_{0-24}$ was 1.9-fold higher on Day 1 and 2.2-fold higher on Day 5. The differences between Groups C and A on Days 1 and Day 5 were less notable.

| Geometric Mean (CV%) for Plasma PK Parameters for Solithromycin | | | |
|---|---|---|---|
| Parameter | Normal Renal Function N=9 | Severely Reduced Renal Function N=8 | Moderately Reduced Renal Function N=8 |
| **Day 1** | | | |
| $T_{max}$ (h) | 3.9 (37) | 4.8 (28.3) | 4.03 (29.9) |
| $C_{max}$ (ng/mL) | 897 (65.9) | 1600 (41.9) | 1020 (72.9) |
| $T_{last}$ (h) | 24 (0.129) | 24 (0.113) | 24 (-) |
| $C_{last}$ (ng/mL) | 188 (77.8) | 381 (73.6) | 202 (101) |
| $AUC_{0-24}$ (ng*h/mL) | 9990 (59.4) | 18900 (48.5) | 10900 (74) |
| **Day 5** | | | |
| $T_{max}$ (h) | 3.49 (39.8) | 3.43 (35.2) | 4.09 (34.5) |
| $C_{max}$ (ng/mL) | 857 (54.8) | 1530 (55) | 1040 (58) |
| $T_{last}$ (h) | 46.5 (8.57) | 48 (0) | 40.4 (26.5) |
| $C_{last}$ (ng/mL) | 29.6 (77.9) | 119 (100) | 81 (144) |
| λz (1/h) | 0.0772 (9.91) | 0.0511 (30.8) | 0.0665 (38.4) |
| $T_{1/2}$ (h) | 8.98 (8.76) | 13.6 (29) | 10.4 (42.4) |
| $AUC_{0-24}$ (ng*h/mL) | 9850 (65.5) | 19700 (68.8) | 12600 (75) |
| $AUC_{0-t}$ (ng*h/mL) | 11600 (68.1) | 25800 (72.8) | 15400 (87.5) |
| CLss/F (L/h) | 33.4 (85.3) | 13.9 (81) | 29.7 (125) [a] |
| Vss/F (L) | 433 (81) | 273 (63.7) | 402 (138) [a] |
| Rac | 1.97 (143) | 2.09 (45.3) | 2.31 (38.2) |
| a. n=7 | | | |

In severe renal impairment the mean apparent total clearance of solithromycin was reduced by 60% and the mean renal clearance was reduced by 70% compared to normal subjects. In subjects with moderately reduced renal function, the corresponding reductions were by 10% and 40%. Based on GM dose normalised $AUC_{(0-24)}$ after 5 days of dosing, accumulation was approximately 2-fold in normal subjects (as expected), with comparable accumulation in subjects with moderate (2.3-fold) and severe (2.1-fold) renal impairment. The metabolites demonstrated increased plasma levels in subjects with moderately and severely reduced renal function as compared to those with normal renal function.

| Analyte | Ratio of $C_{max}$ | | Ratio of $AUC_{0-t}$ | |
|---|---|---|---|---|
| | Day 1 | Day 5 | Day 1 | Day 5 |
| **Severe (Group B) to Normal (Group A)** | | | | |
| CEM-101 | 1.78 | 1.79 | 1.89 | 2.22 |
| N-acetyl-CEM-101 | 1.80 | 2.03 | 1.93 | 2.61 |
| CEM-214 | 1.81 | 2.88 | 2.02 | 4.08 |
| **Moderate (Group C) to Normal (Group A)** | | | | |
| CEM-101 | 1.14 | 1.21 | 1.09 | 1.33 |
| N-acetyl-CEM-101 | 1.14 | 1.29 | 1.08 | 1.45 |
| CEM-214 | 1.13 | 1.59 | 1.14 | 1.75 |

| Geometric Mean (CV%) of Urine PK Parameters for Solithromycin | | | |
|---|---|---|---|
| Parameter | Normal Renal Function N=9 | Severely Reduced Renal Function N=8 | Moderately Reduced Renal Function N=8 |
| **Day 1** | | | |
| Cum Ae (mg) | 71.1 (39.6) | 35.1 (62.9) | 44 (49.7) |
| Fe (%) | 8.88 (39.5) | 4.38 (62.9) | 5.5 (49.7) |
| CLr/F (L/h) | 7.11 (40.5) | 1.86 (57.7) | 4.04 (65.2) |
| **Day 5** | | | |
| Cum Ae (mg) | 55 (43.7) | 28.4 (70.7) | 47.1 (60.2) |
| Fe (%) | 13.8 (43.6) | 7.1 (70.7) | 11.8 (60.1) |
| CLr/F (L/h) | 5.91 (38.5) | 1.62 (65.8) | 3.75 (32) |

Protein binding was assessed by equilibrium dialysis for 50/802 samples. Binding was 81.7% ± 4.16%, 85.8% ± 1.83% and 81.7% ± 2.70% in subjects with normal, moderately impaired and severely impaired

renal function, respectively, indicating that solithromycin is moderately bound to human plasma proteins. Taking standard deviation into account, renal function did not impact plasma protein binding. There was no significant difference in the binding ratios within each subject on Days 1 and 5.

**Impaired hepatic function**

Study 113 compared PK between C-P A, B and C subjects and matched controls (Group D) on dosing with 800 mg on Day 1 and 400 mg on Days 2-5. The Day 5 results showed lower variability in PK parameters vs. Day 1 but %CV was still 55–104%. $AUC_{0\text{-}tau}$ appeared to decrease with increasing degree of hepatic impairment.

**Summary of Statistical Comparisons of Plasma Solithromycin Pharmacokinetic Parameters, Day 5**

| | | Geometric LS Means | | Geometric Mean Ratio (%) (test/reference) | 90% Confidence Interval | Intra-subject %CV |
|---|---|---|---|---|---|---|
| Comparison | Parameter | Test Group | Reference Group | | | |
| Group A vs. Group D | $C_{max}$ (ng/mL) | 785.957 | 649.126 | 121.08 | 64.38 - 227.71 | 85.78 |
| | $AUC_{0\text{-}t}$ (ng*hr/mL) | 8872.658 | 7554.940 | 117.44 | 56.64 - 243.50 | 104.18 |
| | $AUC_{0\text{-}tau}$ (ng*hr/mL) | 7900.103 | 10491.88 | 75.30 | 47.89 - 118.39 | 54.92 |
| Group B vs. Group D | $C_{max}$ (ng/mL) | 683.897 | 649.126 | 105.36 | 56.02 - 198.14 | 85.78 |
| | $AUC_{0\text{-}t}$ (ng*hr/mL) | 8902.279 | 7554.940 | 117.83 | 56.83 - 244.31 | 104.18 |
| | $AUC_{0\text{-}tau}$ (ng*hr/mL) | 7509.789 | 10491.88 | 71.58 | 45.52 - 112.55 | 54.92 |
| Group C vs. Group D | $C_{max}$ (ng/mL) | 504.311 | 649.126 | 77.69 | 41.31 - 146.11 | 85.78 |
| | $AUC_{0\text{-}t}$ (ng*hr/mL) | 8306.315 | 7554.940 | 109.95 | 53.03 - 227.95 | 104.18 |
| | $AUC_{0\text{-}tau}$ (ng*hr/mL) | 6175.788 | 10491.88 | 58.86 | 37.44 - 92.55 | 54.92 |

Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LS Means) are calculated by exponentiating the LSMEANS from the ANOVA.
% Geometric Mean Ratio = 100*(test/reference)

Protein binding of solithromycin at 4 hours post-dose was slightly lower for subjects with moderate and severe hepatic impairment. The decrease in mean %protein bound for the severe impairment vs. control group was approximately 14% on Day 1 (from 74% to 60%) and 9% on Day 5 (from 71% to 62%).

**Table 12 Arithmetic Mean (SD) Unbound and Total Plasma Solithromycin Concentrations (ng/mL) and Percentage of Protein Bound Solithromycin, Day 1**

| Protein Binding Parameters | Group A Mean ± SD (N=8) | Group B Mean ± SD (N=8) | Group C Mean ± SD (N=8) | Group D Mean ± SD (N=8) |
|---|---|---|---|---|
| C (A) (ng/mL) | 306.0 ± 234.63 | 202.8 ± 124.11 | 227.9 ± 164.30 | 411.8 ± 282.26 |
| C (B) (ng/mL) | 96.33 ± 50.078 | 74.96 ± 32.272 | 79.54 ± 39.494 | 100.2 ± 59.040 |
| % Plasma Protein Binding (%) | 71.22 ± 6.8230 | 67.07 ± 1.8870 | 60.17 ± 8.2895 | 73.92 ± 4.5518 |

C(A) = Total concentration in the plasma side (total)
C(B) = Total concentration in the receiver side (unbound)

The urinary excretion of solithromycin over 24 hours on Days 1 and 5 was highly variable but there were no apparent trends with the degree of hepatic impairment. Approximately 8.8 to 11.8% of the dose was recovered in urine over 24 hours post-dose on Day 5 and CrCL was generally similar on Days 1 and 5 within each cohort.

On Day 1 the $AUC_{tau}$ for N-Acetyl-solithromycin ranged from 5.3% to 20.7% of parent exposure and increased with the degree of hepatic impairment. On Day 5 the comparison between those with severe hepatic impairment and controls gave LSM ratios for Cmax and $AUC_{0\text{-}tau}$ of 220.6% and 289.6%, respectively, with 90% CIs > 100%.

The $AUC_{tau}$ for CEM-214 was ≤4.5% of parent exposure in all groups. For those with moderate hepatic impairment, the Day 5 LSM ratios for Cmax and $AUC_{0\text{-}tau}$ were 75.8% and 53.9%, respectively, and the 90% CI was completely below 100% for the latter. For those with severe hepatic impairment, the LSM ratios for Cmax and $AUC_{0\text{-}tau}$ were 48.5% and 38.5%, respectively, and the 90% CIs were completely below 100%.

**Gender**

In the pooled POPPK analysis 52.9% of subjects were male and 47.1% female. Gender was not a significant predictor of IIV in solithromycin PK but it was a significant predictor of elevated ALT in the PK/PD analysis for safety. Males had higher ALT on average than females regardless of the values of other variables retained in the model but simulations carried out to evaluate differences in ALT elevation endpoints for different solithromycin dosing regimens failed to demonstrate differences by gender.

**Race**

The majority (~80%) of patients with CAP included in the POPPK analysis were Caucasian. Asian race was a significant predictor of elevated ALT in the in the PK/PD analysis for safety but the lack of a significant interaction between solithromycin AUC and race suggested that the influence of solithromycin AUC on ALT was not different by race.

**Weight**

BMI and BSA were significant predictors of the variability in solithromycin PK but the relationship between body weight and intrinsic clearance had minimal impact on solithromycin plasma exposure. BMI ≥30 kg/m2 was identified as predictive of elevated ALT in the PK/PD analysis for safety but patients with higher BMI were also more likely to experience lower solithromycin exposures and it was concluded that they were unlikely to be at increased risk of elevations in ALT secondary to solithromycin dosing.

**Age**

In the pooled POPPK analysis, which included patients aged from 18 to 94 years, age was not a significant independent predictor of the IIV in solithromycin PK. This application is for adults only. Limited PK data from adolescents dosed orally showed lower exposures vs. adults but large IIV.

**Interactions**

<u>In-vitro studies</u>

- In pooled human liver microsomes showed that solithromycin 40 μM did not significantly inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, 2C19 and CYP2D6. There was inhibition of CYP3A4 that was time-dependent, concentration-dependent and NADPH-dependent suggesting mechanism-based inhibition of CYP3A4. Solithromycin was also considered to possibly cause clinically significant inhibition of CYP2C8 and CYP2D6.
- Solithromycin 12 μg/mL had a low potential for induction of CYP1A2, CYP2B6, CYP2C9 and CYP3A4. CYP2C9 mRNA levels showed an increase at ≥40% of positive control induction for some solithromycin samples but the increase was not dose dependent and was not considered significant.
- Solithromycin showed potential to inhibit the efflux transporter P-gp to a clinically significant extent in both P-gp expressing vesicles and through bi-directional transport of digoxin across Caco-2 cells as well as MDCKII-MDR1 cells. In transporter inhibition studies, solithromycin inhibited OATP1B3-mediated substrate transport with an $IC_{50}$ value of 23 μM, which is not anticipated to be relevant at therapeutic concentrations. Solithromycin did not significantly inhibit other efflux or uptake transporters including BSEP, BCRP, OATP1B1, OCT1, OCT2, OAT1 and OAT3.

In-vivo studies

*CYP3A inhibition by ketoconazole (107)*
Fasting subjects received solithromycin 400 mg (2×200 mg capsules) on Day 1, ketoconazole 400 mg once daily on Days 7 through 10 and both agents together on Day 11. Solithromycin plasma concentrations were substantially higher on co-administration. Cmax increased 1.6-fold (56%) with 90% CI 1.39-1.76 while $AUC_{inf}$ increased by 2.6-fold (155%) with 90% CI 2.24-2.91.
Changes in *N*-acetyl-solithromycin PK were proportional to parent drug concentration changes and were considered likely due to changes in parent drug kinetics, since ketoconazole is not known to affect N-acetylation. Formation of the metabolite CEM-214 was decreased by ketoconazole.

A population-based PK (PBPK) model was constructed based on in-vitro and in-vivo data in an attempt to understand the possible consequences of concomitant administration of a CYP3A4 inhibitor with solithromycin in patients with severe renal impairment. The predicted exposure of solithromycin after a single oral dose of 400 mg co-administered with ketoconazole was consistent with the observed data in study 107 shown above (AUC ratios 2.48 and 2.55). The PBPK model was then used to simulate the exposure of solithromycin in subjects with normal or impaired renal function. Simulated exposures were reasonably consistent with clinical data. The reduction in renal clearance relative to the steady state oral clearance of solithromycin was predicted with reasonable accuracy in subjects with normal, moderate and severe renal function. Simulations in all 3 groups suggested that less than 5% of active CYP3A4 remained in the gut and liver following multiple dosing of solithromycin. For multiple dose co-administrations the model predicted a 1.25-fold increase in solithromycin AUC in subjects with normal renal function and a 1.12-fold increase for those with moderate or severe impairment. It was concluded that there is no significant change in the kinetics of solithromycin following multiple dosing with a CYP3A4 inhibitor in subjects with moderate or severe renal impairment so that no further dose adjustment is required solely due to co-administration.

*CYP3A induction by rifampicin (110)*
Fasting subjects received treatments as shown in the table and using solithromycin 200 mg capsules.

| Days | Dosing Duration | Study Drug Administration (PO) |
|---|---|---|
| **Dosing Regimen 1** | | |
| Day 1 | 1 day | Solithromycin 800 (4×200) mg QD |
| Days 2-5 | 4 days | Solithromycin 400 (2×200) mg QD |
| ***7 DAY WASHOUT*** | | |
| **Dosing Regimen 2** | | |
| Days 1-6 | 6 days | Rifampin 600 (2×300) mg QD |
| Day 7 | 1 day | Rifampin 600 (2×300) mg QD<br>Solithromycin 800 (4×200) mg QD |
| Days 8-11 | 4 days | Rifampin 600 (2×300) mg QD<br>Solithromycin 400 (2×200) mg QD |
| Days 12-13 | 2 days | Rifampin 600 (2×300) mg QD |

Co-administration with rifampicin decreased the solithromycin GM Cmax by 97.4% after the 800 mg single dose and by 98.2% after 4 additional days of 400 mg dosing. Similarly, the GM $AUC_{inf}$ was decreased by 98.8% and AUCτ was decreased by 99.3% at respective time points with decreases in median half-life of 54% and 53%. Correspondingly, solithromycin CL and Vd increased on co-administration with rifampicin, indicating that as rifampicin induced the gastrointestinal and hepatic CYP3A4 metabolic pathways there was a significant increase in first-pass metabolism of solithromycin, resulting in a decrease in its bioavailability.

**Table 13** **Geometric Mean Ratios and 90% CIs Comparing Solithromycin 400 mg Steady State PK Parameters on Dosing Regimen 1 (Solithromycin 800/400 mg) versus Dosing Regimen 2 (Solithromycin 800/400 mg+Rifampin)**

| Parameter | Geometric Mean | | Geometric Mean Ratio | 90% CI |
|---|---|---|---|---|
| | Solithromycin 400 mg [a] | Solithromycin 400 mg [b] + Rifampin | | |
| $C_{max}$, µg/mL | 1.12 | 0.0233 | 0.0180 | 0.0143, 0.0228 |
| $AUC_{\tau}$, µg*hr/mL | 15.3 | 0.199 | 0.00729 | 0.00553, 0.00962 |
| $AUC_{last}$, µg*hr/mL | 15.2 | 0.0743 | 0.00390 | 0.00254, 0.00600 |

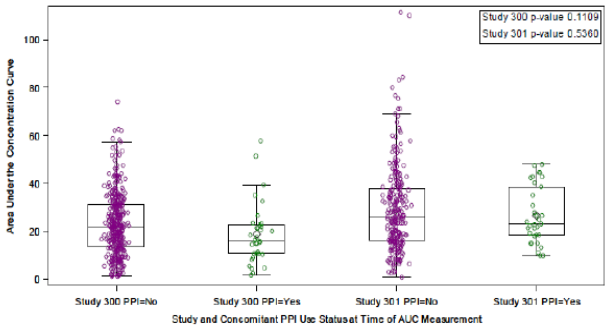
a. Solithromycin 400 mg steady state on Day 5 of Dosing Regimen 1
b. Solithromycin 400 mg steady state+rifampin on Day 11 of Dosing Regimen 2

*N*-acetyl-solithromycin and CEM-214 plasma concentrations decreased on co-administration. The *N*-acetyl-solithromycin vs. parent AUC ratio increased by 6 to 8-fold and the CEM-214 vs. parent ratio increased 1.3 to 1.7-fold.

*Effect of pH modifiers on solithromycin*

Due the marked effect of increasing pH on the solubility of solithromycin the applicant conducted an analysis across the two Phase 3 studies to examine co-administration with PPIs. The distribution of solithromycin AUCs in individuals who were or were not taking PPIs on sampling days were comparable with median values, suggesting no important effect of concomitant PPIs on solithromycin exposure.

**Figure 20** **AUC by Concomitant PPI Use in Solithromycin Patients (Phase 3 CABP Studies) - Safety Patients with AUC Measurements**




Source: Ad-hoc analysis from CE01-300 and CE01-301 (program: AUC_FAA_B1_01.sas)
Notes: PPI was considered concomitant if the PPI was taken on a day which plasma concentration measurements were taken during oral study drug administration
The AUC measurement corresponds to the first day on which plasma concentration was assessed during oral drug administration for a patient or the first day on which plasma concentration was assessed and a PPI was administered.
P-values are generated from an ANCOVA model including PPI usage (Y/N) and day of plasma concentration assessment as fixed effects

*Effect of solithromycin on midazolam (106)*

Fasting subjects received oral dosing with midazolam (single 0.75 mg doses as syrup) and solithromycin regimens with and without an 800 mg loading dose on the first day. Solithromycin significantly decreased the clearance of midazolam, resulting in increased midazolam plasma concentrations and exposures, with a greater effect when solithromycin was dosed to steady state. The effects of solithromycin on midazolam $AUC_{inf}$ were much greater (increases by 3.1 and 4.9-fold after single doses and 9.0-fold for co-administration at solithromycin steady state) than the effects on Cmax (1.18-fold, 1.24-fold and 2.5-fold under respective conditions). The midazolam $t_{1/2}$ was also prolonged. There was no difference in effects of the two solithromycin regimens at steady state on midazolam, reflecting lack of difference between regimens in solithromycin $AUC_{inf}$ on Day 7.

*Effect of solithromycin on digoxin (122)*

Fasting subjects received digoxin on Days 1 (1 mg) to 5 (0.125 mg QD days 2-5) and both digoxin (0.125 mg QD) and solithromycin on Days 6 (800 mg) to 10 (400 mg QD). Plasma digoxin AUC and Cmax were higher following co-administration of solithromycin with increases by ~38% and ~46%, respectively (Day 10 vs. Day 5). The GMRs for Day 6 vs. Day 5 showed that the digoxin $AUC_{0\text{-}tau}$ and Cmax increased by ~26% and ~30%, respectively. The comparison between Days 6 and 10 showed that the 90% CIs for

GMRs of $AUC_{0\text{-}tau}$ and Cmax were within 80 - 125%, suggesting similar effects of solithromycin loading and steady state dosing on digoxin PK and a lack of significant accumulation of digoxin during daily concomitant dosing.

***Comment on pharmacokinetics***

General features of the pharmacokinetics of solithromycin

The mass balance study showed that elimination of solithromycin is mainly through metabolism and excretion in faeces, with ~10 to 20% eliminated unchanged in the urine. CYP 3A4 is proposed to be the main enzyme responsible for metabolism but this is predicted to be inhibited by solithromycin at steady state so that it is not clear which enzyme(s) is/are involved in elimination of parent drug at steady state. In plasma the *N*-Acetyl-solithromycin and CEM-214 [formed by oxidative loss of triazolyl-phenylamino] metabolites each accounted for <10% of systemic radioactivity. However, the LLOQ for radioactivity is high (562 ng/ml equivalents) and it is not clear if an adequate proportion of the AUC of total radioactivity has been profiled or if there are any persistent metabolites which may significantly contribute to the AUC. Based on the mass balance study the applicant states that ~74% of the oral dose (derived from radioactivity) was excreted in faeces. In the faeces, solithromycin, *N*-formyl-CEM-101 and *N*-Acetyl-CEM-101 were not separable by HPLC but LC/MS intensity ratios suggested that approximately 14% of the radioactivity was associated with parent drug. Since rat and monkey data indicated that solithromycin is not eliminated unchanged in the bile, then if the same is true in humans the applicant concludes that solithromycin in faeces would be unabsorbed drug, giving an estimate of 86% for total dose absorption.

However, the absolute bioavailability of solithromycin after oral dosing appears to be ~ 67%. The difference vs. the estimated total absorption is proposed to reflect first pass metabolism, mainly by CYP3A4 in the liver and intestine. Tied into this mechanism is the observation that solithromycin exposure after oral dosing increased in a greater than dose-proportional manner up to ~400 mg and generally in a dose-proportional manner from 400 to 1200 mg. This is proposed to reflect auto-inhibition of CYP3A4 and also possibly the impact of P-gp on solithromycin absorption from the gut at low doses that is overcome at therapeutic doses due to P-gp inhibition by solithromycin. As a result, repeat oral dosing for 7 days at 400 mg/day gave ~2-fold accumulation of solithromycin in plasma by Day 7.

The time dependency of solithromycin PK that was observed following repeated oral dosing is important for understanding the proposed auto-inhibition of CYP 3A4-mediated metabolism. In the multiple dose studies data are provided for Days 1 and 7 with a comment that Cmax is similar between Day 4 and Day 7. This should be further addressed with a focus on change in Cmin over time and it should be considered whether the data can help inform the Ki estimate in the POPPK model.

In contrast to oral dosing, repeat IV dosing resulted in dose-proportional increases in plasma exposures from 25 to 200 mg and a greater than dose-proportional increase from 200 to 1000 mg. This supports a conclusion that the lack of linearity during oral dosing reflected inhibition and then saturation of gut P-gp.

As would be expected from this type of molecule, solithromycin has a large volume of distribution (~400 L) and the ELF study indicated high concentrations in ELF (~10 x plasma) and AM (~200 x plasma) after 5 days oral dosing with 400 mg QD.

It was shown that food (high kcal/high fat) does not have an important effect on the rate or extent of absorption of solithromycin. In Phase 3 studies solithromycin was taken without regard to meals.

The applicant acknowledges that inter-individual variability (IIV) is high, being ~25-85% following oral administration and ~15-60% following IV administration. The various factors that may be contributing to this variability and the clinical implications have not been adequately discussed. For example, to what extent variability in CYP3A4 levels may contribute and the fact that *N*-acetylation of parent drug to form

*N*-acetyl-solithromycin would be expected to vary between slow and fast acetylators have not been discussed in the dossier.

Special populations

The impact of age on pharmacokinetics has not been adequately discussed. It is stated not to be an important covariate in the POPPK model but CrCL, which is a factor in the elderly, is included in the model. The applicant should provide a summary of PK data for age sub-groups 65-74, 75-84 and >84 years.

The possible impact of the increased levels of active metabolites in patients with renal impairment is not clear and should be further addressed.

POPPK model

The validity and reliability of the POPPK model that included the PK data from the Phase 3 CAP patients is especially important in this application since the indications for use of the solithromycin dose regimen for treatment of lung infections due to *B. anthracis* and *F. tularensis* rely on knowledge of the relationship between plasma levels in humans and macaques. Considering this high regulatory impact there are several aspects of the model that need to be addressed and/or require further discussion. These include:

- The impact of ignoring the BLQ values, rather than utilising them (e.g. the M3 method)
- Values for shrinkage of parameters should be reported as this could impact the graphical exploration of covariates
- The final model does not include non-linearity on F or clearance and shows mis-specification for high plasma concentrations (>4 mg/l)
- There are some relatively large differences in values (e.g. the exponent for weight on clearance, differences between healthy volunteers and patients, clearance and Ki values) and an issue of identifiability between the latter two parameters between the original POPPK model and the second model built on intravenous data. The applicant should further support the values in the final model possibly with mechanistic support from clinical studies to support the Ki value.
- The selection of covariates is not adequately supported. For example, the exponent for weight is 0.589 rather than that expected for allometry (0.75) and the impact of shrinkage on the analysis of covariates other than clearance. Plots of ETA clearance versus all important covariates from the final model (including weight, age, CrCL and time since first dose) should be provided.
- Individual plots appear to show a poorer fit to the data following later doses, with under prediction of Cmax in some subjects but a marked over-prediction in others. It is not clear if the Ki and the variability in this parameter are adequately captured in the model.
- An explanation for the difference in clearance between healthy volunteers and patients is required.

Potential for drug-drug-interactions

The applicant's approach to the investigation of DDIs with solithromycin parent drug seems to have been rather minimalistic. The applicant also takes a minimalist approach to the SmPC and proposes only one contraindication: Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. In contrast, in the Ketek SmPC, the DDI-related contraindications include ergot alkaloid derivatives (risk of ergotism noted with other macrolides), HMG CoA reductase inhibitors (simvastatin, atorvastatin and lovastatin) and colchicine (inhibition of CYP3A4). In patients with severely impaired renal and/or hepatic function use of telithromycin with strong CYP3A4 inhibitors is contraindicated. Finally, use with medicinal products that prolong the QT interval and are CYP3A4 substrates is contraindicated.

*Solithromycin as a victim*

Solithromycin is a substrate of CYP3A4 and P-gp. Solithromycin was not found to be a substrate of other CYP isoenzymes tested but it seems that the applicant has not determined whether it is a substrate of other transporters. Since it is mainly eliminated via the liver it should be reported whether it is a substrate of OATP1B1/3 and it is also relevant to understand if it is a substrate of BCRP. It should also be noted that it is not known if the main pharmacologically active human metabolites of solithromycin could interact with CYP isoenzymes or transporters although their plasma levels are <10% of those of parent drug. These omissions must be addressed or further justified.

The effect of steady state ketoconazole on a single 400 mg dose of solithromycin was studied. Since solithromycin is itself an inhibitor of CYP3A4 the interaction study with ketoconazole should have been conducted with co-administration sufficient for both agents to reach steady state.

The total effect of ketoconazole on a single dose of solithromycin reflects the fact that ketoconazole inhibits CYP3A4 and P-gp and it is possible it could also reflect in part inhibition of OATP1B1 (since it is unknown if solithromycin is a substrate for this transporter). The overall effect of ketoconazole on solithromycin was a 1.6-fold increase in Cmax and 2.6-fold increase in $AUC_{inf}$. The latter is a slightly greater increase than is observed with telithromycin.

