22 January 2015
EMA/83337/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sivextro

International non-proprietary name: tedizolid phosphate

Procedure No. EMEA/H/C/002846/0000

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 5520
Send a question via our website www.ema.europa.eu/contact

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List of abbreviation

Abbreviation	Definition
^{14}C	radiolabelled carbon-14
ABSSSI	acute bacterial skin and skin structure infections
AE	adverse event
ANC	absolute neutrophil count
AUC	area under the curve
$AUC_{0-\infty}$	AUC from Hour 0 extrapolated to infinity based on the apparent terminal rate constant
AUC_{0-24}	AUC from Hour 0 to Hour 24.I
BCRP	breast cancer resistance protein
BMI	body mass index
CA-MRSA	community-acquired methicillin-resistant Staphylococcus aureus
CDAD	*Clostridium difficile* associated disease
CE	Clinically Evaluable
CE-PTE	Clinically Evaluable at PTE
Cfr	chloramphenicol-florfenicol resistance
CFU/g	log_{10}
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
CL/F	apparent clearance
CLSI	Clinical and Laboratory Standards Institute
cMITT	Clinical modified ITT
CQAs	Critical Quality Attributes
cSSTI	complicated skin and soft tissue infections
CYP	Cytochrome P450
dL	deciliter

Abbreviation	Definition
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EIE	erythema plus induration or oedema
EMA	European Medicines Agency
EOT	end of therapy
EU	European Union
FA	free acid
TR-701/FA	is used when reference is made to both the disodium salt (TR-701) and the free acid form (TR-701 FA) of the study drug.
*f*AUC/MIC	The area under the unbound concentration-time curve to MIC ratio
FDA	Food and Drug Administration
FT-IR	Fourier transform infrared spectroscopy
g	gram
GC	Gas Chromatography
GI	gastrointestinal
h	hour
HDPE	high density polyethylene
HPLC	High-performance liquid chromatography
IC_{50}	median (50%) inhibitory concentration
ICH	International Conference on Harmonisation
ICP-MS	Inductively coupled plasma mass spectrometry
IR	Infrared Spectroscopy
ISE	Integrated Summary of Efficacy
ITT	Intent-to-Treat
IV	intravenous
KF	Karl Fischer
L	litre

Abbreviation	Definition
LFU	late follow up
LLN	lower limit of normal
MAA	Marketing Authorisation Application
MAO	monoamine oxidase
ME	Microbiologically Evaluable
mg	milligram
mMITT	Microbiological Modified Intent to Treat
MHRA	Medicines and Healthcare Regulatory Agency
MI	myocardial infarction
MIC	minimum inhibitory concentration
MITT	Modified Intent to Treat
mL	millilitre
mm	millimetre
MPS	mitochondrial protein synthesis
MRSA	methicillin-resistant Staphylococcus aureus
MSSA	methicillin-susceptible Staphylococcus aureus
n	number of patients in the specific category
N	number of patients in the analysis set
NI	non-inferiority
NMR	nuclear magnetic resonance spectroscopy
NOAEL	no observed adverse effect level
OAT	organic anion transporter
OCT	organic cation transporter
PD	primary pharmacodynamics
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PIP	Pediatric Investigation Plan
PK	pharmacokinetics

Abbreviation	Definition
popPK	population pharmacokinetics
PSE	pseudoephedrine
PSM	phenol-soluble modulins
PT	Preferred Term
PVC	polyvinyl chloride
PVdC	polyvinylidene chloride
PTE	post therapy evaluation
PVL	Panton-Valentine leukocidin toxin
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTPP	Quality Target Product Profile
RBC	red blood cell
RH	Relative Humidity
SA	substantially abnormal
SAE	serious adverse event
SAP	statistical analysis plans
SD	standard deviation
SmPC	Summary of Product Characteristics
SOC	system organ class
SSTIs	skin and soft tissue infections
TEAE	treatment-emergent adverse event
TOC	test of cure
TR-700	tedizolid; microbiologically active moiety of TR-701 or TR-701 FA prodrug
TR-701	disodium phosphate salt prodrug of TR-700
TR-701 FA	tedizolid phosphate; free acid phosphate prodrug of TR-700
TR-701/FA	TR-701 FA or TR-701
TYR_{30}	tyramine dose required to cause a 30 mmHg increase in systolic blood pressure
µCi	microcurie

Abbreviation	Definition
µg	microgram
UV/VIS	ultraviolet/visible spectroscopy
WBC	white blood cell
WFI	water for injection
XPRD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Cubist (UK) LTD submitted on 31 January 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Sivextro, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 December 2012.

The applicant applied for the following indication:

Treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that tedizolid phosphate was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0249/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0249/2013 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance tedizolid phosphate contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice /Protocol Assistance

The applicant did not seek scientific advice or Protocol Assistance at the CHMP.

Licensing status

Sivextro has been given a Marketing Authorisation in USA.

1.2. Manufacturers

Manufacturers responsible for batch release

Patheon Italia S.P.A.
2° Trav. SX Via Morolense, 5
Ferentino, 03013
Italy

Patheon UK Limited
Kingfisher drive, Covingham
Swindon, SN3 5BZ
United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bruno Sepodes

Co-Rapporteur: Filip Josephson

CHMP Peer reviewer: Karsten Bruins Slot

- The application was received by the EMA on 31 January 2014.
- The procedure started on 26 February 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 21 May 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 May 2014.
- The PRAC RMP assessment overview was adopted by PRAC on 13 June 2014.
- During the meeting on 26 June 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 September 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 October 2014.
- The PRAC RMP assessment overview was adopted by PRAC on 6 November 2014.
- During the CHMP meeting on 20 November 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 18 December 2014.

- The PRAC RMP assessment report was circulated on 30 December 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to list of outstanding issues on 7 January 2015.
- During the meeting on 22 January 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Sivextro.

2. Scientific discussion

2.1. Introduction

Skin and soft tissue infections (SSTI) are among the most common infections in both hospitals and community settings, and remain a significant source of morbidity and mortality. These infections can range in severity from uncomplicated skin and soft tissue infections, such as simple folliculitis, to complicated skin and soft tissue infections, including very serious conditions such as necrotizing fasciitis and Fournier's gangrene. Complicated skin and soft tissue infections involve deeper soft tissue than uncomplicated infections, and may require significant surgical intervention and parenteral antibiotic therapy. Within the hospital or long term care setting, cSSTIs are generally a consequence of surgery or regarded as a secondary infection associated with an underlying disease. Within the community, they are