The risk of ALT elevation increases with plasma exposure to solithromycin. In addition, there is a relationship between plasma levels and tachycardia that could have clinical significance in patients who have other reasons to have tachycardia or have an unstable cardiac condition.
However, in the draft SmPC the applicant states that As solithromycin is a strong metabolism-dependent CYP3A4 inhibitor itself, concomitant use of a CYP3A4 inhibitor is unlikely to appreciably affect solithromycin plasma concentrations following repeat dosing. Co-administration of solithromycin with a strong inhibitor of CYP3A4 and/or P-gp over several days has not been studied and was not allowed in the Phase 3 studies. The applicant should further justify the statement in the draft SmPC and consider the need to strongly warn against or contraindicate the use of solithromycin with moderate or strong inhibitors of CYP3A4 and/or P-gp, especially those with narrow therapeutic windows.

A PBPK model was used to assess i) the combined effect of a concomitant CYP3A4 inhibitor and severe renal impairment on solithromycin and ii) the effect of solithromycin on CYP3A4 substrates. There are details of the model that require clarification before it can be accepted to support statements made in the applicant's proposed SmPC.

- The absorption should be described more clearly, particularly the non-linearity. A mechanistic explanation rather than the fixing of Fa for different doses to fit the data would be preferred.
- Clearance and the contribution of CYP 3A4 to clearance should be better supported with in-vitro data (e.g. investigation of the contribution of the different pathways in human liver microsomes).
- A better discussion of the optimising of Ki should be provided with comparison to similar models for mechanism-based inhibitors.
- A sensitivity analysis for key parameters should be provided including Ki, fraction metabolised (Fmet[CYP3A4]), fraction absorbed (Fa) and degradation rate constant ($K_{deg}$). It is noted that the latter is quite high compared to some literature values.
- Further qualification of the model for time dependency is required to show that the model predicts well other mechanism-based substrates.
- Further qualification of the model is required to show that the model for renal impairment predicts well the effect of renal impairment on other drugs that are cleared by a similar mechanism.

Rifampicin induces CYP3A4, P-gp, *N*-acetyl transferase and some transporters. The net effect of rifampicin on solithromycin was a profound drop in plasma levels but the SmPC says only that solithromycin "should not be used" with agents that induce CYP3A4. It is very clear that use of solithromycin with inducers of CYP3A4 should be contraindicated. Due to the lack of clarity in terms of

categorisation of strong P-gp inducers, the incomplete overlap between inducers of CYP3A and P-gp and lack of additional clinical data, it is considered that use of solithromcyin should be contraindicated with all drugs that induce CYP3A4 and/or P-gp.

There is also the potential for a pH effect on systemic bioavailability after oral administration. Rather than conducting a dedicated DDI study, the effect of increasing pH was assessed from POPPK-predicted AUCs in patients who took PPIs in the two Phase 3 studies on the sampling days. The applicant concluded that there was no difference in the distribution of solithromycin AUCs. However, such analyses are considered to be imprecise and do not necessarily capture the effect of PPI co-administration at steady state. In light of the important effect of pH on solithromycin solubility a DDI study should be conducted in which solithromycin is given when the PPI is at steady state. Until results are available it should be recommended that co-administration of agents that increase gastric pH with oral solithromycin should be avoided.

*Solithromycin as a perpetrator*

Like telithromycin, solithromycin is an inhibitor of CYP3A4 and of P-gp. The report xt022608 states that solithromycin was also considered to possibly cause clinically significant inhibition of CYP2C8 and CYP2D6 (which is inhibited by telithromycin). The reason for this statement is unclear and the applicant has not investigated these possibilities clinically. Clarification is needed.

The effect of oral solithromycin on oral midazolam $AUC_{inf}$ was much greater (increase by 9.0-fold on co-administration at solithromycin steady state) than the effect on Cmax (2.5-fold under same condition). Midazolam is not only a substrate of CYP3A4 but also of P-gp.
Despite this very large effect the draft SmPC states: Co-administration of solithromycin, a strong inhibitor of CYP3A4, and a medicinal product metabolized by CYP3A4 may be associated with elevations in plasma concentrations of the concomitant medicine that could increase or prolong the therapeutic and/or adverse effects, especially if the CYP3A4 substrate has a narrow therapeutic window. Patients who are receiving both medicines may require monitoring, and the dose of the concomitantly administered medicine reduced if appropriate. There is a need to considered whether use of solithromycin with substrates of CYP3A and/or P-gp, especially those with narrow therapeutic windows, should be contraindicated.

In an in-vitro study solithromycin did not appear to induce CYP isoenzymes at 12 μg/mL (~4-fold predicted mean Cmax in patients with CAP given 400 mg IV) except for some question over 2C9. The solithromycin concentration used in the study was not sufficient to rule out induction of CYP isoenzymes. The inductive capacity of solithromycin needs to be considered further. In addition, the applicant should justify the lack of a DDI study with a substrate of 2C9.

Solithromycin inhibited P-gp *in vitro.* In a clinical DDI study plasma digoxin AUC and Cmax were higher following co-administration with solithromycin (increases by ~38% and ~46%, respectively, on Day 10 vs. Day 5). Since digoxin is not a sensitive substrate of P-gp an even more marked effect of solithromycin could occur with substrates such as dabigatran.

Solithromycin inhibited OATP1B3-mediated substrate transport *in vitro* but the $IC_{50}$ value (23 μM) was suggested to be too high to result in inhibition at therapeutic concentrations. This is not agreed as the concentrations do not appear to be sufficient to rule out an effect based on the calculated hepatic inlet concentrations. In addition, an effect cannot be ruled out for the other uptake transporters OATP1B1 and OCT1. In addition it appears that inhibition of BCRP in the gut cannot be discounted. However, it may be agreed that solithromycin did not significantly inhibit other efflux or uptake transporters including BSEP, OCT2, OAT1 and OAT3 *in vitro*.

<u>Conclusions on pharmacokinetics</u>

There are several concerns regarding the minimalistic approach taken by the applicant, the validity of the POPPK and PBPK models and the applicant's proposals for the SmPC.

In particular the concerns regarding the POPPK model add to the many reasons to object to the proposed indications for treatment of anthrax and tularaemia.

Furthermore, as also discussed in the next section, there are concerns that the proposed dose of solithromycin for all three indications claimed is poorly supported by the PK-PD analyses.

### 3.3.2 Pharmacodynamics

**Microbiology**

Solithromycin interferes with bacterial protein synthesis by binding to the peptide tunnel and interacting with domain V (like other macrolides) and domain II (like ketolides). X-ray crystallographic analysis of solithromycin bound to the 70S *E. coli* ribosome demonstrated a third site of interaction between the fluorine at position C-2 of solithromycin and the peptide tunnel. The table below summarises the in-vitro activity of solithromycin against selected species.

**Table 1 Solithromycin Spectrum of Activity**

| Organism | N | Drug | MIC (µg/mL) | | |
|---|---|---|---|---|---|
| | | | $MIC_{50}$ | $MIC_{90}$ | Range |
| **Gram-positive Bacteria** | | | | | |
| *S. pneumoniae* | 150 | Solithromycin | 0.015 | 0.25 | ≤0.008 - 0.5 |
| | | Azithromycin | >16 | >16 | 0.03 - >16 |
| β-hemolytic streptococci [a] | 100 | Solithromycin | 0.015 | 0.03 | ≤0.008 - 0.12 |
| | | Azithromycin | 0.12 | >16 | 0.015 - >16 |
| Viridans group streptococci [b] | 51 | Solithromycin | ≤0.008 | 0.06 | ≤0.008 - 0.12 |
| | | Azithromycin | 0.12 | 4 | ≤0.008 - 16 |
| *S. aureus* | 201 | Solithromycin | 0.12 | >16 | 0.03 - >16 |
| | | Azithromycin | >16 | >16 | 0.5 - >16 |
| *E. faecalis* | 39 | Solithromycin | 0.25 | 2 | 0.015 - 2 |
| | | Azithromycin | >16 | >16 | 0.5 - >16 |
| *E. faecium* | 40 | Solithromycin | 1 | 2 | 0.03 - 2 |
| | | Azithromycin | >16 | >16 | 0.25 - >16 |
| *Micrococcus* spp. [c] | 10 | Solithromycin | 0.015 | 0.03 | ≤0.008 - 0.06 |
| | | Azithromycin | 0.12 | 0.5 | 0.06 - 4 |
| *Bacillus* spp. [d] | 10 | Solithromycin | 0.015 | 0.03 | ≤0.008 - 0.03 |
| | | Azithromycin | 2 | 4 | 0.25 - 4 |
| *Corynebacterium* spp. [e] | 10 | Solithromycin | 0.015 | 0.5 | ≤0.008 - 16 |
| | | Azithromycin | >16 | >16 | 0.12 - >16 |
| *L. monocytogenes* | 10 | Solithromycin | 0.03 | 0.03 | 0.03 |
| | | Azithromycin | 0.5 | 1 | 0.5 - 1 |
| **Gram-negative Bacteria** | | | | | |
| *H. influenzae* | 100 | Solithromycin | 1 | 2 | 0.12 - 4 |
| | | Azithromycin | 2 | 2 | 0.25 - 4 |
| *H. parainfluenzae* | 11 | Solithromycin | 2 | 2 | 1 - 2 |
| | | Azithromycin | 1 | 2 | 0.5 - 2 |
| *M. catarrhalis* | 21 | Solithromycin | 0.12 | 0.12 | ≤0.008 - 0.5 |
| | | Azithromycin | 0.03 | 0.06 | 0.03 - 0.5 |
| *L. pneumophila* | 30 | Solithromycin | ≤0.015 | ≤0.015 | ≤0.015 |
| | | Azithromycin | 1 | 2 | 0.25 - 4 |
| *H. pylori* | 31 | Solithromycin | 0.06 | 0.25 | 0.03 - 4 |
| | | Clarithromycin | 0.03 | 0.12 | ≤0.015 - >16 |
| *C. jejuni* | 20 | Solithromycin | 1 | 4 | 1 - 8 |
| | | Clarithromycin | 2 | 4 | 1 - 8 |
| *Shigella* spp. [f] | 40 | Solithromycin | 8 | 16 | 1 - >16 |
| | | Azithromycin | 4 | 8 | 1 - >16 |
| *Salmonella* spp. [g] | 20 | Solithromycin | 4 | >16 | 1 - >16 |
| | | Azithromycin | 4 | 8 | 2 - 8 |
| *N. gonorrhoeae* | 34 | Solithromycin | 0.06 | 0.12 | 0.03 - 0.25 |
| | | Azithromycin | 0.25 | 0.5 | 0.06 - 2 |

Source: 07-CEM-06 [Broad spectrum screening] and 07-CEM-08 [*H. pylori* and *N. gonorrhoeae*]

a Includes: Group A *Streptococcus* (30), Group B *Streptococcus* (31), Group C *Streptococcus* (14), Group F *Streptococcus* (9), and Group G *Streptococcus* (16).
b Includes: *S. anginosus* (11), *S. constellatus* (11), *S. intermedius* (10), *S. mitis* (9), and *S. oralis* (10).
c Includes: *Micrococcus luteus* (2), and unspeciated *Micrococcus* (8)
d Includes: *B. cereus* (8), *B. circulans* (1), and *B. megaterium* (1)
e Includes: *C. jeikeium* (5), *C. striatum* (3), *C. urealyticum* (1), and *C. xerosis* (1).
f Includes: *S. boydii* (6), *S. dysenteriae* (3), *S. flexneri* (14), and *S. sonnei* (17)
g Includes: *S. dublin* (1), *S. enteritidis* (4), *S. hadar* (1), *S. heidelberg* (1), *S. infantis* (1), *S. paratyphi* (3), *S. typhi* (3), *S. typhimurium* (1), group B *Salmonella* spp. (2), group C *Salmonella* spp. (1), and group D *Salmonella* spp. (2)

Against 272 serotyped macrolide-resistant *S. pneumoniae* isolated from cases of CAP that were collected in 2012 the solithromycin $MIC_{50}$ was 0.06 µg/mL and the $MIC_{90}$ was 0.25 µg/mL, with a maximum at 0.5 µg/mL. Against 33 *S. pneumoniae* (8 azithromycin-susceptible and 25 azithromycin-resistant) in another study 22 had a solithromycin MBC/MIC ratio ≤4. Of 2123 *S. pneumoniae* isolates obtained from patients with CAP in 23 countries in 2009, 5 isolates from China had telithromycin MICs at 8 µg/mL, all of which had erythromycin MICs >256 µg/mL. The solithromycin MICs for these isolates were in the range 0.06 to 0.25 µg/mL. Significant 23S rRNA, L4 and L22 resistance mutations were not present in any isolates. Novel amino acid substitutions in the *ermB* leader peptide were detected in 4 of the 5 isolates and an identical pattern of mutations was found in all 5 isolates in the region between the *ermB* and leader peptide genes.

Solithromycin had similar in-vitro activity against CA-MRSA resistant to erythromycin, azithromycin, and clarithromycin (mostly USA300 clone) as it did against MSSA ($MIC_{90}$ 0.12 µg/mL). However, against HA-MRSA the $MIC_{50}$ was 0.12 µg/mL but the $MIC_{90}$ was >16 µg/mL, which reflected low activity of solithromycin against MRSA with constitutive $MLS_B$ resistance.

As is the case with other macrolides, solithromycin is less active against the cocco-bacillus *H. influenzae* than it is against the diplococcal species *M. catarrhalis* and *N. gonorrhoeae*.

MICs of solithromycin for macrolide-susceptible *M. pneumoniae* are < 0.008 µg/mL but increase to $MIC_{50}$ and $MIC_{90}$ values of 0.5 and 1 µg/mL against macrolide-resistant *M. pneumoniae*. $MIC_{90}$ values against various species of *Legionella* and against *C. pneumoniae* were 0.12 and 0.25 µg/mL, respectively.

The major metabolites of solithromycin (*N*-acetyl-CEM-101 and CEM-214) have at least as much antibacterial activity as the older macrolides but do not show the same level of activity against macrolide- and ketolide-resistant strains as solithromycin. Data for *S. pneumoniae* are shown below as an example.

| Organism | | Phenotype/ Genotype | Drug [a, b] | MIC (µg/mL) |
|---|---|---|---|---|
| *S. pneumoniae* | ATCC 49619 | Pen-I | Solithromycin | ≤0.015 |
| | | | *N*-Acetyl-CEM-101 | ≤0.015 |
| | | | CEM-214 | 0.03 |
| | 117-20B | WT | Solithromycin | ≤0.015 |
| | | | *N*-Acetyl-CEM-101 | ≤0.015 |
| | | | CEM-214 | 0.03 |
| | 014-4331A | *mefA* | Solithromycin | 0.25 |
| | | | *N*-Acetyl-CEM-101 | 0.5 |
| | | | CEM-214 | 1 |
| | 007-4589A | *ermB* | Solithromycin | ≤0.015 |
| | | | *N*-Acetyl-CEM-101 | ≤0.015 |
| | | | CEM-214 | 2 |
| | 120-1037B | *ermB+mefA* | Solithromycin | 0.12 |
| | | | *N*-Acetyl-CEM-101 | 16 |
| | | | CEM-214 | >16 |

**PK-PD analyses and dose selection for CAP**

In-vivo nonclinical studies

Studies conducted to select PK-PD indices and targets are shown in the table.

| Model | Organism; Solithromycin MIC (µg/mL) | Solithromycin Dose, Route, Frequency | PD Endpoint |
|---|---|---|---|
| Subcutaneous Abscess | *S. pneumoniae* 1 $Mac^S$ isolate; ≤0.03 | 0.5 to 10 mg/kg/day, Oral, 2h post-infection, q6h, q8h, q12h, or q24h for 24h | CFU/g abscess (24h post Tx) |
| Neutropenic Thigh Infection | *S. pneumoniae* 1 $Mac^S$ isolate; 0.03 | 1 to 25 mg/kg/day, Oral, 1.5h post-infection, q6h, q8h, q12h, or q24h for 24h | CFU/g thigh (24h post Tx) |
| Neutropenic Pulmonary Infection | *S. pneumoniae* 1 $Mac^S$ isolate; 0.06 | 0.625, 2.5, 10, 40, or 160 mg/kg/day, Oral, 2h post-infection, q3h, q6h, q12h, or q24h for 24h | CFU/g lung (24h post Tx) |
| | *S. pneumoniae* 4 $Mac^R$ isolates; 0.03, 0.06, 0.06, 0.125 | 0.156, 0.625, 2.5, 10, or 40 mg/kg/day, Oral, 2h post-infection, q6h or q12h for 24h | CFU/g lung (24h post Tx) |

The first study showed that the PK/PD index most closely associated with efficacy was Cmax:MIC (r2=0.75), followed by the 24-hour AUC:MIC (r2=0.60).

In the second study dose fractionation showed a trend for greater bacterial reduction when solithromycin was given q24h. The *f*Cmax:MIC ($r^2$=0.83) was the best predictor of in-vivo efficacy followed by *f*$AUC_{24}$:MIC ($r^2$=0.75).

In the first part of the lung infection model study using one strain the plasma *f*$AUC_{0-24}$:MIC ratio ($r^2$ = 0.848) was the PK-PD index best associated with efficacy. In addition, the total-drug ELF $AUC_{0-24}$:MIC ratio was highly predictive of efficacy ($r^2$ = 0.847). Using pooled isolate data the free-drug plasma $AUC_{0-24}$:MIC ratios associated with net bacterial stasis and a 1- and 2-$\log_{10}$ CFU reduction from baseline were 1.65, 6.31 and 12.8, respectively. The total-drug ELF $AUC_{0-24}$:MIC ratios associated with net bacterial stasis and a 1- and 2-$\log_{10}$ CFU reduction from baseline were 1.26, 15.1 and 59.8.

PK-PD analyses supporting dose regimens

The table shows a summary of studies to estimate PTA that were used to select the dose regimen for the Phase 3 studies.

**Table 41 Description of PK/PD Target Attainment Analyses Conducted Prior to Initiation of the Phase 3 Studies**

| Purpose/Outcome | Data Utilized as Basis for Analysis | Report Number |
|---|---|---|
| Initial doses for oral PK studies<br>Loading dose strategy suggested based upon accumulation seen with multiple dosing | Human PK (CE01-102, CE01-103)<br>Murine thigh infection model<br>MIC distribution | ICPD 00188 [a] |
| Update using nonclinical pneumonia model | Additional data from CE01-102<br>Murine pneumonia infection model | ICPD 00182 |
| Update using human ELF PK data<br>Basis for dose selection for CE01-200 | Murine ELF PK<br>Human plasma PK and ELF data from CE01-114 [a] | ICPD 00182-2 |
| Update to allow for simulation of exposures after IV and Oral dosing;<br>Basis for dose selection for CE01-300 | IV PK data from CE01-104 and few patients from Phase 2 study (CE01-200) [b] | ICPD 00232-1 |
| Update to allow for simulation of exposures after IV, IV to Oral, and Oral dosing regimens<br>Basis for dose selection for CE01-301 | IV PK data from CE01-116 [b] | ICPD 00232-2 |

a. Monte Carlo simulation was not employed in this analysis. Rather, median AUC values were related to median AUC:MIC ratio targets using *S. pneumoniae* $MIC_{50}$ and $MIC_{90}$ values in order to assess target attainment for potential dosing regimens.
b. Free-drug plasma and ELF AUC:MIC ratio targets for *S. pneumoniae* efficacy based on the murine pneumonia infection model were used.
c. Included the assessment of the solithromycin dosage regimens that were evaluated in ICPD 00232-1 and additional dosage regimens not previously evaluated.

These analyses were superseded by final analyses (reported in ICPD-00379-3) which took into account the PK data obtained from the patients sampled during the Phase 3 studies in CAP.

PK-PD analyses for efficacy were conducted using data from Phase 3 patients in the ME and ME-2 (evidence of a pathogen by specific methods, mainly culture) populations. Using non-clinical PD targets for *S. pneumoniae* efficacy, the POPPK model and Monte Carlo simulation, the PTA was estimated for simulated patients resembling the PK-PD analysis populations and those with severe renal impairment after administration of various solithromycin dosing regimens. For the assessments of PTA the average 24-hour total drug ELF and free drug plasma $AUC_{0-48}$ were evaluated.

Univariable PK-PD analyses for the efficacy endpoints failed to demonstrate relationships between exposure and response. For ME patients with *S. pneumoniae* at baseline for whom the free drug plasma AUC:MIC ratios ranged from 1.48 to 2,909, the percentage of patients achieving a plasma *f*AUC:MIC of 6.31, which is associated with a 1-$\log_{10}$ CFU reduction from baseline, was 96.4%. A similar result (94%) was obtained from the ME-2 population.

- For pneumococci for which the MIC=0.25 µg/mL the PTA based on the plasma free drug AUC:MIC target for 1-log kill is 82.9% for the oral only regimen but improves to 95.7% if treatment is initiated IV. PTA at MIC=1 µg/mL for the stasis target is 81.7% for the oral only regimen but improves to 94.6% when treatment is initiated IV.
- For pneumococci for which the MIC=1 µg/mL the PTA based on the total-drug ELF AUC:MIC targets associated with net bacterial stasis and 1- and 2-$\log_{10}$ kill were 100, 98.9 and 89.5%, respectively.

**Table 99 Comparison of % Probabilities of PK/PD Target Attainment over First 48 Hours by MIC Value among Solithromycin Dosing Regimens Administered to Simulated Patients**

| Route | Solithromycin Dosing Regimen | % Probability of PK/PD Target Attainment over First 48 Hours by Solithromycin Exposure Measure, AUC:MIC Ratio Target for a Given Bacterial Reduction Endpoint, and MIC Value (µg/mL) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Total-drug ELF [a] | | Free-drug Plasma [b] | | | |
| | | 2-$log_{10}$ CFU Reduction | | 1 $Log_{10}$ CFU Reduction | | Stasis | |
| | | MIC 0.5 | $MIC_{100}$ 1[c] | $MIC_{90}$ 0.12[c] | $MIC_{99}$ 0.25[c] | MIC 0.5 | $MIC_{100}$ 1[c] |
| PO | 800 mg Oral on Day 1 followed by 400 mg Oral on Days 2 - 5 | 96.5 | 89.5 | 94.6 | 82.9 | 93.8 | 81.7 |
| IV to PO | 400 mg IV on Days 1 - 3 followed by 800 mg Oral on Day 4 and 400 mg Oral on Days 5 - 7 | 100 | 98.9 | 99.9 | 95.7 | 99.9 | 94.6 |
| IV | 400 mg IV on Days 1-7 | 100 | 98.9 | 99.9 | 95.7 | 99.9 | 94.6 |

Source: Adapted from ICPD-00379-3

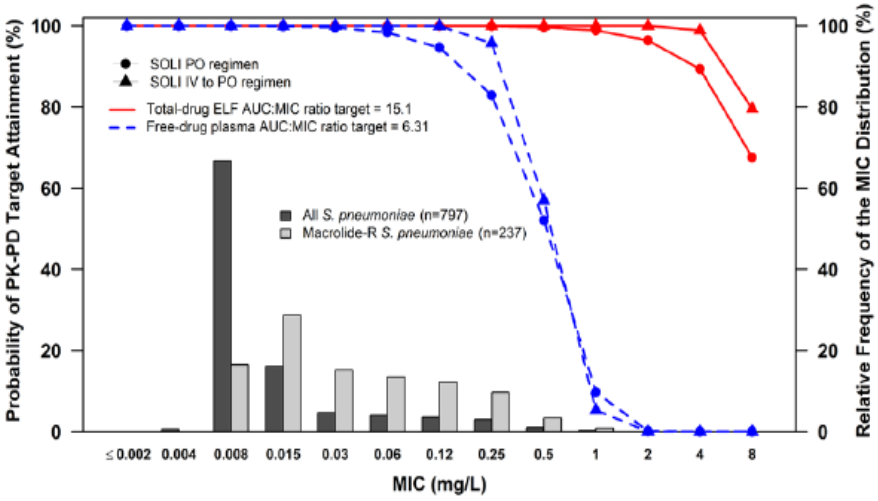
a Represents the percent probability of PK/PD target attainment by MIC value based on the average 24-hour total-drug ELF AUC over 0 to 48 hours and the total-drug ELF AUC:MIC ratio target for *S. pneumoniae* associated with a 2-$log_{10}$ CFU reduction from baseline.

b Represents the percent probability of PK/PD target attainment by MIC value based on the average 24-hour free-drug plasma AUC over 0 to 48 hours and the free-drug plasma AUC:MIC ratio targets for *S. pneumoniae* associated with a 1-$log_{10}$ CFU reduction from baseline or net bacterial stasis.

c $MIC_{90}$, $MIC_{99}$, and $MIC_{100}$ values for *S. pneumoniae* isolates were based on 2014 global surveillance data.

The figure indicates that free drug plasma levels achieved with the oral and IV to oral dose regimens provide PTA > 90% for pneumococci for which MICs are 0.12 µg/mL (the global $MIC_{90}$) and 0.25 µg/mL, respectively, based on the 1-$log_{10}$ kill PD target.

**Figure 15 Percent Probabilities of PK PD Target Attainment over First 48 Hours by MIC Value for Solithromycin Dosing Regimens Based on Total-drug ELF and Free-drug plasma AUC:MIC Ratio Targets Associated with a 1 $log_{10}$ CFU Reduction from Baseline for *S. pneumoniae* Overlaid upon the MIC Distribution for *S. pneumoniae* Isolates Collected from Europe**




Further simulations evaluated PTA at a range of different oral only, IV to PO and IV only dose regimens. As shown below, for a solithromycin MIC=1 µg/mL and the target for plasma free drug AUC/MIC ratio for stasis the PTA range was as shown above, i.e. from 81.7 with oral only regimens to 94.6% for all of the simulated IV to oral regimens.

**Table 42 Comparison of % Probabilities of PK/PD Target Attainment over First 48 Hours by MIC Value and ALT Elevation Endpoints on Days 4 and/or 7 among Solithromycin Dosing Regimens Administered to Simulated Patients**

| Route | | Solithromycin Dosing Regimen | % Probability of PK/PD Target Attainment over First 48 Hours by Solithromycin Exposure Measure, AUC:MIC Ratio Target for a Given Bacterial Reduction Endpoint, and MIC Value (mg/L) | | | | | | % Probability of ALT ≥ Threshold of ULN on Days 4 and/or 7 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Total-drug ELF [a] | | | | Free-drug Plasma [b] | | | | | |
| | | | 2-$log_{10}$ CFU Reduction | | 1-$log_{10}$ CFU Reduction | | Net Bacterial Stasis | | | | | |
| | | | MIC= 0.5 | $MIC_{100}$= 1 [c] | $MIC_{90}$= 0.12 [c] | $MIC_{99}$= 0.25 [c] | MIC= 0.5 | $MIC_{100}$= 1 [c] | ≥3 x ULN | ≥5 x ULN | ≥8 x ULN | ≥10 x ULN |
| Oral | 1 | 800 mg Oral on Day 1 followed by 400 mg Oral on Days 2 - 5 | 96.5 | 89.5 | 94.6 | 82.9 | 93.8 | 81.7 | 5.98 | 1.75 | 0.284 | 0.206 |
| | 2 | 800 mg Oral on Day 1 followed by 400 mg Oral on Days 2 - 6 | 96.5 | 89.5 | 94.6 | 82.9 | 93.8 | 81.7 | 6.68 | 1.91 | 0.309 | 0.206 |
| | 3 | 800 mg Oral on Day 1 followed by 400 mg Oral on Days 2 - 7 | 96.5 | 89.5 | 94.6 | 82.9 | 93.8 | 81.7 | 6.78 | 1.93 | 0.309 | 0.206 |
| IV to Oral | 4 | 400 mg IV on Days 1 - 3 followed by 800 mg Oral on Day 4 and 400 mg Oral on Days 5-7 | 100 | 98.9 | 99.9 | 95.7 | 99.9 | 94.6 | 7.22 | 2.11 | 0.309 | 0.155 |
| | 5 | 400 mg IV on Days 1 - 2 followed by 800 mg Oral on Day 3 and 400 mg Oral on Days 4 - 7 | 100 | 98.9 | 99.9 | 95.7 | 99.9 | 94.6 | 7.71 | 2.37 | 0.464 | 0.206 |
| | 6 | 400 mg IV on Days 1 - 4 followed by 800 mg Oral on Day 5 and 400 mg Oral on Days 6 - 7 | 100 | 98.9 | 99.9 | 95.7 | 99.9 | 94.6 | 7.99 | 2.60 | 0.438 | 0.206 |
| | 7 | 400 mg IV on Days 1 - 5 followed by 800 mg Oral on Day 6 and 400 mg Oral on Day 7 | 100 | 98.9 | 99.9 | 95.7 | 99.9 | 94.6 | 7.99 | 2.65 | 0.438 | 0.180 |
| | 8 | 400 mg IV on Days 1 - 6 followed by 800 mg Oral on Day 7 | 100 | 98.9 | 99.9 | 95.7 | 99.9 | 94.6 | 7.68 | 2.40 | 0.361 | 0.155 |
| IV | 9 | 400 mg IV on Days 1 - 7 | 100 | 98.9 | 99.9 | 95.7 | 99.9 | 94.6 | 6.44 | 1.78 | 0.258 | 0.129 |

Source: ICPD 00379-3 Table 2

a Represents the percent probability of PK/PD target attainment by MIC value based on the average 24-hour total-drug ELF AUC over 0 to 48 hours and the total-drug ELF AUC:MIC ratio target for *S. pneumoniae* associated with a 2-$log_{10}$ CFU reduction from baseline.

b Represents the percent probability of PK/PD target attainment by MIC value based on the average 24-hour free-drug plasma AUC over 0 to 48 hours and the free-drug plasma AUC:MIC ratio targets for *S. pneumoniae* associated with a 1-$log_{10}$ CFU reduction from baseline or net bacterial stasis.

c $MIC_{90}$, $MIC_{99}$, and $MIC_{100}$ values for *S. pneumoniae* isolates were based on global surveillance data.

A similar analysis presented by solithromycin dosing regimens administered to simulated patients with severe renal impairment is shown below.

**Table 43 Comparison of % Probabilities of PK/PD Target Attainment over First 48 Hours by MIC Value and ALT Elevation Endpoints on Days 4 and/or 7 among Solithromycin Dosing Regimens Administered to Simulated Patients with Severe Renal Impairment**

| Route | | Solithromycin Dosing Regimen | % Probability of PK/PD Target Attainment over First 48 Hours by Solithromycin Exposure Measure, AUC:MIC Ratio Target for a Given Bacterial Reduction Endpoint, and MIC Value (mg/L) | | | | | | % Probability of ALT ≥ Threshold of ULN on Days 4 and/or 7 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Total-drug ELF [a] | | | | Free-drug Plasma [b] | | | | | |
| | | | 2-$log_{10}$ CFU Reduction | | 1 $log_{10}$ CFU Reduction | | Net Bacterial Stasis | | | | | |
| | | | MIC= 0.5 | $MIC_{100}$= 1 [c] | $MIC_{90}$= 0.12 [c] | $MIC_{99}$= 0.25 [c] | MIC= 0.5 | $MIC_{100}$= 1 [c] | ≥3 x ULN | ≥5 x ULN | ≥8 x ULN | ≥10 x ULN |
| Oral | 1R | 800 mg Oral on Day 1 followed by 400 mg Oral on Days 2-5 | 98.2 | 94.6 | 97.2 | 91.4 | 96.8 | 90.9 | 8.04 | 2.60 | 0.541 | 0.258 |
| | 2R | 800 mg Oral on Day 1 followed by 200 mg Oral on Days 2-5 | 97.5 | 93.1 | 96.4 | 89.1 | 96.0 | 87.8 | 6.03 | 1.65 | 0.309 | 0.180 |
| | 3R | 400 mg Oral on Day 1 followed by 200 mg Oral on Days 2-5 | 94.6 | 83.6 | 92.0 | 75.0 | 90.9 | 72.6 | 5.67 | 1.42 | 0.232 | 0.155 |
| IV to Oral | 4R | 400 mg IV on Days 1-3 followed by 800 mg Oral on Day 4 and 400 mg Oral on Days 5 - 7 | 100 | 100 | 100 | 99.8 | 100 | 99.7 | 10.4 | 3.56 | 0.670 | 0.361 |
| | 5R | 400 mg IV on Day 1 followed by 200 mg IV on Days 2 - 3 and 200 mg Oral on Days 4 - 7 | 100 | 99.8 | 100 | 98.9 | 100 | 98.6 | 6.44 | 1.78 | 0.258 | 0.129 |
| | 6R | 400 mg IV on Day 1 followed by 200 mg IV on Days 2 - 3, 400 mg Oral on Day 4, and 200 mg Oral on Days 5 - 7 | 100 | 99.8 | 100 | 98.9 | 100 | 98.6 | 6.65 | 1.86 | 0.258 | 0.129 |
| IV | 7R | 400 mg IV on Day 1 followed by 200 mg IV on Days 2 - 7 | 100 | 99.8 | 100 | 98.9 | 100 | 98.6 | 6.34 | 1.75 | 0.258 | 0.129 |
| | 8R | 400 mg IV on Days 1 - 7 | 100 | 100 | 100 | 99.8 | 100 | 99.7 | 7.37 | 2.06 | 0.258 | 0.155 |

Source: ICPD 00379-3 Table 3

a Represents the percent probability of PK/PD target attainment by MIC value based on the average 24-hour total-drug ELF AUC over 0 to 48 hours and the total-drug ELF AUC:MIC ratio target for *S. pneumoniae* associated with a 2-$log_{10}$ CFU reduction from baseline.

b Represents the percent probability of PK/PD target attainment by MIC value based on the average 24-hour free-drug plasma AUC over 0 to 48 hours and the free-drug plasma AUC:MIC ratio targets for *S. pneumoniae* associated with a 1-$log_{10}$ CFU reduction from baseline or net bacterial stasis.

c $MIC_{90}$, $MIC_{99}$, and $MIC_{100}$ values for *S. pneumoniae* isolates were based on global surveillance data.

PK-PD analyses for safety focussed on Phase 3 study patients. The results shown in the tables above demonstrated that elevated ALT was associated with increases in each AUC measure evaluated. Variables retained in the final model that were predictive of increased ALT and for which their model-estimated

associations with ALT were independent of the prior 48-hour average AUC included study visits after baseline, chronic liver disease, higher baseline bilirubin, higher BMI, Asian race and decreased age.
In an additional analysis Phase 3 CAP patients with solithromycin PK data were categorised into quartiles based on highest predicted daily AUC. An effect of higher peak daily plasma exposures on the incidence of ALT elevations was observed, supporting the results from the PK-PD modelling.

**Evidence for efficacy in anthrax and tularaemia**

The table below includes in-vitro data for *B. anthracis* and *F. tularensis*.

**Table 14 Biodefense Pathogen Susceptibility to Solithromycin**

| Organism | N | $MIC_{50}$ (µg/mL) | $MIC_{90}$ (µg/mL) | Range (µg/mL) |
|---|---|---|---|---|
| *Bacillus anthracis* | 30 | 0.03 | 0.06 | ≤0.015 - 0.12 |
| *Francisella tularensis* | 29 [a] | 0.03 | 2 | ≤0.015 - 4 |
| *Yersinia pestis* | 30 | 1 | 2 | 0.25 - 2 |
| *Burkholderia mallei* | 30 | 1 | 1 | 0.25 - 2 |
| *Burkholderia pseudomallei* | 30 | 16 | 16 | 16 |

For *F. tularensis*, the MIC distribution reflects the distinct biovars - the more virulent *F. t. tularensis* (or type A) at the lower end and *F. t. holarctica* (or type B) at the higher end. In contrast, for *B. anthracis*, the MIC values were distributed in a unimodal manner. Solithromycin demonstrated some degree of bactericidal activity against *F. tularensis* but not against the *B. anthracis* Ames strain.

<u>*B. anthracis* nonclinical efficacy study (BBRC-3169)</u>
The study evaluated the efficacy of solithromycin (dosed to mimic exposure with 800 mg followed by 400 mg QD) against a lethal inhalational challenge with *Bacillus anthracis* spores (182 (± 43) Ames strain $LD_{50}$ equivalents via aerosol) in 20 cynomolgus macaques who were randomised by sex and body weight to receive solithromycin (n=12) or vehicle control (n=8). Treatment was initiated following detection of protective antigen (PA) in blood and was administered by oral gavage QD for 21 days. The 7 NHPs that received only vehicle succumbed while 83% (10/12) of the solithromycin treated NHPs survived.

**Table 8 Proportions of Surviving Animals with Clopper-Pearson 95 Percent Confidence Intervals by Group and Results of Two-sided Fisher's Exact Test Comparing Survival (Including Animal C64163)**

| Group | Number Survived/N | Proportion of Survivors (Clopper-Pearson 95% Confidence Interval) | Two-Sided Fisher's Exact P-value |
|---|---|---|---|
| 1 | 10/12 | 0.83 (0.52, 0.98) | 0.0045* |
| 2 | 1/8 | 0.13 (0.00, 0.53) | |

* Significant at the 0.05 level.

**Table 9 Proportions of Surviving Animals with Clopper-Pearson 95 Percent Confidence Intervals by Group and Results of the Two-sided Fisher's Exact Test Comparing Survival (Excluding Animal C64163)**

| Group | Number Survived/N | Proportion of Survivors (Clopper-Pearson 95% Confidence Interval) | Two-Sided Fisher's Exact P-value |
|---|---|---|---|
| 1 | 10/12 | 0.83 (0.52, 0.98) | 0.0007* |
| 2 | 0/7 | 0.00 (0.00, 0.41) | |

* Significant at the 0.05 level.

Samples of the liver, brain, spleen and mesenteric lymph node from all surviving animals were negative for *B. anthracis*. Bacteria consistent with *B. anthracis* were observed 6/10 samples of the lung and 2/10 tracheobronchial lymph nodes of survivors but numbers were < LLOQ. In contrast, the animals that died had quantifiable levels in all tissues assessed.

Solithromycin concentrations ranged from 83.5% to 92.8% of theoretical. After excluding 24 PK samples deemed as significant outliers a model was constructed. The report says that population PK parameters for the final model should be interpreted with caution. Nevertheless, individual cumulative total-drug and

free-drug daily AUC values for infected NHPs after humanised oral treatment were simulated. The mean Day 1 solithromycin free-drug plasma $AUC_{0-24}$ was 8.12 mg•hr/L (%CV=56.8%), which is ~3.7-fold higher than the mean free-drug $AUC_{0-24}$ in patients with CABP treated orally.
The study report states that given the limited sample size of solithromycin-treated NHPs and their high survival rate, the impact of solithromycin exposure on time to death in NHPs infected with *B. anthracis* could not be examined. The applicant concludes that the results of this study suggest that solithromycin is efficacious in the cynomolgus macaque anthrax therapeutic model.

*F. tularensis* study (FY14-020)
Fifteen CM were randomised by sex and body weight to receive Vehicle (n=7) or solithromycin (n=8). They were challenged with an average dose of 449 (±130) CFU of *Francisella tularensis* (Schu S4 strain solithromycin MIC 0.125 µg/mL) via aerosol and treatment commenced following the appearance of fever. The solithromycin IV dosing regimen was intended to mimic human oral dosing as above. Treatment was discontinued after 9-17 days based on the individual animal's tolerance to the infusions.

Control animals declined rapidly and 6/7 were euthanised by Day 8. The other survived until end of study. The group that received solithromycin showed limited clinical signs and no mortality associated with tularaemia, including four that were observed for 9 days following treatment.

Survival and time-to-death analyses were performed for two study populations - all challenged animals and animals from the solithromycin group that had tested positive at least once for bacteraemia. For the second set of data, only one animal receiving solithromycin tested positive for bacteraemia. Therefore, when comparing the survival rate there was no significant difference (p = 0.2500, Fisher Exact Test) between the two groups. In addition, no significant difference was identified in the survival distribution for the two groups (p = 0.1823, Log-Rank Test).

For the population that included all challenged animals, no significant difference (p = 0.1818, Fisher's Exact Test) was found when examining the survival rate between the two groups. Solithromycin-treated animals experienced AEs to the repeated infusions and were scheduled for euthanasia prior to moribund status. An additional survival analysis was performed to examine death *due to tularemia* as determined by bacterial load in tissue and pathology results. This demonstrated a significant difference (p = 0.0014) in the survival rate between groups. The survival distribution was also significantly different between the two groups (p = 0.0006, Log-Rank Test).

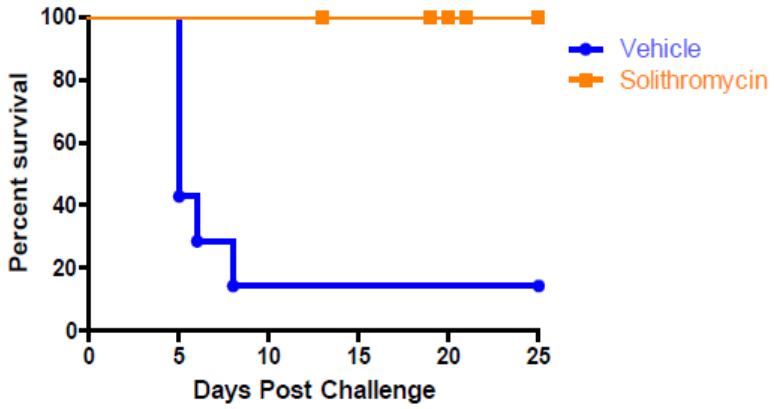



**Figure 2. Percent Survival: Mortality due to *F. tularensis* infection**

After a single day of treatment with solithromycin, macaques showed less severe clinical signs with a reduction in bacterial burden leading to limited pathological changes and there was no bacteraemia on Day 2. While 5 of the 7 control animals were positive for bacteraemia at the time of euthanasia, bacteraemia was not found in any of the animals receiving solithromycin.

Microscopic findings considered consistent with tularaemia were present in all vehicle-treated animals euthanised in moribund condition. Macroscopic observation showed no to minimal lung alternations in the eight animals administered solithromycin.

Solithromycin Cmax values in infected CM were 1.3 to 2.15-fold higher than those in healthy CM administered the humanised IV treatment regimen on Days 2 and 14. The data indicated that solithromycin PK was different between healthy and infected CM and the POPPK model was later refined. There were limitations of this refined model and parameters including CL and Vc could not be precisely estimated.

Additionally, as evidenced by the %CV for CL, inter-individual variability was higher for infected compared to healthy NHPs (%CV for CL of 45.2 vs. 21.7%, respectively). The same pattern for %CV for CL was also evident for patients with CAP vs. healthy subjects (94.0 and 35.8%, respectively). However, given that weight was found to be the only significant covariate for CL and the differences in the distribution of weight between Phase 3 patients with CAP and Phase 1 healthy subjects, the lower population mean CL for patients compared to that for healthy subjects was not considered to be surprising.

The POPPK report concludes that the current analysis can provide solithromycin dose selection support for future pivotal studies in NHPs infected with *F. tularensis.* In contrast to the POPPK report conclusions, the study report concludes that the results demonstrate that solithromycin is an effective treatment in cynomolgus macaques aerosol-challenged with a lethal exposure of *F. tularensis* SCHU S4.

**Secondary pharmacology**

TQT study (109)

This was a 3-way crossover study to evaluate the effects of IV solithromycin 800 mg infused over 40 minutes, IV placebo (normal saline) and oral moxifloxacin. The QTc prolongation observed after dosing with moxifloxacin confirmed the assay sensitivity. The change from baseline QTcF (ΔQTcF) was similar after dosing with 800 mg IV solithromycin and IV placebo. The resulting placebo-corrected ΔQTcF (ΔΔQTcF) was small at each time point for solithromycin. The largest ΔΔQTcF on solithromycin was observed at 4 hours post-dose with an estimate of 2.8 ms and an upper bound of the 90% CI of 4.9 ms. No subject had a QTcF value > 450 ms or ΔQTcF > 30 ms at any post-dosing time point.

In contrast a concentration-dependent increase of solithromycin on HR was identified. Immediately after the end of the solithromycin infusion (0.67 hours), the placebo-corrected change-from-baseline HR (ΔΔHR) peaked at 15.1 bpm and thereafter remained elevated for the first 12 hours, with values above 12 bpm for 8 hours. There were no subjects with outlier HR values, i.e. ΔHR > 25% increase with HR >100 bpm or ΔHR decrease with HR <50 bpm at any post-dose time points. In a concentration-effect analysis the estimated population intercept and slope was -9.377 bpm and 3.007 bpm per log ng/mL, respectively. The predicted ΔΔHR at mean Cmax was an increase of 16.611 bpm with an upper limit 90% CI of 18.375 bpm and a lower limit of 14.847 bpm.

***Comment on pharmacodynamics***

In-vitro activity against CAP pathogens

The in-vitro activity of solithromycin resembles that of telithromycin in most respects. Of most relevance to use for CAP, $MIC_{90}$ values for solithromycin are 0.25 mg/L for *S. pneumoniae*, 2 mg/L for *H. influenzae* and 0.12 mg/L for *M. catarrhalis***.** The $MIC_{90}$ is > 16 mg/L for *S. aureus*, reflecting lack of activity against strains (mostly MRSA) with constitutive $MLS_B$ resistance to macrolides. MICs of solithromycin for macrolide-susceptible *M. pneumoniae* are < 0.008 mg/L but the $MIC_{50}$ and $MIC_{90}$ values are 0.5 and 1 mg/L against macrolide-resistant *M. pneumoniae*. $MIC_{90}$ values against various species of *Legionella* and against *C. pneumoniae* are 0.12 and 0.25 mg/L, respectively.

Since solithromycin shares the binding properties of telithromycin as well as having an additional binding mechanism, it is proposed that it retains activity against organisms with common mechanisms of resistance to the macrolides. Data have been provided on the in-vitro activity of solithromycin against pneumococci that express *mefA, mefE* (efflux) and/or *ermB* (ribosomal methylation) resistance determinants as well as those with L4 ribosomal protein mutations. The $MIC_{90}$ was 0.5 to 1 mg/L in different isolate collections expressing these resistance determinants.

Data have been presented for 5 *S. pneumoniae* resistant to telithromycin (MIC 8 mg/L) and erythromycin (MICs >256 mg/L) for which the solithromycin MIC range was 0.06 to 0.25 mg/L. Against erythromycin-resistant *S. aureus* (*ermA, B, C* genotypes) the solithromycin $MIC_{90}$ was 0.06 mg/L but see above regarding lack of activity against strains with constitutive $MLS_B$ resistance. Against erythromycin-resistant *H. influenzae* (*ermA, B* and *C* genotypes) the solithromycin $MIC_{90}$ was 4 mg/L.

Against several species from different genera elevations in MICs ≥4-fold were observed at pH ≤6. Although the pH effect could mean lower activity at some infection sites, the ELF penetration and Vd were high, suggesting favourable distribution of drug. The applicant also suggests that since human serum decreased MICs, the combined effect of lower pH and serum could mean little net effect. However, this seems to be based on an in-vitro study with *S. aureus* and is considered to be conjectural by the CHMP. Nevertheless, further questioning on these issues is not likely to be fruitful since efficacy data are available in CAP, as discussed in the next section.

Nonclinical efficacy studies against CAP pathogens

The in-vitro data suggest that solithromycin has a suitable spectrum of activity for treatment of CAP but it is less active against *H. influenzae* than against Gram-negative cocci (*M. catarrhalis* and *N. gonorrhoeae* [for which it is also being studied]). There were numerous in-vivo nonclinical studies that examined log kill of various organisms in different species. In a neutropenic mouse thigh infection model using *S. pneumoniae* the effective dose for 2-$\log_{10}$ kill was 7 mg/kg QD for a macrolide-susceptible strain compared to 38 mg/kg for a strain expressing *mefA*. In the immunocompetent mouse pulmonary infection model the effective dose for 2 $\log_{10}$ kill was ~7 mg/kg QD for a macrolide-susceptible strain whereas in a similar model using neutropenic mice and a macrolide-R strain expressing *mefE* and *ermB* the effective dose for 2-$\log_{10}$ kill was 46 mg/kg. These data could be viewed as somewhat at odds with the effect of the same resistance determinants on MICs.

Contribution of the major metabolites to overall efficacy against CAP pathogens

Although the main metabolites are active, they are variably active against strains expressing common mechanisms of resistance to macrolides. They are present in relatively small amounts compared to parent drug in human plasma although there is considerable inter-individual variability. They are found in plasma at considerably higher concentrations in rats, rabbits and monkeys. On this basis the CHMP is concerned that the reported PTA (see below) is based on PDTs derived from four experiments in mice infected with *S. pneumoniae*. Since:

- The major metabolites have some antibacterial activity *in vitro*
- The *S. pneumoniae* strains were macrolide-susceptible in 3 experiments
- The *S. pneumoniae* strains in the 4th experiment are described as macrolide-R but exact details cannot be found; the metabolites may have had some activity against these strains

it is relevant to note the mouse plasma and lung levels of the active metabolites after oral dosing that are reported in Module 4. There were two studies that employed single doses with results as shown below, suggesting considerable amounts of metabolites in lung but lesser amounts in plasma.

**Table 35 Mouse Plasma and Lung PK Parameters for CEM-101 and Metabolites Following a Single Dose**

| | | Plasma | | | Lung | | |
|---|---|---|---|---|---|---|---|
| | Dose (mg/kg) | $T_{max}$ (h) | $C_{max}$ (µg/mL) | $AUC_{0-6}$ (h•µg/mL) | $T_{max}$ (h) | $C_{max}$ (µg/mL) | $AUC_{0-6}$ (h•µg/mL) |
| CEM-101 | 100 | 0.75 | 6.139 | 32.23 | 0.75 | 33.73 | 17.43 |
| *N*-Acetyl-CEM-101 | 100 | 3 | 0.62 | 2.57 | 6 | 6.3 | 18.07 |
| CEM-214 | 100 | 3 | 0.68 | 3.27 | 6 | 3.86 | 8.75 |

**Table 36 Mouse Plasma PK Parameters for CEM-101 Polymorphs and Metabolites**

| Dose | Test Article | Analyte | $C_{max}$ (µg/mL) | $T_{max}$ (h) | $T_{1/2}$ (h) | $AUC_{tau}$ (µg•h/mL) |
|---|---|---|---|---|---|---|
| 100 mg/kg | CEM-101 Form I | CEM-101 | 10.0 | 4.00 | 5.60 | 141 |
| | | *N*-Acetyl-CEM-101 | 1.97 | 6.00 | ND | 22 |
| | | CEM-214 | 0.79 | 6.00 | ND | 10.9 |
| | CEM-101 Form II | CEM-101 | 10.4 | 1.00 | 8.49 | 119 |
| | | *N*-Acetyl-CEM-101 | 0.45 | 4.00 | 8.06 | 5.46 |
| | | CEM-214 | 0.94 | 6.00 | ND | 13.1 |

In a further study in which male mice were dosed orally at 10 and 25 mg/kg BID the mean $AUC_{last}$ and $AUC_{inf}$ values after the higher dose were both ~26 µg.h/mL for solithromycin. Corresponding values for the *N*-acetyl metabolite were 0.34 and 1.5 µg.h/mL and those for CEM-214 were both ~3.4 µg.h/mL.

PK-PD index, PDTs and PTA for CAP pathogens

The PK-PD assessment leading to estimates of PTA for CAP pathogens has been based on parent drug levels but it is unclear whether a contribution of total activity from the metabolites could have significantly impacted on the derivation of PDTs from nonclinical in-vivo studies in mice that have been applied to free parent drug levels. Given the borderline clinical efficacy results in the two Phase 3 CAP studies, this matter requires further clarification since it casts doubt on the adequacy of the IV and PO dose regimens that were selected on the basis of the PTA estimations.

Regarding the PK-PD index and PDTs, the neutropenic mouse thigh model suggested that the *f*Cmax:MIC was the best predictor of in-vivo efficacy followed by *f*AUC24:MIC. Solithromycin peak concentrations at 3x and 7x MIC produced static and bactericidal (maximum 2 $log_{10}$ kill) activity, respectively.

In the neutropenic mouse lung infection model, which is a less well-established model, pooled data from three pneumococci with solithromycin MICs 0.06-0.12 mg/L gave plasma $fAUC_{0-24}$:MIC ratios associated with net bacterial stasis and a 1- and 2-$log_{10}$ CFU reduction from baseline of 1.65, 6.31 and 12.8, respectively, but the actual values were quite variable between strains (e.g. for 1-$log_{10}$ kill they were ~4, 16 and 17, whereas the derived PDT was ~6). The corresponding total-drug ELF $AUC_{0-24}$:MIC ratios were 1.26, 15.1 and 59.8 but the actual values were again very variable between strains (e.g. for 1-$log_{10}$ kill they were ~10, 43 and 46). It should also be noted that the PK model derived from healthy mice was used to generate free-drug plasma concentration vs. time profiles and then solithromycin dosing regimens administered to the infected mice were simulated to estimate plasma $AUC_{0-24}$, Cmax and %*f*T>MIC.

Although it could be considered that the lung infection model data are more relevant to the claimed indications, the PTA has only been estimated based on the PDTs derived as above from the 3 pooled isolates. Furthermore, the applicant has placed considerable weight on the ELF PDT, whereas this approach is not accepted. Estimating the ELF penetration of drugs intended for treatment of pneumonias is certainly encouraged but placing weight on urea-corrected ELF-related PDTs is not an acceptable approach.

Based on what seem to be rather questionable plasma $fAUC_{0-24}$:MIC ratio PDT for 1-$log_{10}$ kill the applicant estimated PTA over the first 48 h against pneumococci at the $MIC_{90}$ of 0.25 mg/L to be 82.9% using the proposed PO regimen and 95.7% using the proposed IV regimen. PTA at 0.5 mg/L is similar for IV and PO regimens and is only 50-60%.

Overall, the PK-PD analyses seem to be rather weak. The applicant should address the derivation of the PDT for free drug in plasma based on only 3 strains and when the actual values observed were so variable and should explain why PTA was estimated over 48 h.

PK-PD analyses used to support dosing in renal impairment

In study 115 using oral dosing the solithromycin AUC approximately doubled in subjects with eGFR < 30 mL/min not on haemodialysis. The SmPC states that no dose adjustment is needed when CrCL is ≥ 30 mL/min and that for patients with CrCL < 30 mL/min the oral dose regimen is 800 mg on day 1 and then 200 mg daily and the IV dose is 400 mg on day 1 and then 200 mg daily. The proposals cannot be accepted on current evidence and PTA estimates.

It is stated that there are no data to support a dose for patients on haemodialysis. The applicant should provide separate assessments for those with ESRD not on HD to determine whether a lower limit of CrCL should be applied.

PK-PD analyses of efficacy using Phase 3 data

There are a number of questions on the POPPK model that limit its perceived reliability for use in PK-PD analyses. Different POPPK models were used to simulate exposure in the Phase 2 and 3 studies. It would be better to have all data included in one model with covariates to account for any differences between studies. Taking the data at face value, there was no clear PK-PD relationship for efficacy, which the applicant proposed to be due to the maximum effect being reached in most individuals. For example, in the ME (any evidence of a pathogen) and ME-2 (mainly culture) populations the PK-PD analyses using the PDTs derived for *S. pneumoniae* failed to demonstrate relationships between exposure and response. It is rather striking that ME patients with *S. pneumoniae* had POPPK-predicted plasma *f*AUC:MIC ratios from 1.48 to 2,909. The high percentage predicted to have plasma *f*AUC:MIC ratios ≥6.31 is of dubious value based on the comments made above.

PK-PD analyses of safety using PK data from Phase 1, 2 or 3 studies

These analyses showed that increases in ALT were associated with increases in plasma AUC. However, see the comments made above regarding the POPPK model. The five single patient variables associated with the highest median individual model-predicted ALT based on the prior 48-hour average AUC were chronic liver disease, baseline bilirubin >1.2 mg/dL, Asian race, male gender and age <70 years. The impact of these covariates on the PK-PD for safety and the implications for possible dose adjustment does not seem to have been adequately explored.

The Phase 3 CAP patient data showed an effect of peak daily plasma exposures on the incidence of ALT elevations and a greater risk with IV to PO dosing. However, 6/8 patients with ALT >5×ULN in the highest exposure quartile were female and all 8 had CRP evidence of a marked systemic inflammatory response.

ALT elevations were asymptomatic and resolved but they are of concern, especially in light of the fact that solithromycin does not address an unmet need and that efficacy in the IV to PO study was borderline. These issues are discussed further under efficacy and safety sections that follow.

*B. anthracis*

The $MIC_{90}$ of solithromycin for this species is 0.06-0.12 mg/L but solithromycin was not bactericidal against the Ames strain.

The nonclinical efficacy study was conducted by a contracted facility, different to the one that conducted the tularaemia study. It is not clear whether the protocol exactly followed that established by NIH as suitable for assessing the potential efficacy of antibacterial agents to treat anthrax in humans. This requires clarification. Based on the methodology used there was a clear difference in survival between the treated and untreated macaques.

The applicant states that the observed mean *f*$AUC_{0-24}$:MIC ratio associated with survival of *B. anthracis*-infected NHPs would be readily achieved in patients administered the oral or IV regimens proposed for CAP. Table 16 shown in the clinical report actually indicates that parent total and free drug plasma AUCs in CAP patients are lower than in macaques. In addition, the table below shows that the predicted *f*$AUC_{0-24}$/MIC ratios, based on MIC 0.25 mg/L, are lower in patients. Therefore the presented data do not substantiate the applicant's conclusions.

The conclusions of Appendix Z are also of note. The contractor concluded that solithromycin plasma concentrations after oral administration were higher and inter-individual variability in PK was substantially larger for NHPs infected with *B. anthracis* as compared to those for healthy NHPs. The mean Day 1 solithromycin *f*$AUC_{0-24}$ in infected NHPs was 8.12 mg•hr/L (CV=56.8%), which was ~2.2-fold the mean value in patients with CABP.

**Table 7** **Model-predicted Oral Solithromycin Individual Daily $AUC_{0-24}$ Values in *B. anthracis*-infected NHPs Compared with Mean Values in Patients with CAP**

| | $AUC_{0-24}$ Day 1 (mg•hr/L) | | | Mean $AUC_{0-24}$ for Days 1 to 3 (mg•hr/L) | | | Mean $AUC_{0-24}$ for Days 1 to 21 (mg•hr/L) | | |
|---|---|---|---|---|---|---|---|---|---|
| NHP ID | Total-drug | Free-drug [b] | $fAUC_{0-24h}$ /MIC [c] | Total-drug | Free-drug | $fAUC_{0-24h}$ /MIC [c] | Total-drug | Free-drug | $fAUC_{0-24h}$ /MIC [c] |
| C55796 | 46.9 | 9.37 | 37.5 | 51 | 10.2 | 40.8 | 39.5 | 7.9 | 31.6 |
| C59632[a] | 64.0 | 12.8 | 51.2 | NA | NA | NA | NA | NA | NA |
| C59676 | 55.9 | 11.2 | 44.8 | 47.1 | 9.42 | 37.68 | 39.3 | 7.85 | 31.4 |
| C60879 | 75.2 | 15.0 | 60.0 | 80.3 | 16.1 | 64.4 | 70.4 | 14.1 | 56.4 |
| C60880 | 34.9 | 6.98 | 27.9 | 30.2 | 6.03 | 24.12 | 16.4 | 3.29 | 13.2 |
| C64047 | 50.7 | 10.1 | 40.4 | 41.8 | 8.36 | 33.44 | 36.5 | 7.31 | 29.2 |
| C64091 | 11.8 | 2.36 | 9.4 | 18.5 | 3.69 | 14.76 | 26.8 | 5.36 | 21.4 |
| C64136 | 6.28 | 1.26 | 5.0 | 10.5 | 2.1 | 8.4 | 28 | 5.61 | 22.4 |
| C64148 | 61.1 | 12.2 | 48.8 | 66.4 | 13.3 | 53.2 | 53.5 | 10.7 | 42.8 |
| C64150 | 9.87 | 1.97 | 7.9 | 10.1 | 2.01 | 8.04 | 9.8 | 1.96 | 7.8 |
| C64159 | 47.2 | 9.44 | 37.8 | 52.5 | 10.5 | 42 | 47.9 | 9.58 | 38.3 |
| C64783[a] | 23.7 | 4.73 | 18.9 | NA | NA | NA | NA | NA | NA |
| **Mean** (%CV) | **40.6** (56.8) | **8.12** (56.8) | **32.5** | **40.8** (57.6) | **8.17** (57.6) | **32.7** | **36.8** (48.5) | **7.37** (48.5) | **29.5** |
| **Patients with CAP [d]** (%CV) | **20.8** (58.5) | **3.74[b]** (58.8) | **13.6** | **17.6** (63.2) | **3.16** (63.2) | **12.6** | - | - | - |

Source: Adapted from BBRC-3169 [Solithromycin against *B. anthracis* in cynomolgus macaques] Appendix Z (ICPD 00322-4) [Population PK in NHP with *B. anthracis*]

a. C59632 was euthanized on Treatment Day 2 (85.5 h after challenge); C64783 was euthanized on Treatment Day 1 (48.5 h after challenge) only two hours post dose. The model-predicted AUC for this animal (23.7 mg•hr/L) reflects exposure that would have been achieved had it survived 24 hours.

b. Free-drug AUC values were derived using total-drug AUC values and a free-fraction estimate for protein binding of 0.20 (in NHPs) and 0.18 (in humans).

c. fAUC/MIC values were derived using MIC of solithromycin for the challenge strain of 0.25 µg/mL.

d. Total-drug AUC values from patients with CAP derived from clinical study CE01-300.

Furthermore, the contribution from metabolites to the overall efficacy and therefore the relevance of the findings in the cynomolgus macaques to humans are not clear. After oral dosing in macaques, as was used in the study, it is quite clear from Module 4 that there is greater first pass metabolism leading to lower solithromycin but relatively higher exposure to *N*-Acetyl-CEM-101 and CEM-214 vs. parent drug compared to humans.

To mimic the plasma profile following human dosing the dose for macaques had to be adjusted because of the lowering effect of first pass metabolism. This would then have affected metabolite levels.

Table 15 in the study report provides the mean plasma concentrations over time for parent drug and the three major metabolites in the macaques but there is no comparison made of metabolite levels with those that could be expected in patients with CAP. The bioanalytical report of the macaques PK data (Appendix Y to the report) presents the individual data by monkey and time point but does not summarise the PK parameters. Appendix Z concentrates on solithromycin levels in healthy and infected animals. Therefore the CHMP is not able to understand whether the dose adjustment to provide "humanised" plasma levels of

solithromycin had a marked impact on metabolite levels and is not able to relate active metabolite levels in macaques to those that can be expected in humans. This issue should be addressed to support the relevance of the observed efficacy for human dosing.

Specifically regarding the POPPK model, the PK data used to build the model were based on the toxicokinetic data. This approach appears to be adequate for the purpose but it has not been reported to the standards expected for a clinical study and in accordance with the requirements in the EMA guideline on reporting of POPPK analyses.

For example there are no VPCs or individual plots of observed versus predicted to allow judgement of the fit to the model. The data show high variability and include functions for weight on parameters based on allometry, which was not the relationship used in the clinical model. Moreover, it is noted that the addition of intravenous data to the clinical model caused significant changes to the model so that it is not clear why the applicant did not use all the primate data (i.e. intravenous and oral) to build a more robust model. The model was used to design optimal sampling regimens for the primate studies. Following the results of the study, which showed higher exposure in infected animals, the model was updated with a shift in Ki but this is described as not precisely estimated. The usefulness of the model is therefore questioned. However exposure data are available suggesting that higher exposures are needed in this indication. Also, it is considered a major oversight that concentrations of active metabolites were not considered in the conclusions.

The applicant acknowledges that the recommended treatment duration with two or more antimicrobial medicinal products is 60 days in order to cover the potential for germination of latent spores weeks or months after inhalation. The SmPC states that the duration of dosing is 7 days for anthrax (due to clinical experience limits) but there is a footnote referring to the duration used in the nonclinical study and the chronic toxicology data. Thus, use beyond 7 days is left to physician discretion. Based on the safety concerns (see further below), especially for hepatic effects, the current SmPC statements cannot be agreed.

In conclusion, there is a major objection to use of solithromycin to treat anthrax due to lack of confidence in the sufficiency of the CAP dose regimen to treat *B. anthracis* and due to safety concerns.

*F. tularensis*
The nonclinical efficacy study was conducted by a contractor in the US. There is no well-established and widely accepted animal model for tularaemia that can be regarded as predictive of human efficacy.

Solithromycin is less active against this species overall than against *B. anthracis* with $MIC_{90}$ of 2 mg/L but this reflects lesser activity against type B vs. type A. For the *F. tularensis* SCHU S4 ATCC 28534 strain that was used in the nonclinical efficacy study the solithromycin MIC was 0.125 μg/mL with a value ≤ 0.125 μg/mL for CEM-214 and 0.25 μg/mL for the *N*-acetyl metabolite.

The efficacy observed in this study is not sufficiently clear or convincing. For the population that included all challenged animals, no significant difference was found when examining the survival rate between the two groups. The survival distribution between the vehicle group and the solithromycin group were significantly different but in this analysis the four animals in Cohort 2 that persisted through the observation period were treated as survivors. The additional survival analysis was performed to demonstrate differences in survival *due to tularaemia* as determined by bacterial load in tissue and pathology results. This demonstrated a significant difference ($p = 0.0014$) in the survival rate between groups when looking at tularaemia-related deaths and the survival distribution was also significantly different between the two groups ($p = 0.0006$, Log-Rank Test). Nevertheless, in an unvalidated model it is not possible to conclude that the results clearly support an expectation of efficacy in humans.

As noted above, the dose regimens were based on a POPPK model built from the intravenous toxicokinetic data. Again it is not clear why one model was not built with both intravenous and oral data.

In addition toxicokinetic data are not ideal to inform a POPPK model as time points are limited and may not fully define the plasma concentration profile. The model was refined following data from a pilot study in four animals although limited refinement was needed. In this case a linear relationship for clearance and weight was used and BLQ samples were analysed using the M3 method. The model was developed using S-Adapt, i.e. different software to that applied in the previous models.

The model is not reported to the standards expected for a clinical model and there are no plots of Cwres versus time and concentration or VPC plots. Figure 4-5 shows some differences between the simulated monkey and human exposure. The data from the 8 monkeys used in the final study were not included in the POPPK report. It is noted that there are stated to be limitations to the refinement of the model and that key parameters could not be precisely estimated.

Also, the POPPK report concludes that, given the limitations of the final model based on data from infected NHPs, future refinement of the population PK model for solithromycin using intensively sampled PK data collected from NHPs infected with *F. tularensis* is required to better characterise the disposition of solithromycin. The current analysis can provide solithromycin dose selection support *for future pivotal studies* in NHPs infected with *F. tularensis.*

As in the *B. anthracis* study, the contribution from metabolites to the overall efficacy observed in the nonclinical model and therefore the relevance of the findings to man are not clear.

In conclusion, there is a major objection to use of solithromycin to treat tularaemia due to unknown validity of the model for this infection, lack of a clear benefit, lack of confidence in the sufficiency of the CAP dose regimen to treat *B. anthracis* and due to safety concerns.

Effects on cardiac conduction

An 800 mg IV dose of solithromycin given over 40 minutes gave a mean Cmax of 5923 ng/mL. After 400 mg IV QD for 7 days in Phase 1 using 30 minute infusions the mean Cmax was typically 3-4,000 ng/mL. The POPPK-predicted mean Cmax in Phase 3 patients was ~3,000 ng/mL but this was using 60-minute infusions in the IV/PO study, as is recommended in the SmPC. Therefore the effects on ECGs have been evaluated at approximately twice the Cmax that can be expected in a typical CAP patient.

The actual effects on ECGs in Phase 3 CAP studies are described and discussed in the section on safety, noting that co-medications which could prolong QT were excluded.

Conclusions on Pharmacodynamics

- The identification of PDTs appears to be rather weak for several reasons.
- Overall, the PK-PD analyses leading to dose selection are not considered robust. The lack of confidence in the PK-PD analyses and PTA is of importance when taking into account the efficacy data.
- It is not acceptable to base dose selection on PTA against ELF PDTs.
- The possible contribution of active metabolites to efficacy and the potential impact on the validity of the PDTs requires further thought.
- The claimed indications for treatment of *B. anthracis* and *F. tularensis* are rejected.

### *3.3.3 Clinical efficacy*

The three studies in CABP to support the indication are as follows:

| Study number | Design | Subjects | Study drug | Type of study |
|---|---|---|---|---|
| Phase 2 and 3 studies- CABP | | | | |
| Phase 2 CE01-200 | Randomised, DB, MC 2 study of oral solithromycin vs. oral levofloxacin in CABP | 64 solithromycin 68 levofloxacin | 800 mg Day 1, 400 mg Days 2 to 5 Levofloxacin 750 mg Days 1 to 5 | Efficacy and Safety |
| Phase 3 CE01-300 | Randomised, DB MC study of oral solithromycin vs. oral moxifloxacin in CABP | 426 solithromycin 434 moxifloxacin | 800 mg Day 1, 400 mg Days 2 to 5 moxifloxacin 400 mg Days 1 to 7 | Efficacy, safety |
| Phase 3 CE01-301 | Randomised, DB MC of IV/PO solithromycin vs. IV/PO moxifloxacin in CABP | CABP patients N=860 (430/group planned) | 400 mg IV QD; switch to oral regimen with 800 mg first day and then 400 mg/day (total 7 days) moxifloxacin 400 mg IV QD; switch to 400 mg oral QD (total 7 days) | Efficacy, safety |

**Phase 2 study in CAP (200)**

Patients were to have PORT Risk Class II, III or IV (scores ≤105) and pulmonary imaging studies (CXR or CT) within 48 hours prior to the first dose of study drug showing a new infiltrate(s) consistent with acute bacterial pneumonia. Clinical success rates were numerically higher in the levofloxacin treatment group for the CE population but were numerically higher in the solithromycin treatment group for the microITT and ME populations. Rates for the ITT population were similar between treatments.

**Table 20 Clinical Response at TOC**

| Population | Clinical Response | Solithromycin 800/400 mg | Levofloxacin 750 mg |
|---|---|---|---|
| **Primary Outcomes** | | | |
| ITT | N | 65 | 67 |
| | Success, n (%) [95% CI] | 55 (84.6) [73.5-92.4] | 58 (86.6) [76.0-93.7] |
| | Failure, n (%) | 10 (15.4) | 9 (13.4) |
| | Failure | 9 (13.8) | 7 (10.4) |
| | Indeterminate | 1 (1.5) | 2 (3.0) |
| CE | N | 55 | 58 |
| | Success, n (%) [95% CI] | 46 (83.6) [71.2-92.2] | 54 (93.1) [83.3-98.1] |
| | Failure, n (%) | 9 (16.4) | 4 (6.9) |
| **Secondary Outcomes** | | | |
| microITT | N | 18 | 14 |
| | Success, n (%) [95% CI] | 14 (77.8) [52.4-93.6] | 10 (71.4) [41.9-91.6] |
| | Failure, n (%) | 4 (22.2) | 4 (28.6) |
| | Failure | 3 (16.7) | 4 (28.6) |
| | Indeterminate | 1 (5.6) | 0 (0.0) |
| ME | N | 15 | 13 |
| | Success, n (%) [95% CI] | 12 (80.0) [51.9-95.7] | 10 (76.9) [46.2-95.0] |
| | Failure, n (%) | 3 (20.0) | 3 (23.1) |

**Phase 3 studies in CAP**

The two studies were conducted in the years 2013-2015 across several continents. Eligible patients were to have at least 3 of cough, production of purulent sputum, shortness of breath (dyspnoea) and chest pain due to pneumonia and at least one of the following:
a. Fever (>38°C oral, >78.5°C axillary (301 only), >38.5°C tympanic or >39°C rectal)
b. Hypothermia (<35°C oral, <34.5°C axillary (301 only), <35.5°C tympanic or <36°C rectal)

c. Pulmonary rales and/or evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds, or aegophony)

Additional eligibility requirements included:
- PORT Risk Class II, III or IV (PSS 51 to 105 in 300 and 51-130 in 301, inclusive)
- Lobar, multilobar or patchy parenchymal infiltrate(s) consistent with acute bacterial pneumonia on CXR or CT thorax within 48 hours before the first dose of study drug
- Had not received systemic antibacterial therapy other than a single dose of a short-acting agent (penicillin, cephalosporin [not ceftriaxone], tetracycline or trimethoprim-sulfamethoxazole in the 7 days prior to enrolment

Patients were assigned (1:1) to receive solithromycin or moxifloxacin. Randomisation was stratified by geographic region, history of asthma and/or COPD and PORT class II vs. III/IV. Patients with PORT II severity pneumonia were limited to 50% in 300 and 25% in 301 (in which 25% were to be PORT IV). Patients who had received a single dose of a short-acting antibacterial agent prior to randomisation were limited to 25%. Patients <65 years of age were limited to 80%. About 25% in each study were to be enrolled in North America.

Both studies had a double-blind and, for the oral portion, double-dummy design. Oral dosing with either treatment was without regard to food. In study 301 the IV to PO switch was based on meeting defined criteria. Treatment was as follows:
Study 300 - Oral solithromycin 800 mg on Day 1, followed by 400 mg daily on Days 2 through 5 and placebo capsules on Days 6 and 7 or oral moxifloxacin 400 mg daily on Days 1 through 7.
Study 301 – IV solithromycin 400 mg IV QD (250 mL over 60 minutes) followed by oral dosing with 800 mg and then 400 mg QD OR moxifloxacin 400 mg IV QD (250 mL over 60 minutes) followed by oral dosing with 400 mg QD, each for a total of 7 days/doses. Patients who did not meet the predefined criteria to switch to oral (see below) were maintained on once daily IV treatment for up to 7 days.

The co-primary efficacy outcomes were Investigator assessment of clinical response at the SFU visit in the ITT and CE-SFU populations. Clinical success at SFU was defined as a complete or near complete resolution of baseline signs and symptoms of CAP at EOT that continued through the SFU visit. The Investigator assessment at SFU was also applied to the mITT and mITT-EMA populations.

For the EMA primary endpoint it was assumed that the true rates of clinical success as determined by the investigators at SFU were 80% in the ITT population in both treatment groups and 85% in the CE-SFU population in both treatment groups. The evaluability rate was estimated at 80%. Assuming an NI margin of 10% and 1-sided alpha of 0.025, 860 patients provides 95% power to show NI for the EMA primary endpoint in the ITT population and 688 patients provide 95% power to show NI for the EMA primary endpoint in the CE-SFU population.

The following study populations were defined:

ITT population: all randomised

mITT population (300 only) and mITT-EMA population: all treated with a baseline bacterial pathogen known to cause CAP. In the mITT population pathogens were identified by any of culture of relevant specimens, urinary antigen test, culture from an oropharyngeal swab, PCR assay of oropharyngeal swabs, PCR assay of nasopharyngeal swabs, semi-quantitative PCR positivity from sputum and diagnostic rises in antibody responses for atypical pathogens. In the mITT-EMA population pathogens were identified by any of the above except for PCR methods.
CE: all treated who adhered to key inclusion/exclusion criteria and had no factor confounding outcome
Microbiologically Evaluable (ME) (300 only): CE with a pathogen as for mITT
ME-EMA: mITT-EMA patients also eligible for the CE population

The investigator assessment of clinical response at the SFU visit was analysed by determining adjusted (for the randomisation stratification factors) 2-sided 95% CIs for the observed difference in the clinical success rates in the ITT and CE-SFU populations. If the lower limit of the 95% CI for the difference in clinical success rates in both the ITT and CE-SFU populations was > -10%, NI of solithromycin to moxifloxacin was concluded.

Results of study 300

There were 860 patients enrolled from 114 centres, of which 856 received study treatment. The majority of patients completed the study (>95% in each treatment group). The mean (SD) age was 58.5 (±14.7) years in the solithromycin and 56.7 (±15.5) years in the moxifloxacin group. The majority was aged ≥55 years with > 30% ≥65 years. More than half were male (~53%) and the majority was white (>80%). Treatment groups had similar CABP disease characteristics and ~50% were PORT risk class III/IV.

**Table 16 Baseline CABP Disease Severity (ITT Population)**

| Characteristic | Statistic | Solithromycin 800/400 mg QD N=426 | Moxifloxacin 400 mg QD N=434 |
|---|---|---|---|
| History of asthma and/ or COPD from IWRS | n (%) | 62 (14.6) | 64 (14.7) |
| | p-value [a] | 1.0000 | |
| PORT score from IWRS | mean ± SD | 71.5 ± 13.3 | 71.2 ± 13.3 |
| | median (min, max) | 70.5 (51, 105) | 70.5 (51, 102) |
| | p-value [b] | 0.7559 | |
| PORT score from eCRF | mean ± SD | 71.7 ± 13.4 | 71.2 ± 13.3 |
| | median (min, max) | 71.0 (48, 108) | 69.0 (51, 112) |
| | p-value [b] | 0.6130 | |
| PORT risk class from IWRS | n (%) | | |
| II | | 213 (50.0) | 217 (50.0) |
| III, IV | | 213 (50.0) | 217 (50.0) |
| | p-value [a] | 1.0000 | |
| PORT risk class from eCRF | n (%) | | |
| I | | 1 (0.2) | 0 |
| II | | 209 (49.1) | 223 (51.4) |
| III | | 168 (39.4) | 173 (39.9) |
| IV | | 48 (11.3) | 38 (8.8) |
| | p-value [a] | 0.4508 | |
| CURB-65 [c] | n (%) | | |
| 0 | | 135 (31.7) | 138 (31.8) |
| 1 | | 175 (41.1) | 166 (38.2) |
| 2 | | 97 (22.8) | 110 (25.3) |
| 3 | | 8 (1.9) | 14 (3.2) |
| 4 | | 1 (0.2) | 1 (0.2) |
| | p-value [a] | 0.5049 | |
| Met modified ATS severity criteria [c] | n (%) | 24 (5.6) | 40 (9.2) |
| | p-value [a] | 0.0890 | |
| Met SIRS criteria [c] | n (%) | 231 (54.2) | 262 (60.4) |
| | p-value [a] | 0.0411 | |

Percentages reporting each of the 4 symptoms of CABP were high and similar between treatment groups. The treatment groups were also similar with respect to baseline signs and symptoms of CAP. The baseline mean WBC counts (leukocytes) were 9.9 $x10^9$/L and 9.3 $x10^9$/L while the mean CRP and mean procalcitonin levels were 89.2 mg/L and 1.5 ng/mL (solithromycin) and 90.8 mg/L and 2.1 ng/mL (moxifloxacin). Most patients (~80%) had unilobar infiltrates while < 20% had pleural effusions.

Patients could be treated in or out of hospital. Mean treatment adherence was > 99% based on pill counts.

The primary analysis demonstrated that solithromycin was non-inferior to moxifloxacin in the ITT and CE-SFU populations. The most frequently reported reasons for clinical failure were lack of resolution of baseline symptoms or development of new symptoms that required additional antibacterial therapy.

In a sensitivity analysis of the primary endpoint in the ITT population the unadjusted 95% CIs were (-7.1, 2.8) for the difference in clinical success rate at SFU.

**Table 35 Investigator's Assessment of Clinical Response at SFU (ITT and CE-SFU Populations)**

| Population<br>Clinical Response at SFU | Solithromycin 800/400 mg QD n (%) | Moxifloxacin 400 mg QD n (%) |
|---|---|---|
| **ITT Population** | N=426 | N=434 |
| **Success** | **360 (84.5)** | **376 (86.6)** |
| Difference (adjusted 95% CI) [a] | -2.13 (-6.9, 2.6) | |
| **Failure (including indeterminates)** | **66 (15.5)** | **58 (13.4)** |
| Failure [b] | 49 (11.5) | 38 (8.8) |
| Reasons for clinical failure: | | |
| Failure at EOT assessment and carried forward to SFU | 43 (10.1) | 31 (7.1) |
| Lack of resolution or worsening of baseline signs and symptoms and required additional antibacterial medication | 25 (5.9) | 10 (2.3) |
| Development of new signs and symptoms, complications, or radiologic findings of CABP and required additional antibacterial medication | 13 (3.1) | 19 (4.4) |
| Study drug discontinued due to an AE and required additional antibacterial medication | 13 (3.1) | 7 (1.6) |
| Classified as failure at SFU | | |
| Development of new signs and symptoms, complications, or radiologic findings of CABP and required additional antibacterial medication | 14 (3.3) | 10 (2.3) |
| Death from any cause | 4 (0.9) | 4 (0.9) |
| **Indeterminate** | 17 (4.0) | 20 (4.6) |
| Reasons for indeterminate clinical response: | | |
| Indeterminate at the EOT Assessment | 10 (2.3) | 11 (2.5) |
| Lost to follow-up prior to EOT assessment, or missed visit | 3 (0.7) | 3 (0.7) |
| Other | 7 (1.6) | 8 (1.8) |
| Lost to follow up | 3 (0.7) | 6 (1.4) |
| Other | 4 (0.9) | 3 (0.7) |
| **CE-SFU Population** | N=388 | N=390 |
| **Success** | **342 (88.1)** | **356 (91.3)** |
| Difference (adjusted 95% CI) [a] | -3.14 (-7.6, 1.1) | |
| **Failure** | **46 (11.9)** | **34 (8.7)** |
| Failure | 46 (11.9) | 33 (8.5) |
| Indeterminate [c] | 0 | 1 (0.3) |

The tables show clinical success rates at SFU in the ITT population by randomisation strata. Other sub-group analyses suggested slightly higher response rates to moxifloxacin vs. solithromycin in females but no difference between treatments in males. There was no consistent trend to decreasing efficacy with increasing age.

| Geographic Region<br>Clinical Response at SFU | ITT | | |
|---|---|---|---|
| | Solithromycin 800/400 mg QD N=426 n (%) | Moxifloxacin 400 mg QD N=434 n (%) | Difference (95% CI) [a] |
| **Europe** | n=223 | n=225 | -1.93 (-9.3, 5.4) |
| Success | 184 (82.5) | 190 (84.4) | |
| **European Union** | n=142 | n=160 | 6.39 (-1.8, 14.6) |
| Success | 128 (90.1) | 134 (83.8) | |
| **North America** | n=99 | n=105 | -8.37 (-17.2, 0.4) |
| Success | 86 (86.9) | 100 (95.2) | |
| **Latin America** | n=52 | n=54 | 10.75 (-4.5, 26.0) |
| Success | 47 (90.4) | 43 (79.6) | |
| **South Africa** | n=52 | n=50 | -3.31 (-19.3, 12.7) |
| Success | 43 (82.7) | 43 (86.0) | |

| Characteristic<br>Clinical Response at SFU | ITT<br>Solithromycin IV to Oral N=426 n (%) | ITT<br>Moxifloxacin IV to Oral N=434 n (%) | ITT<br>Difference (95% CI) [a] |
|---|---|---|---|
| **No history of asthma and/or COPD** | n=364 | n=370 | |
| Success | 303 (83.2) | 321 (86.8) | -3.51 (-8.9,1.9) |
| **History of asthma and/or COPD** | n=62 | n=64 | |
| Success | 57 (91.9) | 55 (85.9) | 6.00 (-6.5,18.5) |

| Characteristic<br>Clinical Response at SFU | ITT<br>Solithromycin 800/400 mg QD N=426 n (%) | ITT<br>Moxifloxacin 400 mg QD N=434 n (%) | ITT<br>Difference (95% CI) [a] |
|---|---|---|---|
| **PORT Risk Class II (IWRS)** | n=213 | n=217 | -3.02 (-9.8, 3.7) |
| Success | 183 (85.9) | 193 (88.9) | |
| **PORT Risk Class I / II (eCRF)** | 210 | 223 | -3.05 (-9.7,3.6) |
| Success | 181 (86.2) | 199 (89.2) | |
| Difference (95% CI) [a] | | | |
| **PORT Risk Class III / IV (IWRS)** | n=213 | n=217 | -1.23 (-8.7, 6.2) |
| Success | 177 (83.1) | 183 (84.3) | |
| **PORT Risk Class III / IV (eCRF)** | 216 | 211 | -1.02 (-8.5,6.5) |
| Success | 179 (82.9) | 177 (83.9) | |

Solithromycin was comparable to moxifloxacin in patients with high baseline disease severity indices.

**Table 41 Clinical Success at SFU in Patients in the Upper Quartile of Baseline C-Reactive Protein, Procalcitonin, and White Blood Cell (ITT and CE-SFU Populations, and their PORT III/IV Subgroups)**

| Clinical Success at SFU by Population | Solithromycin n (%) | Moxifloxacin n (%) |
|---|---|---|
| **ITT Population, N** | 49 | 33 |
| Success Rate | 38 (77.6%) | 26 (78.8%) |
| **ITT-PORT III/IV, N** | 34 | 25 |
| Success Rate | 26 (76.5%) | 19 (76.0%) |
| **CE-SFU, N** | 43 | 32 |
| Success Rate | 35 (81.4%) | 26 (81.3%) |
| **CE-SFU, III/IV, N** | 29 | 24 |
| Success Rate | 24 (82.8%) | 19 (79.2%) |

Results of planned secondary analyses in patients with evidence of documented pathogens are summarised below. There was consistent numerical inferiority for solithromycin. The lower bounds of the 95% CI are around -10-12% but the study was not powered for these analyses.

**Table 42 Investigator Assessment of Clinical Response at SFU (Microbiological Populations)**

| Clinical Response at SFU | mITT Soli 800/400 mg QD N=235 n (%) | mITT Moxi 400 mg QD N=226 n (%) | ME-SFU Soli 800/400 mg QD N=220 n (%) | ME-SFU Moxi 400 mg QD N=211 n (%) | mITT-EMA Soli 800/400 mg QD N=199 n (%) | mITT-EMA Moxi 400 mg QD N=190 n (%) | ME-EMA-SFU Soli 800/400 mg QD N=189 n (%) | ME-EMA-SFU Moxi 400 mg QD N=177 n (%) |
|---|---|---|---|---|---|---|---|---|
| Success | 197 (83.8) | 196 (86.7) | 190 (86.4) | 190 (90.0) | 165 (82.9) | 163 (85.8) | 159 (84.1) | 157 (88.7) |
| Difference (95% CI) [a] | -2.90 (-9.8, 4.0) | | -3.68 (-10.2, 2.9) | | -2.87 (-10.6,4.9) | | -4.57 (-12.1,3.0) | |
| Failure | 38 (16.2) | 30 (13.3) | 30 (13.6) | 21 (10.0) | 34 (17.1) | 27 (14.2) | 30 (15.9) | 20 (11.3) |
| Failure | 31 (13.2) | 22 (9.7) | N/A | N/A | 30 (15.1) | 21 (11.1) | N/A | N/A |
| Indeterminate | 7 (3.0) | 8 (3.5) | N/A | N/A | 4 (2.0) | 6 (3.2) | N/A | N/A |

Clinical outcomes at SFU for major pathogens in the mITT population are shown below. Generally, moxifloxacin was numerically superior. Similar trends were observed in the mITT-EMA and ME-EMA SFU populations. Microbiological responses were inferred from clinical responses. Against *S.*

*pneumoniae*, solithromycin $MIC_{50}/MIC_{90}$ values were 0.008/0.015 µg/mL (maximum 0.5 µg/mL). The same highest value applied to *S. aureus*. For *H. influenzae* the $MIC_{50/90}$ values were 2 and 4 µg/mL, for *M. catarrhalis* 0.12 and 0.25 µg/mL and for *M. pneumoniae* and *Legionella spp*. the highest MIC observed was 0.25 µg/mL. For these species there was no relationship between MIC and outcome. For 8 *K. pneumoniae* per treatment group the solithromycin MICs were 16 µg/mL or more while the moxifloxacin MICs did not exceed 0.25 µg/mL. For mITT patients with *K. pneumoniae* the clinical success rates were 4/6 for solithromycin and 2/3 for moxifloxacin.

In those with *S. pneumoniae* bacteraemia at baseline 3/5 solithromycin and 6/10 moxifloxacin were clinical successes at SFU in mITT and mITT-EMA populations.

**Table 43 Investigator Assessment of Clinical Response at SFU by Baseline Pathogens (mITT Population)**

| Baseline Pathogen | mITT | |
|---|---|---|
| | Solithromycin 800/400 mg QD N=235 n/N1 (%) | Moxifloxacin 400 mg QD N=226 n/N1 (%) |
| **Gram-Positive Bacteria (aerobes)** | | |
| *Staphylococcus aureus* | 15/22 (68.2) | 11/14 (78.6) |
| MSSA | 11/17 (64.7) | 6/9 (66.7) |
| Macrolide resistant | 2/2 (100.0) | 1/1 (100.0) |
| *Streptococcus pneumoniae* | 81/96 (84.4) | 89/102 (87.3) |
| MDRSP | 12/13 (92.3) | 9/10 (90.0) |
| PSSP | 24/29 (82.8) | 36/44 (81.8) |
| PISP | 12/13 (92.3) | 10/11 (90.9) |
| PRSP | 7/8 (87.5) | 4/4 (100.0) |
| Macrolide resistant | 12/12 (100.0) | 8/8 (100.0) |
| **Gram-Negative Bacteria (aerobes)** | | |
| *Haemophilus influenzae* | 64/80 (80.0) | 49/55 (89.1) |
| *Moraxella catarrhalis* | 23/28 (82.1) | 20/23 (87.0) |
| Any *Legionella* spp. | | |
| *Legionella pneumophila* | 54/61 (88.5) | 59/63 (93.7) |
| *Legionella dumoffii* | 0/0 | 0/1 (0.0) |
| *Mycoplasma pneumoniae* | 33/37 (89.2) | 38/42 (90.5) |
| Macrolide resistant | 0/0 | 2/2 (100.0) |

Five patients in the ITT population had a superinfection (4 solithromycin) and one additional patient who received solithromycin became colonised with *H. influenzae*. All patients with superinfection received systemic antibacterial therapy for these pathogens and were counted as clinical failures at SFU.

Results of study 301

A total of 863 patients were enrolled at 147 centres. Of the 863, 661 were in PORT class III-V of which all except 3 received study medication and >93% completed the study. The mean age was 64 years and the majority was ≥55 years of age, with >50% aged ≥ 65 years. Slightly more than half were male (55%) and 77% were White. PORT scores and proportions of patients with each PORT risk class, CURB-65 severity scores, modified ATS severity criteria and SIRS criteria were similar between treatment groups.

**Table 15 Baseline CABP Disease Severity - ITT Population (PORT III/IV/V Patients)**

| Characteristic | Statistic | Solithromycin IV to Oral N=328 | Moxifloxacin IV to Oral N=333 |
|---|---|---|---|
| History of asthma and/ or COPD from IWRS | n (%) | 77 (23.5) | 80 (24.0) |
| PORT score from eCRF | mean ± SD | 89.2 ± 14.43 | 89.1 ± 13.92 |
| | median (min, max) | 85.0 (71, 133) | 85.0 (71, 139) |
| PORT risk class from IWRS | n (%) | | |
| II | | 7 (2.1) | 14 (4.2) |
| III, IV | | 321 (97.9) | 319 (95.8) |
| PORT risk class from eCRF | n (%) | | |
| III | | 196 (59.8) | 204 (61.3) |
| IV | | 130 (39.6) | 125 (37.5) |
| V | | 2 (0.6) | 4 (1.2) |
| CURB-65 [a] | n (%) | | |
| 0 | | 30 (9.1) | 39 (11.7) |
| 1 | | 135 (41.2) | 131 (39.3) |
| 2 | | 119 (36.3) | 113 (33.9) |
| 3 | | 28 (8.5) | 29 (8.7) |
| 4 | | 1 (0.3) | 1 (0.3) |
| Met modified ATS severity criteria [a] | n (%) | 52 (15.9) | 45 (13.5) |
| Met SIRS criteria [a] | n (%) | 239 (72.9) | 226 (67.9) |

Mean treatment adherence was >98% for all populations in both treatment groups.

Non-inferiority was demonstrated in the ITT population but the lower bound of the 95% CI was -10% in the CE-SFU population and the upper bound did not exceed zero.

**Table 30 Investigator Assessment of Clinical Response at SFU - ITT and CE-SFU Populations (PORT III/IV/V Patients)**

| Population<br>Clinical Response at SFU | Solithromycin IV to Oral n (%) | Moxifloxacin IV to Oral n (%) | Difference (95% CI) [a] |
|---|---|---|---|
| **ITT population (PORT III/IV/V)** | **N = 328** | **N = 333** | |
| Success | 281 (85.7) | 293 (88.0) | -2.32 (-7.8, 2.7) |
| Failure (including indeterminates) | 47 (14.3) | 40 (12.0) | |
| Failure | 38 (11.6) | 30 (9.0) | |
| Indeterminate[b] | 9 (2.7) | 10 (3.0) | |
| **CE-SFU population (PORT III/IV/V)** | **N = 295** | **N = 300** | |
| Success | 257 (87.1) | 276 (92.0) | -4.88 (-10.0, 0.0) |
| Failure | 38 (12.9) | 24 (8.0) | |
| Clinical response of failure at SFU (ITT and CE populations)c | 38 (11.6) | 30 (9.0) | |
| Reasons for clinical failure: | | | |
| Classified as failure at the EOT assessment | 29 (8.8) | 26 (7.8) | |
| Lack of resolution or worsening of baseline signs and symptoms and required additional antibacterial medication[c] | 13 (4.0) | 7 (2.1) | |
| Development of new signs and symptoms, complications, or radiologic findings of CABP and required additional antibacterial medication[c] | 7 (2.1) | 8 (2.4) | |
| Study drug discontinued due to an AE and required additional antibacterial medication[c] | 7 (2.1) | 9 (2.7) | |
| Development of new signs and symptoms, complications, or radiologic findings of CABP and required additional antibacterial medication at the EOT or SFU assessments[c] | 10 (3.0) | 7 (2.1) | |
| Death from any cause[c] | 4 (1.2) | 5 (1.5) | |
| Indeterminate at SFU for ITT population[b] | 9 (2.7) | 10 (3.0) | |
| Reasons for indeterminate clinical response | | | |
| Indeterminate at the EOT Assessment | 7 (2.1) | 8 (2.4) | |
| Lost to follow-up prior to EOT assessment, or missed visit | 1 (0.3) | 1 (0.3) | |
| Other | 6 (1.8) | 7 (2.1) | |
| Other reason at the EOT or SFU assessments | 2 (0.6) | 3 (0.9) | |

Source Data: Table 14.2.3.1e, Table 14.2.3.5e, Table 14.2.3.6e.

AE=adverse event; CABP=community-acquired bacterial pneumonia; CE=clinically evaluable; CI=confidence interval; EOT=end of therapy; ITT=intent-to-treat; SFU=short-term follow-up.

a. Difference in clinical success rates (solithromycin minus moxifloxacin). Adjusted confidence intervals are calculated using the Miettinen and Nurminen method with adjustment for the randomization stratification factors of geographic region, asthma/ COPD, and PORT risk class. Cochran-Mantel-Haenszel weights are used for the strata. Due to small numbers in the cells, adjustment for asthma/COPD could not be done and Europe and North America were combined into one region.

b. Only patients in the ITT population could be classified as indeterminate response. Indeterminate response was one of the reasons for exclusion from the CE-SFU population.

c. The CE-SFU population is a subset of the ITT population. Therefore, the numbers of patients for each reason for clinical failure in the CE-SFU population are subsets of the numbers of patients in the ITT population. The percentages shown for clinical response of failure at SFU and the reasons for failure are based on the ITT population.

There were 5 CE patients declared failures because they received non-study treatment due to insufficient supply of solithromycin. Excluding these patients gives clinical success rates (CE-SFU PORT III/IV/V) of 88.0% for solithromycin and 92.0% for moxifloxacin with 95% CI for the difference (-9.2%, 1.2). In a sensitivity analysis of unadjusted clinical response in the ITT and CE-SFU populations for PORT III/IV/V patients the lower bound of the 95% CI when calculated by the continuity corrected Z-test was -7.8% in the ITT population but -10.1% in the CE-SFU population.

Investigator assessments of clinical success rates were generally similar by randomisation strata.

**Table 34 Investigator Assessment of Clinical Response at SFU by History of Asthma/COPD from the IWRS - ITT Population (PORT III/IV/V Patients)**

| Characteristic<br>Clinical Response at SFU | ITT (PORT III/IV/V) | | |
|---|---|---|---|
| | Solithromycin IV to Oral N=328 n (%) | Moxifloxacin IV to Oral N=333 n (%) | Difference (95% CI) [a] |
| **No history of asthma and/or COPD** | n=251 | n=253 | |
| Success | 213 (84.9) | 222 (87.7) | -2.89 (-9.3, 3.5) |
| **History of asthma and/or COPD** | n=77 | n=80 | |
| Success | 68 (88.3) | 71 (88.8) | -0.44 (-11.7, 10.8) |

**Table 33 Investigator Assessment of Clinical Response at SFU by Region - ITT Population (PORT III/IV/V Patients)**

| Geographic Region<br>Clinical Response at SFU | ITT (PORT III/IV/V) | | |
|---|---|---|---|
| | Solithromycin IV to Oral N=328 n (%) | Moxifloxacin IV to Oral N=333 n (%) | Difference (95% CI) [a] |
| **North America** | n=24 | n=29 | |
| Success | 20 (83.3) | 23 (79.3) | 4.02 (-20.8, 28.8) |
| **Latin America** | n=4 | n=8 | |
| Success | 3 (75.0) | 8 (100.0) | -25.00 (-86.2, 36.2) |
| **Eastern Europe** | n=179 | n=186 | |
| Success | 150 (83.8) | 172 (92.5) | -8.67 (-15.8, -1.5) |
| **Western/Southern/Northern Europe** | n=54 | n=35 | |
| Success | 48 (88.9) | 31 (88.6) | 0.32 (-15.5, 16.1) |
| **South Africa** | n=14 | n=19 | |
| Success | 12 (85.7) | 16 (84.2) | 1.50 (-29.3, 32.3) |
| **Asia Pacific** | n=53 | n=56 | |
| Success | 48 (90.6) | 43 (76.8) | 13.78 (-1.6, 29.2) |
| **European Union** | n=122 | n=108 | |
| Success | 108 (88.5) | 97 (89.8) | -1.29 (-10.2, 7.6) |

There was no appreciable effect of prior antibacterial therapy, gender or age on the clinical response at SFU. There was no disadvantage for solithromycin in patients who were in the upper quartile for CRP, WBC and procalcitonin. Clinical responses by CURB-65 score are shown below.

**Table 37 Investigator Assessment of Clinical Response at SFU by CURB-65 Score - ITT Population (PORT III/IV/V Patients)**

| CURB-65 Score[a] Clinical Response at SFU | ITT (PORT III/IV/V) | | |
|---|---|---|---|
| | Solithromycin IV to Oral N=328 n (%) | Moxifloxacin IV to Oral N=333 n (%) | Difference (95% CI) [b] |
| **0** | n=30 | n=39 | |
| Success | 25 (83.3) | 34 (87.2) | -3.85 (-23.8, 16.1) |
| **1** | n=135 | n=131 | |
| Success | 125 (92.6) | 116 (88.5) | 4.04 (-3.7, 11.8) |
| **2** | n=119 | n=113 | |
| Success | 98 (82.4) | 99 (87.6) | -5.26 (-15.3, 4.8) |
| **3** | n=28 | n=29 | |
| Success | 21 (75.0) | 24 (82.8) | -7.76 (-32.4, 16.9) |

Investigator assessments of clinical response at SFU in patients with a pathogen are shown below. In both populations there was numerical inferiority for solithromycin. The lower bounds of the 95% CI are < -10% but the study was not powered for a formal comparison of outcomes in these sub-populations.

**Table 41 Investigator Assessment of Clinical Response at SFU - mITT-EMA and ME-EMA-SFU Populations (PORT III/IV/V Patients)**

| Clinical Response at SFU | mITT-EMA | | | ME-EMA-SFU | | |
|---|---|---|---|---|---|---|
| | Solithromycin IV to Oral N=124 n (%) | Moxifloxacin IV to Oral N=97 n (%) | Difference (95% CI) [a] | Solithromycin IV to Oral N=114 n (%) | Moxifloxacin IV to Oral N=93 n (%) | Difference (95% CI) [a] |
| Success | 105 (84.7) | 88 (90.7) | -6.04 (-13.9, 4.1) | 100 (87.7) | 85 (91.4) | -3.68 (-11.5, 6.1) |
| Failure | 19 (15.3) | 9 (9.3) | | 14 (12.3) | 8 (8.6) | |
| Failure | 14 (11.3) | 9 (9.3) | | 14 (12.3) | 8 (8.6) | |
| Indeterminate | 5 (4.0) | 0 | | N/A | N/A | |

Source Data: Table 14.2.3.7e. CI=confidence interval; ME-EMA-SFU=microbiologically evaluable short-term follow-up; mITT-EMA=microbiological intent-to-treat; N/A=not applicable.

a. Difference in clinical success rates (solithromycin minus moxifloxacin); Adjusted CIs are calculated using the Miettinen and Nurminen method adjusted for the randomization stratification factors of geographic region and asthma/ COPD.

Investigator assessment of clinical response at SFU by the most relevant baseline pathogens generally demonstrated numerical inferiority for solithromycin. Microbiological responses were inferred and therefore reflected the numerical inferiority of solithromycin that was observed for clinical responses.

**Table 42 Investigator Assessment of Clinical Response at SFU by Baseline Pathogens - mITT-EMA Population (PORT III/IV/V Patients)**

| Baseline Pathogen | SFU | |
|---|---|---|
| | Solithromycin IV to Oral N=124 n/N (%) [a] | Moxifloxacin IV to Oral N=97 n/N (%) [a] |
| **Gram-positive Bacteria (Aerobes)** | | |
| *Staphylococcus aureus* | 27/35 (77.1) | 18/19 (94.7) |
| MRSA | 1/2 (50.0) | 2/2 (100.0) |
| MSSA | 26/33 (78.8) | 16/17 (94.1) |
| Macrolide resistant | 7/10 (70.0) | 8/9 (88.9) |
| Quinolone resistant | 0/1 (0.0) | 3/3 (100.0) |
| *Streptococcus pneumoniae* [b] | 29/34 (85.3) | 24/26 (92.3) |
| MDRSP | 6/6 (100.0) | 11/12 (91.7) |
| PSSP | 18/21 (85.7) | 9/10 (90.0) |
| PISP | 2/2 (100.0) | 12/13 (92.3) |
| PRSP | 1/1 (100.0) | 1/1 (100.0) |
| Macrolide resistant | 5/5 (100.0) | 10/11 (90.9) |

| | | |
|---|---|---|
| **Gram-negative Bacteria (Aerobes)** | | |
| *Haemophilus influenzae* | 21/24 (87.5) | 21/22 (95.5) |
| *Moraxella catarrhalis* | 3/3 (100.0) | 4/4 (100.0) |
| **Atypical Pathogens (Aerobes)** | | |
| Any *Mycoplasma pneumoniae* | 14/17 (82.4) | 10/11 (90.9) |
| Any *Legionella* spp. | 12/13 (92.3) | 12/13 (92.3) |
| Any *Legionella pneumophila* | 12/13 (92.3) | 12/13 (92.3) |

There were 19 solithromycin patients with 25 by-pathogen failures (some had 2 pathogens) and 9 moxifloxacin patients with 10 by-pathogen failures.

- For patients with staphylococcal pneumonia, 5/8 treatment failures were considered successes at EOT of which one withdrew consent but did not receive additional therapy while 4 had relapse of symptoms at the SFU visit. One of the 8 patients withdrew consent after receiving two doses of intravenous therapy and two were withdrawn from solithromycin due to failure.
- Among 5 patients with pneumococcal pneumonia one stopped dosing on Day 4 due to QTcF of 480 msec. One patient who also had *S. aureus* was a success at EOT but relapsed at SFU.
- Two of three failures with *H. influenzae* withdrew consent (on Days 1 and 4). The third also had pneumococcal infection and developed empyema.
- One failure with *K. pneumoniae* discontinued due to an AE of psychosis, one withdrew consent on the first day and one had newly diagnosed HIV with *Salmonella* spp. in blood cultures.
- Of three failures with *M. pneumoniae* one had ECR but an interruption of study drug led the investigator to initiate alternative therapy and two were treatment successes at EOT but had relapse of symptoms at SFU. One of these also had staphylococcal infection.
- The patient with *Legionella* (serologic diagnosis) who failed also had pneumococcal infection; this is the patient who was responding to therapy but stopped on Day 4 due to a QTcF value of 480 msec.

For patients with bacteraemia at baseline 9/12 in the solithromycin group (4/5 with pneumococci) and 3/3 in the moxifloxacin group were clinical successes at SFU.

The solithromycin $MIC_{50/90}$ values for *S. aureus* were 0.06/0.12 µg/mL with a maximum > 32 µg/mL and for *S. pneumoniae*, values were 0.008/0.06 µg/mL with a maximum 1 µg/mL. For *S. aureus* with MICs ≤ 0.06 µg/mL, the clinical success rate at SFU was 19/22 with a rate of 7/10 for macrolide-resistant strains. All of 11 patients with pneumococci for which MICs were ≥ 0.008 µg/mL were treatment successes (including 5 macrolide-resistant). The three treatment failures had pneumococci with MICs of 0.004 µg/mL (discontinuation for QTcF; *S. pneumoniae* and *H. influenzae* with empyema; relapse at SFU).

There were no superinfections or colonisation events in this study.

***Discussion on clinical efficacy in CAP***

Phase 2 study

There was no dose-finding study. In the Phase 2 study >75% of patients were PORT score 2 although ~50 % met the SIRS criteria. This study was not intended for inferential testing. It indicated numerical inferiority for solithromycin vs. levofloxacin (750 mg QD dose) based on clinical responses in the ITT and CE populations but slightly higher success rates in the patients with pathogens. The study provided preliminary support for the oral dosing regimen in this low PORT score population.

Phase 3 studies - general issues

These were generally of an acceptable double blind design against an appropriate comparative regimen. The patient selection criteria, pre-defined primary endpoints and non-inferiority margins were compliant with CHMP recommendations. The studies used a range of different established and unestablished tests to

detect pathogens. This is acceptable since the applicant provided analyses for defined populations with any evidence of a pathogen and with the more established (culture, urinary antigen for pneumococci and legionella or serological) evidence of a pathogen.

It was appropriate that patients with PORT II severity pneumonia were limited to ~50% in 300 and 25% in 301 (in which ~25% were to be PORT IV). In the IV/PO study (301) the applicant provided separate analyses confined to patients with PORT score III or IV only as was required since, as per CHMP guidance, PORT score II patients are not considered appropriate in CAP studies to support initial IV use.

Phase 3 PO study (300)

In this study > 30% of the total was aged ≥65 years and ~50% were PORT risk class III/IV as was targeted. Just under half of patients had some evidence of a pathogen and ~40% of these patients had *S. pneumoniae*. The primary analysis demonstrated that solithromycin was non-inferior to moxifloxacin in the ITT and CE populations, with lower bounds of 95% CI around the treatment differences of -6.9 and -7.6%. The numerical inferiority for solithromycin observed in these analyses also applied to most of the sensitivity and subset analyses that were conducted. However, success rates were comparable in the patients with PORT scores III-IV at baseline and there was no consistent trend to decreasing efficacy with increasing age or disadvantage for solithromycin at the upper end of the age range (noting there were > 60 per group aged ≥ 75 years). Additionally, solithromycin was comparable to moxifloxacin in patients with high baseline disease severity indices.

Clinical success rates in mITT patients with the major CAP pathogens were generally numerically higher for moxifloxacin. Microbiological responses were inferred and therefore showed the same pattern by pathogen as for clinical success. This pattern applied to pathogens in typical and atypical pneumonia.

Phase 3 IV/PO study (301)

The mean age was 64 years, with a majority ≥55 years. More than a third had PORT score IV. Just under half had evidence of a pathogen but only about a quarter of these patients had *S. pneumoniae*. The primary analysis showed that in the ITT population the 95% CI around the treatment difference were -7.8, 2.7. In the CE-SFU population the lower bound of the 95% CI was -10% and the upper bound did not cross zero. If the 5 patients counted as failures secondary to drug supply problems are eliminated then the clinical success rates in the CE-SFU population (PORT III/IV/V) become 88.0% for solithromycin and 92.0% for moxifloxacin with 95% CI for the difference (-9.2%, 1.2).

Investigator assessment of clinical success rates were generally similar in the analyses by randomization strata (geographic region and history of asthma/COPD) compared to the overall population. There was no appreciable effect of gender or age on the clinical response at SFU and no disadvantage for solithromycin in the small subset in the upper quartile for CRP, WBC and procalcitonin levels at baseline.
Investigator assessments of clinical response at SFU in patients with a pathogen showed numerical inferiority for solithromycin overall and for most of the major pathogens. Microbiological responses were inferred and therefore reflected the numerical inferiority of solithromycin that was observed for clinical responses.

Conclusions on the use of solithromycin (PO or IV/PO) to treat CAP

In patients with PORT scores II-III (only ~10% were PORT score IV in study 300) oral solithromycin met the required non-inferiority margin vs. moxifloxacin but there was rather consistent numerical inferiority. In patients with PORT scores ≥ III in the IV/PO study the primary analysis showed that in the ITT population the 95% CI around the treatment difference were -7.8, 2.7. In the CE-SFU population the lower bound of the 95% CI was -10% and the upper bound did not cross zero.

There is a need to view this demonstration of efficacy in the context of the safety concerns. Even with PO only dosing there was a substantial risk of ALT elevation and it may be expected that in routine use there will be cases of serious hepatotoxicity as have been observed with telithromycin (see the next section for the discussion of safety). Furthermore, solithromycin cannot be regarded as an agent that can address an unmet need. There may be a very few patients who cannot receive a beta-lactam and have a pathogen that is resistant both to the older macrolides and fluoroquinolones for whom solithromycin, like telithromycin, could be an option. There are too few telithromycin-resistant but solithromycin-susceptible organisms to consider that this use would be important.

Overall, the current evidence does not suggest that the benefit-risk relationship would be favourable for use of solithromycin (PO or IV/PO) to treat CAP.

Section 5.1 of the SmPC

If the patients with any evidence of a pathogen in study 300 are taken into account they do not markedly increase the numbers with a pathogen or the microbiologically evaluable totals. Furthermore, the comparison of outcomes in these slightly larger populations in study 300 do not change the conclusion that solithromycin was generally numerically inferior to moxifloxacin.

Regarding which species can be listed in section 5.1 of the SmPC under a heading of organisms treated successfully there are adequate numbers of patients with evidence of the commonest CAP pathogens based on well-established methods. Therefore it is not necessary to raise issues over the more experimental methods that were applied although the details of sensitivity and specificity reported in the dossier do cause some concerns due to low specificity for some methods. Therefore no further comment is made on the claims made for demonstration of clinical efficacy by species except to point out that qualifications regarding irrelevant mechanisms of resistance must be removed from the list.

***Conclusion on clinical efficacy against CAP***

The benefit-risk relationship does not support an indication for use of PO or IV/PO solithromycin to treat CAP.

### 3.3.4 Clinical safety

The integrated safety analysis focusses on the studies shown in the table below. The tables showing integrated Phase 3 safety data include the PORT II patients in study 301.

**Table 1 Number of Subjects and Patients in Pooled Studies**

| Clinical Phase | Total Number of Subjects | Number of Subjects Administered Solithromycin | Number of Subjects Administered Comparator |
|---|---|---|---|
| Integrated Analysis Studies | | | |
| **Phase 3 and Phase 2 Patients (All)** | **1846** | **920** | **926** |
| Phase 3 and Phase 2 Patients (excluding PORT II in CE01-301) | 1646 | 815 | 831 |
| Phase 3 Patients | 1714 | 856 | 858 |
| Phase 3 Patients (excluding PORT II in CE01-301) | 1514 | 751 | 763 |
| Phase 2 Patients | 132 | 64 | 68 |
| **Phase 1 Subjects (All)** | **671** [a] | **554** | **176** |
| Phase 1 Clinical Pharmacology Subjects | 662 | 531 | 191 |
| Oral Clinical Pharmacology Subjects | 212 | 188 | 38 [b] |
| IV Clinical Pharmacology Subjects | 363 | 270 | 138 |
| Phase 1 Biopharmaceutics Oral Subjects | 96 | 96 | 0 |
| TOTAL | | | |
| **Integrated Studies** | **N=2517** [a] | **N=1474** | **N=1102** |

Non-integrated studies include ongoing studies in treatment of gonorrhoea, in children with CAP and the separate programme that is ongoing in Japan. There have been no deaths and there have been in 9 SAEs in 8 patients.

**Adverse events**

Phase 3 CAP studies

Between-treatment differences were mainly due to IV-related AEs with solithromycin in study 301.

**Table 26 Summary of Patients with TEAEs in Individual and Pooled Phase 3 CAP Studies**

| | Study CE01-300 | | Study CE01-301 MAA | | Pooled Phase 3 Studies | |
|---|---|---|---|---|---|---|
| | Soli (N=424) n (%) | Moxi (N=432) n (%) | Soli (N=327) n (%) | Moxi (N=331) n (%) | Soli (N=856) n (%) | Moxi (N=858) n (%) |
| **TEAEs (all)** | 155 (36.6) | 154 (35.6) | 164 (50.2) | 124 (37.5) | 378 (44.2) | 302 (35.2) |
| TEAEs (excluding infusion site events) | 155 (36.6) | 154 (35.6) | 113 (34.6) | 116 (35.0) | 304 (35.5) | 294 (34.3) |
| TEAEs related to study drug (including infusion site events) | 43 (10.1) | 54 (12.5) | 104 (31.8) | 47 (14.2) | 191 (22.3) | 110 (12.8) |
| TEAEs leading to premature discontinuation of drug | 16 (3.8) | 13 (3.0) | 14 (4.3) | 15 (4.5) | 41 (4.8) | 29 (3.4) |
| **Severe TEAEs** | 21 (5.0) | 21 (4.9) | 23 (7.0) | 17 (5.1) | 49 (5.7) | 39 (4.5) |
| **Serious TEAEs (SAEs)** | 28 (6.6) [a] | 27 (6.3) | 25 (7.6) | 20 (6.0) | 58 (6.8) [a] | 50 (5.8) |
| SAEs related to study drug | 0 | 0 | 1 (0.3) | 1 (0.3) | 2 (0.2) | 1 (0.1) |
| SAEs leading to premature discontinuation of drug | 11 (2.6) | 4 (0.9) | 4 (1.2) | 6 (1.8) | 18 (2.1) | 11 (1.3) |
| SAEs leading to death | 6 (1.4) | 6 (1.4) | 5 (1.5) | 6 (1.8) [b] | 11 (1.3) | 13 (1.5) |

The table below shows TEAEs which occurred in >2% of patients in either treatment group by study. Leaving aside AEs of pneumonia, which presumably reflect efficacy, only dizziness (PO and IV), headache (PO), nausea (IV), hypokalaemia (IV) and insomnia (IV) appear to have been more common with solithromycin. Diarrhoea was more common with moxifloxacin in both studies. Most TEAEs were of mild or moderate intensity. Most severe AEs were also SAEs. Excluding infusion-related AEs, the most common drug-related AEs (Investigators' judgment) were diarrhoea (5.4% solithromycin; 3.7% moxifloxacin), nausea (1.5% vs. 1.6%) and dizziness (1.2% vs. 0.5%).

**Table 28 Summary of Most Frequently Reported (≥2%) TEAEs in Individual and Pooled Phase 3 Trials**

| | Study CE01-300 | | Study CE01-301 MAA | | Pooled Phase 3 | |
|---|---|---|---|---|---|---|
| | Soli Oral N=424 n (%) | Moxi Oral N=432 n (%) | Soli IV to Oral N=327 n (%) | Moxi IV to Oral N=331 n (%) | Soli N=856 n (%) | Moxi N=858 n (%) |
| **Patients with ≥1 TEAE (all)** | **155 (36.6)** | **154 (35.6)** | **164 (50.2)** | **124 (37.5)** | **378 (44.2)** | **302 (35.2)** |
| **Patients with ≥1 TEAE (excluding infusion site events)** | **155 (36.6)** | **154 (35.6)** | **113 (34.6)** | **116 (35.0)** | **304 (35.5)** | **294 (34.3)** |
| **Preferred Term (Excluding Infusion Site Events), n (%)** | | | | | | |
| Diarrhea | 18 (4.2) | 28 (6.5) | 11 (3.4) | 22 (6.6) | 37 (4.3) | 53 (6.2) |
| Headache | 19 (4.5) | 11 (2.5) | 7 (2.1) | 16 (4.8) | 34 (4.0) | 29 (3.4) |
| Nausea | 15 (3.5) | 17 (3.9) | 8 (2.4) | 3 (0.9) | 29 (3.4) | 24 (2.8) |
| Dizziness | 9 (2.1) | 7 (1.6) | 7 (2.1) | 2 (0.6) | 20 (2.3) | 12 (1.4) |
| Pneumonia | 7 (1.7) | 5 (1.2) | 4 (1.2) | 5 (1.5) | 18 (2.1) | 10 (1.2) |
| Vomiting | 10 (2.4) | 10 (2.3) | 2 (0.6) | 2 (0.6) | 14 (1.6) | 13 (1.5) |
| Hypokalemia | 2 (0.5) | 3 (0.7) | 10 (3.1) | 7 (2.1) | 13 (1.5) | 12 (1.4) |
| Hypertension | 6 (1.4) | 5 (1.2) | 6 (1.8) | 8 (2.4) | 12 (1.4) | 15 (1.7) |
| Insomnia | 2 (0.5) | 4 (0.9) | 7 (2.1) | 3 (0.9) | 11 (1.3) | 9 (1.0) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Infusion Site Preferred Terms, n (%)** | | | 99 (30.3) | 22 (6.6) | | |
| Infusion site pain | - | - | 33 (10.1) | 6 (1.8) | 45 (5.3) | 6 (0.7) |
| Infusion site phlebitis | - | - | 32 (9.8) | 4 (1.2) | 43 (5.0) | 4 (0.5) |
| Infusion related reaction | - | - | 19 (5.8) | 1 (0.3) | 28 (3.3) | 1 (0.1) |
| Infusion site erythema | - | - | 12 (3.7) | 2 (0.6) | 19 (2.2) | 2 (0.2) |
| Infusion site thrombosis | - | - | 9 (2.8) | 6 (1.8) | 9 (1.1) | 7 (0.8) |
| Infusion site paresthesia | - | - | 8 (2.4) | 0 | 9 (1.1) | 0 |

**Table 32 Summary of Study Drug-Related TEAEs (≥1%) in Individual and Pooled Phase 3 Trials**

| | Study CE01-300 | | Study CE01-301 MAA | | Pooled Phase 3 | |
|---|---|---|---|---|---|---|
| | Soli Oral N=424 n (%) | Moxi Oral N=432 n (%) | Soli IV to Oral N=327 n (%) | Moxi IV to Oral N=331 n (%) | Soli N=856 n (%) | Moxi N=858 n (%) |
| **Patients with ≥1 TEAE (all)** | **43 (10.1)** | **54 (12.5)** | **104 (31.8)** | **47 (14.2)** | **191 (22.3)** | **110 (12.8)** |
| **Preferred Term (Excluding Infusion Site Events), n (%)** | | | | | | |
| Diarrhoea | 10 (2.4) | 15 (3.5) | 7 (2.1) | 15 (4.5) | 21 (5.4) | 32 (3.7) |
| Nausea | 8 (1.9) | 11 (2.5) | 2 (0.6) | 2 (0.6) | 13 (1.5) | 14 (1.6) |
| Dizziness | 3 (0.7) | 2 (0.5) | 4 (1.2) | 1 (0.3) | 10 (1.2) | 4 (0.5) |
| Vomiting | 3 (0.7) | 5 (1.2) | 2 (0.6) | 2 (0.6) | 6 (0.7) | 7 (0.8) |

Phase 2 study

The majority of AEs were mild or moderate in intensity. The most frequently reported were diarrhoea (5.9% levofloxacin; 7.8% solithromycin group), nausea (10.3% vs. 1.6%) and vomiting (4.4% vs. 0.0%). Most treatment-related AEs were associated with GI disorders, and were reported in 10.3% levofloxacin and 7.8% solithromycin patients.

Phase 1 studies

The difference between oral only and IV solithromycin groups reflected the infusion-related problems. The differences vs. placebo also reflected gastrointestinal TEAEs in the solithromycin groups.

**Table 27 Summary of Patients with TEAEs in Pooled Phase 1 Solithromycin Studies**

| | Solithromycin | | | | Phase 1 Control |
|---|---|---|---|---|---|
| **Subjects with at least 1:** | Oral (N = 296) n (%) | IV to Oral (N = 27) n (%) | IV (N = 243) n (%) | Total (N = 554) n (%) | (N = 176) n (%) |
| **TEAE** | 142 (48.0) | 23 (85.2) | 191 (78.6) | 355 (64.1) | 60 (34.1) |
| TEAE related to study drug | 117 (39.5) | 23 (85.2) | 179 (73.7) | 318 (57.4) | 43 (24.4) |
| TEAE leading to premature discontinuation of drug | 3 (1.0) | 0 | 20 (8.2) | 23 (4.2) | 1 (0.6) |
| **Severe TEAE** | 1 (0.3) | 0 | 3 (1.2) | 4 (0.7) | 0 |
| **Serious TEAE (SAE)** | 0 | 0 | 0 | 0 | 0 |
| SAE related to study drug | 0 | 0 | 0 | 0 | 0 |
| SAE leading to premature discontinuation of drug | 0 | 0 | 0 | 0 | 0 |
| SAE leading to death | 0 | 0 | 0 | 0 | 0 |

Adverse events of special interest for macrolides

*Cardiac effects*

In the pooled Phase 3 CAP studies the mean changes from baseline in QTcF interval were 5.6 vs. 13.7 ms on Day 4 and 5.5 vs. 11 ms at EOT for the solithromycin and moxifloxacin groups, respectively. The mean heart rate decreased from baseline to each visit in both treatment arms. In study 300, with more data points, there were nearly identical declines in heart rate between treatment groups.

In the pooled Phase 3 studies, 63 (7.4%) solithromycin vs. 49 (5.7%) moxifloxacin patients had treatment-emergent tachycardia while rates determined from ECGs were 62 (7.2%) vs. 38 (4.4%). The mean changes from baseline to maximum rate were 19.5 bpm (range: 1 to 65 bpm) vs. 21.1 bpm (range: 3 to 87 bpm). Post-baseline heart rates of >120 bpm occurred in 34 (4.0%) vs. 29 (3.4%), respectively. Cardiac AESIs were reported more often in moxifloxacin patients (cardiac failure 1.3% vs. 2.1%; tachyarrhythmia 0.6% vs. 1.2%; torsade de pointes/QT prolongation (0.7% vs. 1.0%).

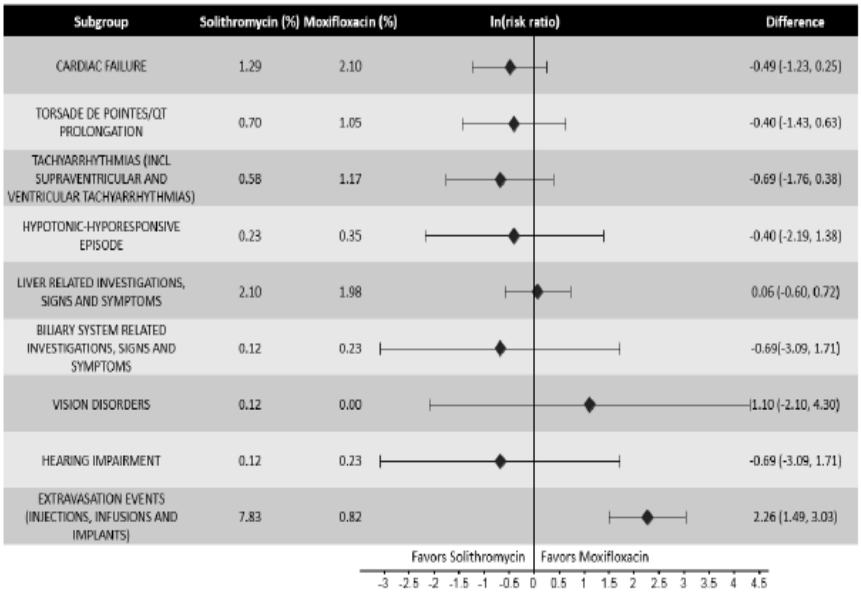
*Hepatic effects*

Laboratory abnormalities (including ALT or AST elevation) not associated with symptoms, resulting in study drug discontinuation or requiring treatment were not considered AEs. The AEs are shown below.

**Table 47 Liver-related TEAEs - Phase 1, 2, and 3 Studies**

| Outcome Measure | Phase 1 Studies | | Phase 2/3 CAP Studies | | Phase 3 CAP Studies | |
|---|---|---|---|---|---|---|
| | Solithromycin N=554 | Comparator N=176 | Solithromycin (N=920) | Moxi/Levo (N=926) | Solithromycin N=856 | Moxifloxacin N=858 |
| **Liver-related TEAEs (any)** | **4 (0.7)** | **0** | **19 (2.1)** | **18 (2.1)** | **18 (2.1)** | **17 (2..0)** |
| Hepatic enzyme increased | 1 (0.2) | 0 | 7 (0.8) | 4 (0.4) | 7 (0.8) | 4 0.5) |
| ALT increased | 2 (0.4) | 0 | 6 (0.7) | 9 (1.0) | 5 (0.6) | 8 (0.9) |
| AST increased | 1 (0.2) | 0 | 5 (0.5) | 5 (0.5) | 4 (0.5) | 4 (0.5) |
| Hepatomegaly | 0 | 0 | 2 (0.2) | 0 | 2 (0.2) | 0 |
| LFT abnormal | 0 | 0 | 2 (0.2) | 1 (0.1) | 2 (0.2) | 1 (0.1) |
| Transaminases increased | 0 | 0 | 2 (0.2) | 2 (0.2) | 2 (0.2) | 2 (0.2) |
| ALP increased | 0 | 0 | 1 (0.1) | 1 (0.1) | 1 (0.1) | 1 (0.1) |
| Ascites | 0 | 0 | 0 | 1 (0.1) | 0 | 1 (0.1) |
| Hepatosplenomegaly | 0 | 0 | 0 | 1 (0.1) | 0 | 1 (0.1) |
| GGT Increased | 0 | 0 | 0 | 1 (0.1) | 0 | 0 |

**Figure 13 AESI Incidence (%) and ln (Risk Ratio)**




## Deaths

In the pooled Phase 3 studies there were 11 deaths in the solithromycin and 13 in the moxifloxacin group. One additional death in CE01-301 occurred in a PORT II patient who received moxifloxacin. Most deaths in each treatment group were attributable to underlying respiratory or cardiac diseases in patients presenting with multiple comorbidities and risk factors. No TEAEs resulting in death were considered related to study drug.

Table 35 SAEs with Outcome of Death (Phase 2/3 CAP Pool)

| Patient / Sex /Age (years) | Preferred Term | Day of Onset [a] | Duration # Days | Intensity | Relationship |
|---|---|---|---|---|---|
| **Study CE01-300** | | | | | |
| **Solithromycin 800/400 mg QD** | | | | | |
| [redacted] / Female / [redacted] | Multi-organ failure | 10 | 4 | Severe | Unrelated |
| [redacted] / Female / [redacted] | Acute respiratory failure | 1 | 22 | Severe | Unrelated |
| [redacted] / Female / [redacted] | Bronchospasm | 2 | 2 | Severe | Unrelated |
| [redacted] / Female / [redacted] | Cerebrovascular accident | 5 | 1 | Severe | Unrelated |
| [redacted] / Male / [redacted] | Acute myocardial infarction | 3 | 1 | Severe | Unrelated |
| [redacted] / Male / [redacted] | Cerebrovascular accident | 13 | 7 | Severe | Unrelated |
| **Moxifloxacin 400 mg QD** | | | | | |
| [redacted] / Male / [redacted] | Acute respiratory distress syndrome | 2 | 9 | Severe | Unrelated |
| [redacted] / Female / [redacted] | Cardiac failure congestive | 8 | 3 | Severe | Unrelated |
| [redacted] / Male / [redacted] | Respiratory failure | 4 | 19 | Severe | Unrelated |
| | Cardiac failure | 8 | 15 | Severe | Unrelated |
| [redacted] / Male / [redacted] | Pulmonary embolism | 4 | 2 | Severe | Unrelated |
| [redacted] / Female / [redacted] | Acute respiratory failure | 4 | 7 | Severe | Unrelated |
| [redacted] / Male / [redacted] | Hepatorenal syndrome | 7 | 1 | Severe | Unrelated |
| **Study CE01-301** | | | | | |
| **Solithromycin 400 mg QD** | | | | | |
| [redacted] / Female / [redacted] | Cardiac arrest | 8 | 1 | Severe | Unrelated |
| [redacted] / Male / [redacted] | Cardiac arrest | 3 | 1 | Severe | Unrelated |
| [redacted] / Male / [redacted] | Myocardial infarction | 25 | 1 | Severe | Unrelated |
| [redacted] / Female / [redacted] | Upper airway obstruction | 3 | 6 | Severe | Unrelated |
| | Myocardial infarction | 5 | 4 | Severe | Unrelated |
| | Septic shock | 8 | 1 | Severe | Unrelated |
| [redacted] / Male / [redacted] | Cardiac failure | 7 | 1 | Severe | Unrelated |
| **Moxifloxacin 400 mg QD** | | | | | |
| [redacted] / Male / [redacted] | Respiratory failure | 1 | 14 | Severe | Unrelated |
| | Sepsis | 2 | 13 | Severe | Unrelated |
| | Influenza | 5 | 10 | Severe | Unrelated |
| [redacted] / Female / [redacted] | Cardiac arrest | 6 | 1 | Severe | Unrelated |
| [redacted] / Male / [redacted] | Gastric haemorrhage | 5 | 3 | Severe | Unrelated |
| | Septic shock | 6 | 2 | Severe | Unrelated |
| | Renal failure acute | 6 | 2 | Severe | Unrelated |
| [redacted] / Female/ [redacted] | Aspiration | 2 | 1 | Severe | Unrelated |
| [redacted] / Male / [redacted] | Myocardial infarction | 2 | 3 | Severe | Unrelated |
| | Acute respiratory failure | 2 | 3 | Severe | Unrelated |
| | Chronic obstructive pulmonary disease | 2 | 3 | Severe | Unrelated |
| [redacted] / Male / [redacted] | Cardiac failure congestive | 17 | 11 | Severe | Unrelated |
| [redacted] / Male / [redacted] | Adrenal gland cancer | 1 | 12 | Severe | Unrelated |
| **Study CE01-200** | | | | | |
| **Levofloxacin 750 mg QD** | | | | | |
| [redacted] / Male / [redacted] | Pulmonary embolism | 4 | 2 | Severe | Unrelated |

**SAEs**

In the Phase 3 studies the overall incidence of SAEs was comparable between solithromycin (6.8%) and moxifloxacin (5.8%) groups. With the exception of worsening pneumonia (13 [1.5%] vs. 6 [0.7%]) and acute respiratory failure (6 [0.7%] vs. 2 [0.2%]) the incidence of SAEs by PT was ≤3 patients in either treatment group. Most SAEs were attributable to underlying respiratory or cardiac diseases. There were no SAEs at infusion sites. In 301 patients in PORT II/IV/V 3 SAEs were considered related to study drug by the investigators (urticaria and anaphylactic reaction in single solithromycin patients and anaphylactic reaction in a moxifloxacin patient).

In the Phase 2 study non-fatal SAEs were reported for 2 solithromycin (3.1%) and 6 (8.8%) levofloxacin patients. Two SAEs were considered related to study drug by the investigators (convulsion and hyponatremia in 1 levofloxacin patient).

No SAEs occurred in Phase 1 studies.

**Laboratory findings**

Hepatobiliary parameters

- With 5 days oral dosing in study 300 the incidence of ALT elevation >5×ULN was 7 (1.7%) vs. 5 (1.2%) and the rates for AST elevation to >5×ULN and bilirubin elevation to >ULN were similar between groups. An additional solithromycin patient had such elevations and met Hy's Law criteria

(see further below on this case) but is not shown in the table because the laboratory parameters were collected from an outside hospital. This patient had multi-organ failure and died.

- With 7 days IV to PO dosing in 301 the rates for ALT >5×ULN were 3.1% vs. 0.7%. These events mostly occurred earlier and resolved more rapidly than among moxifloxacin recipients. Most patients were completely asymptomatic and did not have bilirubin elevations.

**Table 46 Liver-related Laboratory Elevations in Phase 3 Studies**

| Outcome Measure | | CE01-300 | | CE01-301 | | Phase 3 CAP Studies | |
|---|---|---|---|---|---|---|---|
| | | Solithromycin | Moxifloxacin | Solithromycin | Moxifloxacin | Solithromycin | Moxifloxacin |
| ALT | >ULN | 172/411 (41.8) | 141/422 (33.4) | 198/417 (47.5) | 122/413 (29.5) | 370/828 (44.7) | 263/835 (31.5) |
| | >3×ULN | 22/411 (5.4) | 15/422 (3.6) | 38/417 (9.1) | 15/413 (3.6) | 60/828 (7.2) | 30/835 (3.6) |
| | >5×ULN | 7/411 (1.7) | 5/422 (1.2) | 13/417 (3.1) | 3/413 (0.7) | 20/828 (2.4) | 8/835 (1.0) |
| | >10×ULN | 1/411 (0.2) | 2/422 (0.5) | 0/417 | 0/413 | 1/828 (0.1) | 2/835 (0.2) |
| | >20×ULN | 1/411 (0.2) | 1/422 (0.2) | 0/417 | 0/413 | 1/828 (0.1) | 1/835 (0.1) |
| AST | >ULN | 130/406 (32.0) | 112/416 (26.9) | 154/416 (37.0) | 97/409 (23.7) | 284/822 (34.5) | 209/825 (25.3) |
| | >3×ULN | 10/406 (2.5) | 8/416 (1.9) | 20/416 (4.8) | 10/409 (2.4) | 30/822 (3.6) | 18/825 (2.2) |
| | >5×ULN | 4/406 (1.0) | 4/416 (1.0) | 9/416 (2.2) | 2/409 (0.5) | 13/822 (1.6) | 6/825 (0.7) |
| | >10×ULN | 2/406 (0.5) | 2/416 (0.5) | 2/416 (0.5) | 0/409 | 4/822 (0.5) | 2/825 (0.2) |
| | >20×ULN | 0/406 | 1/416 (0.2) | 0/416 | 0/409 | 0/822 | 1/825 (0.1) |
| ALT or AST | >ULN | 193/412 (46.8) | 159/422 (37.7) | 219/417 (52.5) | 143/413 (34.6) | 412/829 (49.7) | 302/835 (36.2) |
| | >3×ULN | 25/412 (6.1) | 17/422 (4.0) | 42/417 (10.1) | 19/413 (4.6) | 67/829 (8.1) | 36/835 (4.3) |
| | >5×ULN | 8/412 (1.9) | 5/422 (1.2) | 13/417 (3.1) | 3/413 (0.7) | 21/829 (2.5) | 8/835 (1.0) |
| | >10×ULN | 2/412 (0.5) | 3/422 (0.7) | 2/417 (0.5) | 0/413 | 4/829 (0.5) | 3/835 (0.4) |
| | >20×ULN | 1/412 (0.2) | 1/422 (0.2) | 0/417 | 0/413 | 1/829 (0.1) | 1/835 (0.1) |
| Total Bilirubin | >ULN<br>(and proportion with elevated direct bilirubin) | 15/412 (3.6)<br>6/14 (42.9) | 16/422 (3.8)<br>9/14 (64.3) | 21/416 (5.0)<br>10/21 (47.6) | 17/413 (4.1)<br>7/17 (41.2) | 36/828 (4.3)<br>16/35 (45.7) | 33/835 (4.0)<br>16/31 (51.6) |
| | >2×ULN<br>(and proportion with elevated direct bilirubin) | 2/412 (0.5)<br>1/2 (50) | 0/422<br>N/A | 2/416 (0.5)<br>2/2 (100) | 2/413 (0.5)<br>2/2 (100) | 4/828 (0.5)<br>3/4 (75) | 2/835 (0.2)<br>2/2 (100) |
| ALP | >1.5×ULN | 22/411 (5.4) | 17/423 (4.0) | 21/417 (5.0) | 7/415 (1.7) | 48/828 (5.2) | 24/838 (2.9) |
| ALT or AST >3×ULN | & with Total Bilirubin >1.5×ULN | 1/412 (0.2) | 1/422 (0.2) | 1/416 (0.2) | 1/413 (0.2) | 2/828 (0.2) | 2/835 (0.2) |
| | & with Total Bilirubin >2.0×ULN | 0/412 | 0/422 | 1/416 (0.2) | 1/413 (0.2) | 1/828 (0.1) | 1/835 (0.1) |
| | & with ALP >1.5×ULN | 10/412 (2.4) | 5/422 (1.2) | 11/416 (2.6) | 3/413 (0.7) | 21/827 (2.5) | 8/835 (1.0) |

| Outcome Measure | CE01-300 | | CE01-301 | | Phase 3 CAP Studies | |
|---|---|---|---|---|---|---|
| | Solithromycin | Moxifloxacin | Solithromycin | Moxifloxacin | Solithromycin | Moxifloxacin |
| AEs associated with nausea, vomiting, anorexia, abdominal pain, or fatigue | 32/412 (7.8) | 31/423 (7.3) | 23/418 (5.5) | 12/415 (2.9) | 55/830 (6.6) | 43/838 (5.1) |
| ALT or AST >ULN and AEs associated with nausea, vomiting, anorexia, abdominal pain, or fatigue | 6/52 (11.5) | 0/6 | 25/431 (5.8) | 24/320 (7.5) | 24/412 (5.8) | 20/302 (6.6) |
| ALT or AST >3×ULN and AEs associated with nausea, vomiting, anorexia, abdominal pain, or fatigue | 0/3 | N/A | 2/69 (2.9) | 2/39 (5.1) | 2/67 (3.0) | 1/36 (2.8) |
| Liver Related Study Drug Discontinuation | 2/549 (0.4) | 0/175 | 2/891 (0.2) | 1/903 (0.1) | 2/827 (0.2) | 1/835 (0.1) |

The applicant considers that the higher rate of ALT elevation with solithromycin in 301 is not likely due to the additional 2 days of therapy since 11/13 with ALT >5×ULN had their peak ALT on Day 4 with improvement, typically during continued dosing, observed by Day 7. In study 300 5/7 solithromycin patients with such elevations also had their peak ALT on Day 4. The applicant considers that the higher solithromycin plasma exposures in 301 plus disease severity most likely explain the difference.

In the Phase 2 study Grade 3 ALT elevations (3.0-8.0×ULN) were observed for 1 solithromycin and 2 levofloxacin patients. The solithromycin patient was found at baseline to be HCV positive and had a baseline ALT of 90 IU that increased to 222 IU. This same patient was the only one in the solithromycin group to have a Grade 3 AST elevation.

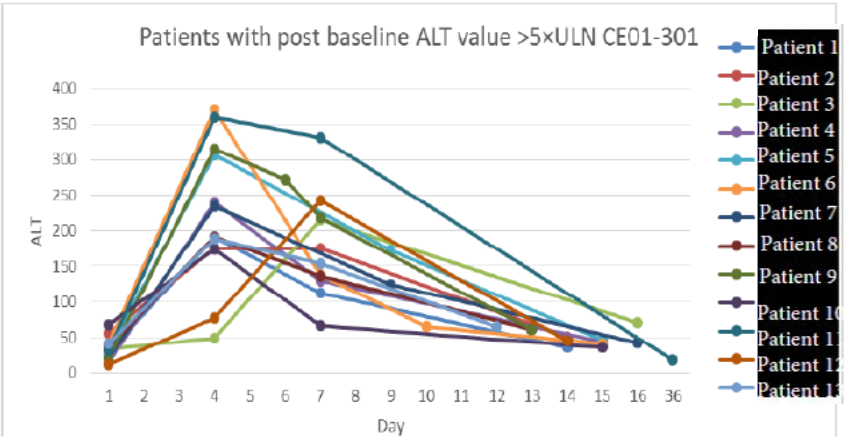
- There were two subjects in Phase 1 studies who had transaminase elevations >5×ULN, one of whom had an ALT >3×ULN.

- There were 3 non-CAP patients who received longer durations (>7 days) of treatment who had transaminase elevations >5×ULN.

Across the Phase 1-3 studies most patients with transaminases >3×ULN had their peak result between Days 1-5 (median Day 4) and then decreased subsequently.

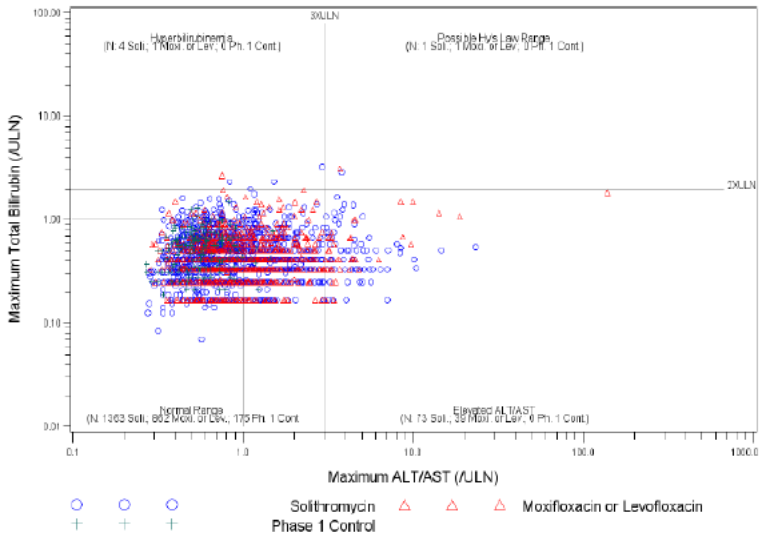
- In 300 5/8 solithromycin patients with ALT >5×ULN reached peak ALT at Day 4 and the other 3 at the SFU visit. One (see above) died in hospital with sepsis and multi-organ system failure. One had marked ALT elevation without symptoms or bilirubin elevation and had normalisation of ALT at follow-up on Day 29.
- In 301 11/13 solithromycin patients with ALT >5×ULN reached peak ALT at Day 4 and the other 2 at Day 7. At SFU (Day 12 to 17), the ALT had normalised or was nearly normal. The majority was still receiving study drug on Day 7 when declines from peak elevations in ALT were observed. In contrast, for moxifloxacin/levofloxacin 75% cases of ALT >5×ULN occurred at EOT or later. For the 9 solithromycin patients in 301 with AST >5×ULN the peak was at Day 4 with great improvement by Day 7 and normal or near normal values at SFU.

**Figure 10 ALT Values over Time for Patients with ALT >5×ULN in Study CE01-301**




The drug-induced serious hepatotoxicity (eDISH) plot below compares ALT or AST values with peak total bilirubin in 1474 subjects (ALT and AST >3×ULN and total bilirubin >2×ULN are plotted).

**Figure 8 Evaluation of Drug Induced Serious Hepatotoxicity Plot - Maximum of AST and ALT vs. Total Bilirubin (All Studies)**



In the Phase 3 studies 3 patients met laboratory parameters consistent with Hy's Law. Two received solithromycin - one per Phase 3 study), of which one was the patient who died with multi-organ failure for whom laboratory parameters were collected from an outside hospital. The applicant considers that none met Hy's Law criteria for drug-induced liver injury.

Details of the two solithromycin patients are as follows:

- A 34-year-old white female with an unremarkable medical history was enrolled with PORT II pneumonia after one dose of Augmentin. No bacterial pathogen was identified. She completed 3 IV and 4 oral doses and was a clinical success at SFU visits. Baseline and Day 7 labs were normal. At the SFU visit on Day 12 her ALT was 130 U/L (3.8×ULN) with normal bilirubin. She was asymptomatic and on Day 26 she had normal aminotransferase levels but elevated total bilirubin (2.9 mg/dL) and ALP without symptoms or jaundice. She refused additional evaluations. Less than 20% of the total serum bilirubin was conjugated (direct), which is not expected for a Hy's Law case. Reviewers in the expert panel of hepatic safety consultants concurred with the Sponsor's assessment that Hy's Law was not met.
- The second patient had an ALT elevation that occurred after admission to a second hospital and local labs were not entered into the clinical database but were captured in the SAE reports. This case was a 58-year-old white female with a history of inflammation of liver, non-obstructive biliary calculi, morbid obesity, hypertension, COPD, poly-substance abuse, anxiety, oedema and hyperbilirubinaemia who had multi-lobar PORT III pneumonia. She had no concomitant medications. Baseline labs showed elevated hepatic aminotransferase levels and bilirubin, impaired coagulation and low albumin. In retrospect, she had decompensated end stage liver disease and she met Hy's Law laboratory criteria at study baseline (AST 3.1×ULN and total bilirubin >2×ULN). She received oral solithromycin for 5 days and had improvement at Days 4 and 7 with stable LFTs. A toxicology panel was positive for benzodiazepines, cocaine and opiates and an ultrasound indicated underlying cirrhosis. Respiratory failure occurred shortly after admission and mechanical ventilation was initiated. She developed renal and hepatic impairment consistent with shock liver and progressive pre-renal azotaemia. On Day 11 liver function deteriorated with multi-organ failure and she died on Day 13. No autopsy was performed. Due to the alternative explanation for hepatic decompensation this was not considered a Hy's Law case by the sponsor or the hepatic safety panel.

Serum Chemistry Parameters

In Phase 3 studies serum glucose levels fell over time in both treatment groups. There were no clinically relevant differences between treatment groups in the shift analyses except for the higher incidence of shifts of ≥2 toxicity grades in ALT, AST and ALP parameters in solithromycin-treated patients.

**Table 62 Summary of Post-Baseline Shifts of ≥2 Toxicity Grades for Selected Serum Chemistry Parameters in Pooled Phase 3 Studies**

| Parameter (Unit) | Condition | Solithromycin N=856 n/N1 (%) | Moxifloxacin N=858 n/N1 (%) |
|---|---|---|---|
| ALT (U/L) | Elevation | 84/825 (10.2) | 47/835 (5.6) |
| AST (U/L) | Elevation | 48/816 (5.9) | 29/825 (3.5) |
| Total bilirubin (mg/dL) | Hyperbilirubinemia | 3/825 (0.4) | 4/834 (0.5) |
| ALP (U/L) | Elevation | 8/774 (1.0) | 2/783 (0.3) |
| Albumin (g/dL) | Hypoalbuminemia | 22/731 (3.0) | 42/736 (5.7) |
| Bicarbonate (mmol/L) | Low | 5/727 (0.7) | 7/734 (1.0) |
| BUN (mg/dL) | Elevation | 3/801 (0.4) | 4/807 (0.5) |
| Calcium (mg/dL) | Hypercalcemia | 0/772 | 1/784 (0.1) |
| | Hypocalcemia | 5/772 (0.6) | 9/784 (1.1) |
| Creatine kinase (U/L) | Elevation | 8/717 (1.1) | 12/718 (1.7) |
| Creatinine (mg/dL) | Elevation | 3/829 (0.4) | 5/838 (0.6) |
| Glucose (mg/dL) | Hyperglycemia | 47/827 (5.7) | 56/834 (6.7) |
| | Hypoglycemia | 5/827 (0.6) | 3/834 (0.4) |
| Phosphorus (mg/dL) | Hypophosphatemia | 9/770 (1.2) | 16/781 (2.0) |
| Potassium (mEq/L) | Hyperkalemia | 3/758 (0.4) | 5/762 (0.7) |
| | Hypokalemia | 4/758 (0.5) | 8/762 (1.0) |
| Sodium (mEq/L) | Hypernatremia | 1/828 (0.1) | 4/838 (0.5) |
| | Hyponatremia | 3/828 (0.4) | 3/838 (0.4) |

**Table 63 Treatment-emergent Grade 3 and 4 Abnormalities for Selected Clinical Chemistry Laboratory Parameters - Serum Chemistry in Pooled Phase 3 Studies**

| Parameter (Unit) | Condition | Toxicity Grade | Solithromycin N=856 n/N1 (%) | Moxifloxacin N=858 n/N1 (%) |
|---|---|---|---|---|
| ALT (U/L) | Elevation | 3 | 53/825 (6.4) | 23/835 (2.8) |
| | | 4 | 5/825 (0.6) | 7/835 (0.8) |
| Albumin (g/dL) | Hypoalbuminemia | 3 | 4/731 (0.5) | 5/736 (0.7) |
| | | 4 | 0/731 | 0/736 |
| ALP (U/L) | Elevation | 3 | 5/774 (0.6) | 3/783 (0.4) |
| | | 4 | 1/774 (0.1) | 0/783 |
| AST (U/L) | Elevation | 3 | 25/816 (3.1) | 14/825 (1.7) |
| | | 4 | 4/816 (0.5) | 4/825 (0.5) |
| Bicarbonate (mmol/L) | Low | 3 | 0/727 | 0/734 |
| | | 4 | 0/727 | 0/734 |
| BUN (mg/dL) | Elevation | 3 | 0/801 | 1/807 (0.1) |
| | | 4 | 0/801 | 0/807 |
| Calcium (mg/dL) | Hypercalcemia | 3 | 0/772 | 0/784 |
| | | 4 | 1/772 (0.1) | 0/784 |
| | Hypocalcemia | 3 | 2/772 (0.3) | 2/784 (0.3) |
| | | 4 | 0/772 | 1/784 (0.1) |
| Creatine kinase (U/L) | Elevation | 3 | 1/717 (0.1) | 4/718 (0.6) |
| | | 4 | 2/717 (0.3) | 2/718 (0.3) |
| Creatinine (mg/dL) | Elevation | 3 | 0/829 | 2/838 (0.2) |
| | | 4 | 0/829 | 0/838 |
| Glucose (mg/dL) | Hyperglycemia | 3 | 29/827 (3.5) | 27/834 (3.2) |
| | | 4 | 1/827 (0.1) | 2/834 (0.2) |
| | Hypoglycemia | 3 | 1/827 (0.1) | 1/834 (0.1) |
| | | 4 | 0/827 | 1/834 (0.1) |
| Phosphorus (mg/dL) | Hypophosphatemia | 3 | 1/770 (0.1) | 2/781 (0.3) |
| | | 4 | 1/770 (0.1) | 1/781 (0.1) |
| Potassium (mEq/L) | Hyperkalemia | 3 | 0/758 | 1/762 (0.1) |
| | | 4 | 2/758 (0.3) | 1/762 (0.1) |
| | Hypokalemia | 3 | 0/758 | 2/762 (0.3) |
| | | 4 | 0/758 | 1/762 (0.1) |
| Sodium (mmol/L) | Hypernatremia | 3 | 0/828 | 0/838 |
| | | 4 | 1/828 (0.1) | 0/838 |
| | Hyponatremia | 3 | 1/828 (0.1) | 1/838 (0.1) |
| | | 4 | 0/828 | 0/838 |
| Total Bilirubin (mg/dL) | Hyperbilirubinemia | 3 | 3/825 (0.4) | 1/834 (0.1) |
| | | 4 | 0/825 | 1/834 (0.1) |

Haematology parameters

In the pooled Phase 3 studies neutrophil counts decreased as expected with treatment and platelet counts increased slightly in both groups. Mean changes from baseline were not considered clinically meaningful. Increases in leukocytes occurred more often in solithromycin-treated patients. Although 7.6% of solithromycin patients had a Grade 3 or Grade 4 increase in leukocyte count almost none had a corresponding marked increase in neutrophils and 5 discontinued study drug (due to worsening pneumonia).

**Safety in special populations**

The incidences of TEAEs and SAEs increased with increasing age.

**Table 76 Summary of TEAEs (Excluding Infusion Site Events) and SAEs by Age Subgroup**

| | Solithromycin | | Moxifloxacin | |
|---|---|---|---|---|
| | N | n (%) | N | n (%) |
| Any TEAEs | | | | |
| <65 Years of Age | 514 | 171 (33.3) | 526 | 162 (30.8) |
| ≥65 Years of Age | 342 | 133 (38.9) | 332 | 132 (39.8) |
| ≥75 Years of Age | 144 | 60 (41.7) | 139 | 57 (41.0) |
| Any SAE | | | | |
| <65 Years of Age | 514 | 31 (6.0) | 526 | 26 (4.9) |
| ≥65 Years of Age | 342 | 27 (7.9) | 332 | 24 (7.2) |
| ≥75 Years of Age | 144 | 14 (9.7) | 139 | 10 (7.2) |

The most frequently reported TEAEs in solithromycin-treated patients aged <65 years, ≥65 years and ≥75 years were diarrhoea (4.1%, 4.7% and 6.3%, respectively), headache (3.9%, 4.1%, 5.6%) and nausea (3.5%, 3.2%, 2.8%).
For the 144 and 139 patients aged ≥75 years the overall TEAE rates were similar (41.7% vs. 41.0% for moxifloxacin). The highest incidence was for the Gastrointestinal Disorders SOC (18.1% vs. 20.1%) and the most frequently reported PTs were diarrhoea (6.3% vs. 11.5%), headache (5.6% vs. 2.2%), dizziness (4.2% vs. 1.4%), nausea (2.8% vs. 3.6%), vomiting (2.8% vs. 0.7%), constipation (2.1% vs. 1.4%), hypokalaemia (2.8% vs. 2.2%), insomnia (2.1% vs. 0.7%), hypertension and pain in limb (each 2.1% vs. 0). SAEs occurred in 9.7% vs. 7.2%, most in the Respiratory, Thoracic and Mediastinal Disorders and Cardiac Disorders SOCs.

Incidences of TEAEs among female and male patients were similar. In each treatment group, the incidence of SAEs was higher in male patients reflecting rates for the Infections and Infestations SOC (3.9% vs. 1.9%) and Cardiac Disorders SOC (1.6% vs. 0.5%).

The incidences of TEAEs (46.7% vs. 32.8%) and SAEs (8.3% vs. 6.4%) were higher among non-white vs. white solithromycin-treated patients. A similar pattern applied in the moxifloxacin group. SAEs reported more frequently in non-whites were in the Infections and Infestations SOC (4.1% vs. 2.6%) and Respiratory, Thoracic and Mediastinal SOC (4.1% vs 1.7%), reflecting the higher incidence of (worsening) pneumonia vs. white patients (2.4% vs. 1.3%).

Incidences of TEAEs and SAEs were higher in the PORT risk class III/IV vs. II subgroup in both treatment groups with a similar pattern observed.

Hepatic impairment at baseline occurred in 42 solithromycin and 53 moxifloxacin patients. The incidence of SAEs was higher in hepatically-impaired patients in both treatment groups. No SAE was reported by >1 patient with hepatic impairment in the solithromycin treatment group. The highest incidence of TEAEs was reported in the Gastrointestinal Disorders SOC (11.9% solithromycin; 1.9% moxifloxacin).

**Discontinuation due to AES**

In the pooled Phase 3 CAP studies AEs leading to discontinuation of study drug were reported for 41 (4.8%) solithromycin and 29 (3.4%) moxifloxacin patients but rates based on non-infusion site AEs were 3.7% vs. 3.4%. Also, in the PORT III/IV/V patients in 301 the rates were 4.3% vs. 4.5% in respective groups and withdrawals from treatment due to infusion site events in the study occurred in 6 vs. 1 patients.

In 301 drug-related SAEs resulting in study drug discontinuation occurred in 2 solithromycin patients (moderate urticaria and moderate anaphylactic reaction) and in one moxifloxacin patient (moderate anaphylactic reaction). Urticaria occurred in a PORT II solithromycin patient with onset 10 minutes into the first infusion in a young female asthmatic patient. The two anaphylactic reactions were reported from the same site in the Republic of Georgia several minutes after an uneventful 60-minute infusion and were described as sweating, tachycardia and hypotension without any signs of rash, redness, or itching. Hypersensitivity and allergic non-serious TEAEs leading to study drug discontinuation occurred in 7 moxifloxacin patients (rash in 3, pruritus in 2 and single patients with dermatitis allergic and urticarial).

In the Phase 3 pooled studies one solithromycin-treated patient and 3 moxifloxacin-treated patients discontinued study drug due to development of a clinically significant laboratory abnormality. The solithromycin patient was enrolled in study 301 and had a clinically significant laboratory abnormality of elevated hepatic transaminases, considered an AE.

No patient withdrew from treatment due to AEs in the Phase 2 study and none discontinued due to laboratory abnormalities.

In Phase 1 the most frequent AEs leading to study withdrawal were infusion site events. Two subjects discontinued study drug due to abnormal laboratory values. One in study 116 received 800 mg IV solithromycin × 3 days and had a clinically significant elevation of ALT and AST, considered an AE. One in study 111 received 400 mg oral solithromycin × 1 and had a clinically significant elevation of AST.

***Discussion on clinical safety***

Extent of the safety database

The total safety database comprises 920 patients with CAP who received PO or IV/PO solithromycin in Phase 2 and 3 studies. An additional 554 subjects received at least one dose of solithromycin in the Phase 1 studies. Although the total exposed is 1474 individuals this has to be viewed in light of the fact that solithromycin does not address an unmet need and that it is closely related to telithromycin, for which serious hepatotoxicity reactions have been documented. The exact cause of hepatotoxicity related to telithromycin is unknown.

Telithromycin was recently voluntarily discontinued in the US for commercial reasons. The US prescribing information had been considerably amended following review of post-marketing safety data, including fatal cases of drug-induced liver damage. Telithromycin is still authorised in the EU at the time of preparing this report; the SmPC contains warnings regarding the risk of hepatotoxicity. It is therefore pertinent to understand that lack of any cases of hepatic damage in the available safety database for solithromycin cannot be regarded as reassuring.

AEs in Phase 3 CAP patients

The overview of the safety data suggested similar profiles for solithromycin and moxifloxacin except that a higher rate of AEs, drug-related AEs and AEs leading to discontinuation occurred with IV/PO solithromycin vs. IV/PO moxifloxacin. This imbalance mostly reflected the poor tolerability of IV solithromycin despite adjustments to the buffering solution and infusion rate as a result of the problems encountered in the Phase 1 studies. However, there was a higher rate of discontinuation of PO solithromycin due to SAEs. Leaving aside the infusion-related AEs, rates for other common and very common AEs suggested a greater risk of headache (PO), dizziness (PO and IV), nausea (IV), hypokalaemia and insomnia (IV) with solithromycin. The most common drug-related AEs in solithromycin-treated patients were diarrhoea, nausea and dizziness.

Deaths and SAEs

There has been no excess of deaths in solithromycin-treated patients vs. moxifloxacin-treated patients. In the Phase 3 studies the overall incidence of SAEs was only slightly higher in the solithromycin (6.8%) vs. moxifloxacin (5.8%) group. Many of these SAEs seem to be associated with the underlying infection and co-morbidity. It is of note that urticaria and anaphylactic reaction have occurred in a solithromycin patient. In one ongoing study there has been a case of elevated LFTs (elevated ALT, ALP, GGT and bilirubin) which was considered drug-related and resolved post discontinuation.

Hepatotoxicity

The application dossier contains a separate report on hepatotoxicity that attempts to distinguish the very clear effect of solithromycin on markers of liver toxicity from that of telithromycin.

There was a relationship between increasing plasma exposures to solithromycin and increasing rates of ALT elevations. Laboratory abnormalities (including ALT or AST elevations) were only reported as AEs in Phase 3 studies if they were associated with symptoms, resulted in study drug discontinuation or required treatment. The AEs reported occurred at similar rates in solithromycin and moxifloxacin groups.

In contrast, the rates of laboratory-reported elevations in transaminases, including rates at >3, >5 and >10xULN were higher in the solithromycin group while elevations in total bilirubin >2×ULN occurred in 0.5% solithromycin vs. 0.2% moxifloxacin patients. The difference between treatments was present in PO and IV/PO studies although more marked in the latter. These instances were more likely to be symptomatic and result in discontinuation in the solithromycin group.

It seems that when these elevations occurred during solithromycin treatment they were most often apparent by day 4 and sometimes improved on treatment. After stopping treatment most patients had (near) normalisation by the SFU visit. Nevertheless, the CHMP considers that the data indicate that it is very likely that post-marketing usage will reveal cases of severe liver damage as has been observed with telithromycin. It may be that the mechanism involved is somewhat different to that of moxifloxacin, with which the peak effects seemed to occur slightly later. Nevertheless, taking into account the higher rate of transaminase abnormalities for solithromycin vs. moxifloxacin, it should be remembered that the hepatotoxicity of moxifloxacin documented post-approval was one of the reasons that use of the IV and oral formulations was restricted in the EU so that it is indicated *only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections*.

Cardiac effects

In keeping with the TQT study in Phase 3 CAP studies the mean changes from baseline in QTcF interval were 5.6 vs. 13.7 ms on Day 4 and 5.5 vs. 11 ms at EOT for the solithromycin and moxifloxacin groups, respectively. Co-administration with CYP3A4 substrates with a potential to prolong QT interval is listed as a potential risk in the RMP.

In the Phase 3 CAP studies the overall mean heart rate decreased from baseline to each visit in both treatment arms to a very comparable extent. However 7.2% solithromycin vs. 4.4% moxifloxacin patients had treatment-emergent tachycardia determined from ECG data. The combined effects of solithromycin and other drugs and conditions that increase heart rate and the possible clinical consequences are unclear. Meanwhile, the draft SmPC contains the following:

Unstable heart disease
Patients with pneumonia often experience tachyarrhythmia as a consequence of hypoxia, fever, stress, age and anaemia. Patients with pneumonia who also have unstable coronary syndromes or decompensated congestive heart failure may be at increased risk for adverse reactions due to tachycardia (see section 4.8). Physicians should be mindful of this possibility in patients with underlying unstable heart disease.

This section completely misses the point in that it does not mention that solithromycin is associated with increases in HR. The section must be re-written to accurately reflect the effect of solithromycin on heart rate and the potential clinical consequences that merit a warning statement.

Other safety issues

Problems associated with telithromycin include visual disturbances. Vision and hearing testing was not conducted in Phase 2/3 studies. One solithromycin patient experienced an AE related to visual disturbances ('black spots in eyes') but this was not considered to be study-drug related. At present there does not seem to be evidence supporting mention of visual disturbance as an identified or potential risk in the SmPC.

Increases in leukocytes occurred more often in solithromycin-treated patients. Although 7.6% of solithromycin patients had a Grade 3 or Grade 4 increase in leukocyte count almost none had a corresponding marked increase in neutrophils. There is a need to better understand the role of uncontrolled infection in these abnormalities and why there was a higher rate of leukocyte but not neutrophil abnormal results with solithromycin vs. moxifloxacin.

The incidences of TEAEs and SAEs increased with increasing age and PORT score but this pattern applied in both treatment groups. The incidences of TEAEs and SAEs in both treatment groups were higher among non-whites but it does not seem that the total reflected specific issues except that SAEs reported more frequently in non-whites reflected the higher incidence of (worsening) pneumonia vs. white patients. There were some regional differences in reporting rates that did not always consistently apply in both treatment groups but there were anomalies for both treatments (e.g. higher for solithromycin in US and higher for moxifloxacin in Latin America). The applicant should explain which AEs drove these differences.

Additional safety data

Any data that have become available from ongoing studies should be reported when answering the LOQ. Although the GC studies involve a single dose studies they do involve high doses that are intended to provide adequate plasma levels to treat uncomplicated gonorrhoea and the safety data could be useful.

SmPC issues related to safety

The applicant proposes only one contraindication: Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. A risk of cross-hypersensitivity cannot be ruled out. Therefore, the contraindication should include hypersensitivity to any macrolide or ketolide. In addition, section 4.3 does not adequately reflect the risk of clinically significant drug-drug-interactions.

Table 6.2.1.1 in the ISS provides the full listing of AEs considered drug-related by investigators in Phase 3 CAP studies. A cross-check with the draft section 4.8 shows that the majority of PTs are reflected but there are a few (e.g. eosinophilia, tachypnoea, dyspnoea, herpes simplex) that are not. The applicant should provide a justification for omitting some of the ADRs shown in table 6.2.1.1 from the SmPC.

***Conclusions on clinical safety***

There is considerable concern regarding the transaminase abnormalities that have been observed with solithromycin, not only because of the expectation that there will be cases of severe hepatotoxicity during routine use as have occurred with telithromycin but also because rates were higher than for moxifloxacin, for which the indications have been qualified in part because of hepatic safety concerns. It is acknowledged that while transaminase abnormalities are an identified risk, severe hepatotoxicity is a potential risk that cannot be gauged except during use in a much larger population.

In addition, the overall benefit risk is impacted by the rates of infusion-related problems with the IV formulation, which may lead to an earlier than desirable switch to PO solithromycin.

## 3.4 Risk management plan

The Applicant's summary of the safety concerns in the RMP is shown below.

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | 1. Hypersensitivity to solithromycin or to any of the excipients<br>2. Infusion site reactions with injectable formulation<br>3. Asymptomatic elevated hepatic transaminases<br>4. Loss of therapeutic effect on concomitant use with strong or moderate CYP3A and/or P-gp inducers. |
| Important potential risks | 1. Increased exposure to solithromycin with concomitant use of CYP3A4 inhibitors<br>2. Risk of development of drug resistance<br>3. Use in patients known to be hypersensitive to other macrolides<br>4. Concomitant use of substrates of, P-gp, or OATP1B3 with narrow therapeutic windows and CYP3A4 substrates with a potential to prolong QT interval<br>5. Medication error<br>6. Use in patients with pneumonia caused by organisms not susceptible to solithromycin<br>7. Use in patients with unstable cardiac disease<br>8. Use in patients with severe renal impairment<br>9. Antibiotic associated diarrhoea including pseudomembranous colitis |
| Missing information | 1. Use in paediatric patients<br>2. Use during pregnancy and lactation<br>3. Use for more than 7 days |

***Comment on the safety specification***

The CHMP and PRAC do not agree that the safety concerns listed by the applicant are appropriate. There are numerous issues that need to be addressed, as listed in section 6.3. These include, but are not limited to the following:

It is not adequately clarified that there is no experience in use of solithromycin to treat human anthrax or tularaemia. In addition, the RMP does not adequately reflect or discuss the lack of data to support prolonged dosing to treat these infections.

It is not agreed that hypersensitivity to other macrolides can be a warning; it should remain as a contraindication. The proposals regarding co-administration with strong inhibitors and inducers of CYP3A4 and with CYP3A4 substrates with narrow therapeutic windows are also not agreed.

The section on potential for medication errors is inadequate. It discusses only IV errors and only briefly. The fact that the oral regimen and the oral follow-on regimen require an initial 800 mg dose and then 400 mg daily raises the real possibility that some patients will inadvertently take 800 mg daily, with risk of toxicity, or take only 400 mg on all days, with the risk of impacting efficacy.

The section on potential for off-label use is inadequate. It does not discuss the considerable possibility that solithromycin will be used to treat infections outside of the indications. In addition, at present the indications regarding anthrax and tularaemia are very unclear and poorly written in the draft SmPC. Greater clarity is needed and then the RMP should be updated accordingly. Furthermore, although the SmPC specifically states that safety and efficacy of solithromycin in CAP have not been established in the paediatric population, there is a strong possibility that solithromycin might be used in case of anthrax or tularaemia in preference to fluoroquinolones. This should be added.

Despite the applicant acknowledging that dizziness occurred commonly there is no reflection of this risk for driving and operating machinery in the RMP although there is such a statement in the SmPC. This should be addressed.

The PRAC also has multiple comments on the Pharmacovigilance Plan and the propsoed Risk Minimization measures (see section 6.3).

### *3.5 Pharmacovigilance system*

The Rapporteur considers that the Pharmacovigilance system as described by the applicant 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.

## 4. Orphan medicinal products

N/A

## 5. Benefit risk assessment

### *5.1 Therapeutic context*

The proposed indications are as follows:

{Invented name} is indicated for the treatment of the following bacterial infections in adults aged 18 years and older (see section 5.1):

- Community-acquired pneumonia (CAP)
- Treatment of inhalation anthrax following exposure to *Bacillus anthracis*
- Treatment of inhalation tularaemia following exposure to *Francisella tularensis*

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

The applicant proposed the same daily IV and PO doses to treat anthrax and tularaemia as for CAP.

There are numerous treatments approved for treatment of CAP. In this regard, solithromycin (IV/PO) does not address an unmet need. Recognising this fact the applicant conducted two Phase 3 trials, one with IV/PO and one with PO.

There are several treatments approved or at least widely recommended in official guidance for treatment of anthrax. Where approvals have been made they have been based on nonclinical in-vitro and in-vivo studies and PK-PD analyses. This approach has been taken by the applicant to support the proposed indication for use. However, no clinical data have been generated to cover the required duration of therapy to address both spores and vegetative forms of the organism.

There are no treatments approved for treatment of tularaemia but several are widely recommended in official guidance. Unfortunately there is also no well-established nonclinical in-vivo model to strongly support the likelihood of clinical efficacy.

## 5.2 Favourable effects

The applicant conducted two Phase 3 studies in CAP, one with PO dosing in a population that was ~50% PORT score II at baseline and one with IV/PO dosing in a population that was mainly PORT score III but with at least a third having PORT score IV. The general design and conduct of the studies was acceptable and in line with CHMP recommendations. Use of PO an IV/PO moxifloxacin as the comparator was appropriate since this is a valid comparator for efficacy. The proportions of patients with evidence of a pathogen were not particularly high, being under a half in both studies.

In the primary analysis of the PO study the lower bound of the 95% CI around the treatment difference was -6.9% in the ITT and -7.6% in the CE populations. In the primary analysis of the IV/PO study, the 95% CI around the treatment difference was -7.8, 2.7 in the ITT population. In the CE-SFU population the lower bound of the 95% CI was -10% and the upper bound did not cross zero. In the PO study success rates were comparable in the patients with PORT scores III-IV at baseline and there was no consistent trend to decreasing efficacy with increasing age or disadvantage for solithromycin at the upper end of the age range. Additionally, in both studies solithromycin was comparable to moxifloxacin in those with high baseline disease severity indices.

## 5.3 Uncertainty and limitations about favourable effects

CAP

The PO and IV/PO studies showed fairly consistent numerical inferiority for solithromycin vs. moxifloxacin, including in the subsets with evidence of a pathogen.

The in-vitro activity of solithromycin resembles that of telithromycin and therefore it retains some activity against pneumococci resistant to older macrolides. Overall, solithromycin is not expected to have any advantage in spectrum over telithromycin except perhaps for some rare pathogens that may be resistant to telithromycin. It is much less active on a *wt/wt* basis against *H. influenzae* than against other common CAP pathogens and against erythromycin-resistant *H. influenzae* (*ermA, B* and *C* genotypes) the solithromycin $MIC_{90}$ was 4 mg/L. The $MIC_{90}$ is > 16 mg/L for *S. aureus*, reflecting lack of activity against strains (mostly MRSA) with constitutive $MLS_B$ resistance to macrolides. In addition, MICs of solithromycin are slightly higher against pneumococci that express more than one of *mefA, mefE* (efflux) and/or *ermB* (ribosomal methylation) resistance determinants as well as those with L4 ribosomal protein mutations. In the immunocompetent mouse pulmonary infection model the effective dose for 2 $\log_{10}$ kill of pneumococci was ~7 mg/kg QD for a macrolide-susceptible strain whereas in a similar model using neutropenic mice and a macrolide-R strain expressing *mefE* and *ermB* the effective dose for 2-$\log_{10}$ kill was 46 mg/kg. At present the MIC breakpoint is not known but PK-PD analyses and PTA throw doubt on the sufficiency of the proposed solithromycin dose regimens when the $MIC_{90}$ is 0.5 to 1 mg/L.

Against several species from different genera elevations in MICs ≥4-fold were observed at pH ≤6. Although the pH effect could mean lower activity at some infection sites, the ELF penetration and Vd were high, suggesting favourable distribution of drug. The applicant also suggests that since human serum decreased MICs, the combined effect of lower pH and serum could mean little net effect. However, this seems to be based on an in-vitro study with *S. aureus* and is considered to be conjectural.

Although the main metabolites are active, they are variably active against strains expressing common mechanisms of resistance to macrolides. They are present in relatively small amounts compared to parent drug in human plasma although there is considerable inter-individual variability. They are found in plasma at considerably higher concentrations in rats, rabbits and monkeys vs. man and in mice there are considerable amounts of metabolites in lung but lesser amounts in plasma.

On this basis there is concern that the reported PTA is based on PDTs applied only to parent drug and were derived from four experiments in mice infected with *S. pneumoniae*. It is unclear whether a contribution of total activity from the metabolites could have significantly impacted on the derivation of PDTs from nonclinical in-vivo studies in mice that have been applied to free parent drug levels.

There is also concern that the PDTs are based on the neutropenic mouse lung infection model, which is less well-established than the thigh model, in which pooled data from three pneumococci with solithromycin MICs 0.06-0.12 mg/L gave plasma *f*$AUC_{0-24}$:MIC ratios associated with net bacterial stasis and a 1- and 2-$log_{10}$ CFU reduction from baseline of 1.65, 6.31 and 12.8, respectively. However, the actual values were quite variable between strains (e.g. for 1-$log_{10}$ kill they were ~4, 16 and 17, whereas the derived PDT was ~6). The corresponding total-drug ELF $AUC_{0-24}$:MIC ratios were 1.26, 15.1 and 59.8 but the actual values were again very variable between strains (e.g. for 1-$log_{10}$ kill they were ~10, 43 and 46).
It should also be noted that the PK model derived from healthy mice was used to generate free-drug plasma concentration vs. time profiles and then solithromycin dosing regimens administered to the infected mice were simulated to estimate plasma $AUC_{0-24}$, Cmax and %*f*T>MIC.

Although it could be considered that the lung infection model data are more relevant to the claimed indications, the PTA has only been estimated based on the PDTs derived as above from the 3 pooled isolates. Furthermore, the applicant has placed considerable weight on the ELF PDT, whereas this approach is not accepted. Estimating the ELF penetration of drugs intended for treatment of pneumonias is certainly encouraged but placing weight on urea-corrected ELF-related PDTs is not an acceptable approach.

Based on what seems to be rather questionable plasma *f*$AUC_{0-24}$:MIC ratio PDT value for 1-$log_{10}$ kill the applicant estimated PTA over the first 48 h against pneumococci at the $MIC_{90}$ of 0.25 mg/L to be 82.9% using the proposed PO regimen and 95.7% using the proposed IV regimen. PTA at 0.5 mg/L is similar for IV and PO regimens and is only 50-60%. Overall, taking into account also the efficacy observed in the two Phase 3 studies, the PK-PD analyses seem to be rather weak.

There is additional concern regarding the PK-PD analyses used to support dosing in renal impairment. The SmPC states that no dose adjustment is needed when CrCL is ≥ 30 mL/min and that for patients with CrCL < 30 mL/min the oral dose regimen is 800 mg on day 1 and then 200 mg daily and the IV dose is 400 mg on day 1 and then 200 mg daily. These regimens are based on the modelling results for exposure and PTA over the first 48 but the results do not strongly support the dose adjustments. The applicant should provide separate assessments for those with ESRD not on HD to determine whether a lower limit of CrCL should be applied.

*<u>B. anthracis</u>*

There are no clinical data. There are several concerns regarding the nonclinical data and the adequacy of the proposed application of the CAP dosing regimen to treat pulmonary anthrax. The $MIC_{90}$ of solithromycin for this species is 0.06-0.12 mg/L but solithromycin was not bactericidal against the Ames strain. The nonclinical efficacy study was conducted by a contracted facility, different to the one that conducted the tularaemia study. It is not clear whether the protocol exactly followed that established by NIH as suitable for assessing the potential efficacy of antibacterial agents to treat anthrax in humans. This requires clarification.

Based on the methodology used there was a clear difference in survival between the treated and untreated macaques. The applicant states that the observed mean *f*$AUC_{0-24}$:MIC ratio associated with survival of *B. anthracis*-infected NHPs would be readily achieved in patients administered the oral or IV regimens proposed for CAP. In reality, the mean Day 1 solithromycin *f*$AUC_{0-24}$ in infected NHPs was 8.12 mg•hr/L (CV=56.8%), which was ~2.2-fold the mean value in patients with CABP. The predicted *f*$AUC_{0-24}$/MIC ratios, based on MIC 0.25 mg/L, are also lower in patients Therefore the presented data do not substantiate the applicant's conclusions regarding the adequacy of the solithromycin dose.

Furthermore, the contribution from metabolites to the overall efficacy and therefore the relevance of the findings in the cynomolgus macaques to humans are not clear.

After oral dosing in macaques, as was used in the study, there is greater first pass metabolism leading to lower solithromycin but relatively higher exposure to *N*-Acetyl-CEM-101 and CEM-214 vs. parent drug compared to humans.

To mimic the plasma profile following human dosing the dose for macaques had to be adjusted because of the lowering effect of first pass metabolism. This would then have affected metabolite levels. The CHMP is not able to understand whether the dose adjustment to provide "humanised" plasma levels of solithromycin had a marked impact on metabolite levels and is not able to relate active metabolite levels in macaques to those that can be expected in humans. This issue should be addressed to support the relevance of the observed efficacy for human dosing.

The applicant acknowledges that the recommended treatment duration with two or more antimicrobial medicinal products is 60 days in order to cover the potential for germination of latent spores weeks or months after inhalation. The SmPC states that the duration of dosing is 7 days for anthrax (due to clinical experience limits) but there is a footnote referring to the duration used in the nonclinical study and the chronic toxicology data. Thus, use beyond 7 days is left to physician discretion. Based on the safety concerns (see further below) especially for hepatic effects the current SmPC statements cannot be agreed.

In conclusion, there is a major objection to use of solithromycin to treat anthrax due to lack of confidence in the sufficiency of the CAP dose regimen to treat *B. anthracis* and due to safety concerns.

*F. tularensis*

There are no clinical data. There is no well-established and widely accepted animal model for tularaemia that can be regarded as predictive of human efficacy. Solithromycin has lesser activity against type B vs. type A *F. tularensis*. For the strain used in the nonclinical efficacy study the solithromycin MIC was 0.125 μg/mL. The CEM-214 MIC was ≤ 0.125 μg/mL and the MIC was 0.25 μg/mL for the *N*-acetyl metabolite.

The efficacy observed in this study is not sufficiently clear or convincing. For the population that included all challenged animals, no significant difference was found when examining the survival rate between the two groups. The survival distribution between the vehicle group and the solithromycin group were significantly different but in this analysis the four animals in Cohort 2 that persisted through the observation period were treated as survivors. The additional survival analysis was performed to demonstrate differences in survival *due to tularaemia* as determined by bacterial load in tissue and

pathology results. This demonstrated a significant difference (p = 0.0014) in the survival rate between groups when looking at tularaemia-related deaths and the survival distribution was also significantly different between the two groups (p = 0.0006, Log-Rank Test). Nevertheless, in an unvalidated model it is not possible to conclude that the results clearly support an expectation of efficacy in humans.

The POPPK report concludes that the current analysis can provide solithromycin dose selection support *for future pivotal studies* in NHPs infected with *F. tularensis.* Additionally, as in the *B. anthracis* study, the contribution from metabolites to the overall efficacy observed in the nonclinical model and therefore the relevance of the findings to man are not clear.

In conclusion, there is a major objection to use of solithromycin to treat tularaemia due to unknown validity of the model for this infection, lack of a clear benefit, lack of confidence in the sufficiency of the CAP dose regimen to treat *B. anthracis* and due to safety concerns.

Other issues related to efficacy

Rifampicin induces CYP3A4, P-gp, *N*-acetyl transferase and some transporters. The net effect of rifampicin on solithromycin was a profound drop in plasma levels but the SmPC says only that solithromycin "should not be used" with agents that induce CYP3A4. It is very clear that use of solithromycin with inducers of CYP3A4 and/or P-gp should be contraindicated due to risk of suboptimal exposure and treatment failure. Due to the lack of clarity in terms of categorisation of strong P-gp inducers, the incomplete overlap between inducers of CYP3A and P-gp and lack of additional clinical data, it is considered that use of solithromcyin should be contraindicated with all drugs that induce CYP3A4 and/or P-gp.

There is also the potential for a pH effect on systemic bioavailability after oral administration. Rather than conducting a dedicated DDI study, the effect of increasing pH was assessed from POPPK-predicted AUCs in patients who took PPIs in the two Phase 3 studies on the sampling days.
The applicant concluded that there was no difference in the distribution of solithromycin AUCs. However, such analyses are considered to be imprecise and do not necessarily capture the effect of PPI co-administration at steady state. In light of the important effect of pH on solithromycin solubility a DDI study should be conducted in which solithromycin is given when the PPI is at steady state. Until results are available it should be recommended that co-administration of agents that increase gastric pH with oral solithromycin should be avoided.

## 5.4 Unfavourable effects

The overview of the safety data suggested similar profiles for solithromycin and moxifloxacin except that a higher rate of AEs, drug-related AEs and AEs leading to discontinuation occurred with IV/PO solithromycin vs. IV/PO moxifloxacin. This imbalance mostly reflected the poor tolerability of IV solithromycin despite adjustments to the buffering solution and infusion rate as a result of the problems encountered in the Phase 1 studies. However, there was a higher rate of discontinuation of PO solithromycin due to SAEs. Leaving aside the infusion-related AEs, rates for other common and very common AEs suggested a greater risk of headache (PO), dizziness (PO and IV), nausea (IV), hypokalaemia and insomnia (IV) with solithromycin. The most common drug-related AEs in solithromycin-treated patients were diarrhoea, nausea and dizziness.

Hepatotoxicity

PK-PD analyses of safety using PK data from Phase 1, 2 or 3 studies showed that increases in ALT were associated with increases in solithromycin plasma AUC. In Phase 3 the rates of laboratory-reported elevations in transaminases, including rates at >3, >5 and >10xULN were higher in the solithromycin group while elevations in total bilirubin >2×ULN occurred in 0.5% solithromycin vs. 0.2% moxifloxacin patients. There was an effect of peak daily plasma exposures on the incidence of ALT elevations and a

greater risk with IV to PO dosing. ALT elevations were mostly asymptomatic and resolved after stopping treatment but they are of concern, especially in light of the fact that solithromycin does not address an unmet need.

The CHMP considers that the data indicate that it is very likely that post-marketing usage will reveal cases of severe liver damage as has been observed with telithromycin. It may be that the mechanism involved is somewhat different to that of moxifloxacin, with which the peak effects seemed to occur slightly later. Nevertheless, taking into account the higher rate of transaminase abnormalities for solithromycin vs. moxifloxacin, it should be remembered that the hepatotoxicity of moxifloxacin documented post-approval was one of the reasons that use of the IV and oral formulations was restricted in the EU so that it is indicated *only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections*.

Cardiac effects

In the TQT study the effects on ECGs were evaluated at approximately twice the Cmax that can be expected in a typical CAP patient. In Phase 3 CAP studies the mean changes from baseline in QTcF interval were 5.6 vs. 13.7 ms on Day 4 and 5.5 vs. 11 ms at EOT for the solithromycin and moxifloxacin groups, respectively. Co-administration with CYP3A4 substrates with a potential to prolong QT interval is listed as a potential risk in the RMP.

In the Phase 3 CAP studies the overall mean heart rate decreased from baseline to each visit in both treatment arms to a very comparable extent. However 7.2% solithromycin vs. 4.4% moxifloxacin patients had treatment-emergent tachycardia determined from ECG data, which is in line with the effect observed in the TQT study. The combined effects of solithromycin and other drugs and conditions that increase heart rate and the possible clinical consequences are unclear. Meanwhile, the draft SmPC contains a very unsuitable and confusing statement about use in patients with unstable heart disease.

Other issues

Increases in leukocytes occurred more often in solithromycin-treated patients. There is a need to better understand the role of uncontrolled infection in these abnormalities and why there was a higher rate of leukocyte but not neutrophil abnormal results with solithromycin vs. moxifloxacin.

The applicant proposes only one contraindication: Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. A risk of cross-hypersensitivity cannot be ruled out. Therefore, the contraindication should include hypersensitivity to any macrolide or ketolide. In addition, section 4.3 does not adequately reflect the risk of clinically significant drug-drug-interactions.

Table 6.2.1.1 in the ISS provides the full listing of AEs considered drug-related by investigators in Phase 3 CAP studies. A cross-check with the draft section 4.8 shows that the majority of PTs are reflected but there are a few (e.g. eosinophilia, tachypnoea, dyspnoea, herpes simplex) that are not. The applicant should provide a justification for omitting some of the ADRs shown in table 6.2.1.1 from the SmPC.

## 5.5 Uncertainties and limitations about unfavourable effects

The total safety database comprises 920 patients with CAP who received PO or IV/PO solithromycin in Phase 2 and 3 studies. Solithromycin does not address an unmet need and it is closely related to telithromycin, for which serious hepatotoxicity reactions have been documented. The exact cause of hepatotoxicity related to telithromycin is unknown. Telithromycin was recently voluntarily discontinued in the US for commercial reasons. The US prescribing information had been considerably amended following review of post-marketing safety data, including fatal cases of drug-induced liver damage. Telithromycin is still authorised in the EU at the time of preparing this report; the SmPC contains warnings regarding the risk of hepatotoxicity. It is therefore pertinent to understand that lack of any cases of hepatic damage in the available safety database for solithromycin cannot be regarded as reassuring.

The applicant acknowledges that inter-individual variability (IIV) is high, being ~25-85% following oral administration and ~15-60% following IV administration. The various factors that may be contributing to this variability and the clinical implications have not been adequately discussed. For example, to what extent variability in CYP3A4 levels may contribute and the fact that N-acetylation of parent drug to form *N*-acetyl-solithromycin would be expected to vary between slow and fast acetylators have not been discussed in the dossier.

The applicant's approach to the investigation of DDIs with solithromycin parent drug as well as the appropriate contraindications in the SmPC seems to have been rather minimalistic. For example, the investigation of solithromycin as a substrate does not seem to be complete. Since the risk of ALT elevation increases with plasma levels of solithromycin and there is also a relationship between plasma levels and tachycardia that could have clinical significance in patients who have other reasons to have tachycardia or have an unstable cardiac condition there is a need to fully understand the risk of DDIs leading to elevated solithromycin exposures. Co-administration of solithromycin with a strong inhibitor of CYP3A4 and/or P-gp over several days has not been studied and was not allowed in the Phase 3 studies. The applicant should consider the need to strongly warn against or contraindicate the use of solithromycin with moderate or strong inhibitors of CYP3A4 and/or P-gp.

There is also a need to understand the potential for solithromycin to exert clinically significant inhibition of CYP2C8 and CYP2D6 (which is inhibited by telithromycin) and induction of 2C9. Also, the effect of oral solithromycin on oral midazolam $AUC_{inf}$ was very considerable and the possible need to contraindicate use of solithromycin with substrates of CYP3A and/or P-gp should be considered.

Finally, at this time there are Major Objections regarding the quality aspects of the powder for concentrate for solution for infusion, with unknown implications for patient safety.

## 5.6 Effects Table

| Effect | Short Description | Treatment | Control | Uncertainties/ Strength of evidence |
|---|---|---|---|---|
| **Favourable** | CAP Phase 3 study 300 of PO solithromycin 800 mg day 1 then 400 mg QD vs. moxifloxacin PO 400 mg QD | ITT clinical cure at TOC<br>84.5%<br>CE clinical cure at TOC<br>88.1%<br>mITT with *S. pneumoniae*<br>84.4% | <br>86.6%<br><br>91.3%<br><br>87.3% | Non-inferiority margin was met in ITT and CE populations<br>(-6.9, 2.6)<br><br>(-7.6, 1.1)<br>There was fairly consistent numerical inferiority for solithromycin vs. moxifloxacin, including in patients with a pathogen |
| | CAP Phase 3 study 301 of solithromycin 400 mg QD IV; | ITT clinical cure at TOC<br>85.7% | <br>88.0% | <br>(-7.8, 2.7) |

| Effect | Short Description | Treatment | Control | Uncertainties/ Strength of evidence |
|---|---|---|---|---|
| | switch to PO as above vs. moxifloxacin IV/PO 400 mg QD | CE clinical cure at TOC 87.1%<br>mITT with *S. pneumoniae* 85.3% | 92.0%<br>92.3% | (-10.0%, 0.0%)<br>Non-inferiority margin was only just met in the CE patients; there was fairly consistent numerical inferiority for solithromycin vs. moxifloxacin including in patients with a pathogen |
| | Nonclinical efficacy study in NHP infected with *B. anthracis* vs. placebo; PO gavage | 10/12 animals survived | 0/7 who received only placebo survived | Protective efficacy cannot be related to human dose due to higher plasma levels in macaques and unknown contribution from active metabolites |
| | Nonclinical efficacy study in NHP infected with *F. tularensis* vs. placebo; PO gavage | No deaths attributed to tularaemia but no significant difference vs. placebo for all challenged animals | | There is no widely accepted animal model for tularaemia. Exact protective effect of solithromycin is not really clear from this study. Protective efficacy cannot be related to human dose due to higher plasma levels in macaques and unknown contribution from active metabolites |
| **Unfavourable** | ALT elevation | >3×ULN 7.2%;<br>>5×ULN 2.4%;<br>>10×ULN 0.1% | 3.6%<br>1.0%<br>0.2% | Related to plasma levels of solithromycin; higher risk with IV than PO, higher rates vs. moxifloxacin; unknown risk of serious hepatotoxicity as has been observed with telithromycin; Moxifloxacin itself is known to be associated with a risk of serious hepatotoxicity |
| | Increased HR; tachycardia reported as AE | 7.4% | 5.7% | Noted to increase HR in TQT study; related to plasma levels of solithromycin. Unknown risk in patients already predisposed to tachycardia or with unstable cardiac conditions |
| | Potential enhanced ALT elevation and tachycardia if co-administered with CYP3A4/P-gp inhibitors | | | Risk of higher solithromycin levels; SmPC insufficient |
| | Potential loss of effect if co-administered with CYP3A4/P-gp inducers | | | Risk of lower solithromycin levels; SmPC insufficient |
| | Potential toxicity if given with CYP3A4 substrates | | | Effect of solithromycin on MDZ was 9-fold AUC increase; SmPC insufficient |

## *5.7 Benefit-risk assessment and discussion*

### 5.7.1 Importance of favourable and unfavourable effects

In the primary analysis of the PO study the lower bound of the 95% CI around the treatment difference was -6.9% in the ITT and -7.6% in the CE populations. In the primary analysis of the IV/PO study, the 95% CI around the treatment difference was -7.8, 2.7 in the ITT population. In the CE-SFU population the lower bound of the 95% CI was -10% and the upper bound did not cross zero.

Even with PO only dosing there was a substantial risk of ALT elevation that was greater than observed with moxifloxacin. There is considerable concern regarding the transaminase abnormalities that have been observed with solithromycin, not only because of the expectation that there will be cases of severe

hepatotoxicity during routine use as have occurred with telithromycin but also because rates were higher than for moxifloxacin, for which the indications have been qualified in part because of hepatic safety concerns.

Regarding use of solithromycin to treat *B. anthracis* or *F. tularensis* there is concern due to uncertainties regarding plasma exposures to parent drug and active metabolites in animals vs. humans, leading to lack of support for use of the CAP dose regimen to treat these pathogens. For tularaemia there are additional concerns regarding the model used and the results.

Finally, at this time there are Major Objections regarding the quality aspects of the powder for concentrate for solution for infusion, with unknown implications for patient safety.

### 5.7.2 Balance of benefits and risks

Solithromycin cannot be regarded as an agent that can address an unmet need. There may be a very few patients who cannot receive a beta-lactam and have a pathogen that is resistant both to the older macrolides and fluoroquinolones for whom solithromycin, like telithromycin, could be an option. There are too few telithromycin-resistant but solithromycin-susceptible organisms to consider that this use would be important. Transaminase abnormalities are an identified risk, while severe hepatotoxicity is a potential risk that cannot be gauged except after exposure of a much larger number of patients.

There are inadequate data to support application of the dose regimen proposed for treatment of CAP to treatment of anthrax and tularaemia. There are additional concerns regarding the efficacy of solithromycin based on the tularaemia model used and for both there are concerns regarding the fact that the safety of solithromycin has not been established beyond short-term therapy.

## *5.8 Conclusions*

The overall B/R of solithromycin for treatment of CAP, anthrax and tularaemia is currently negative.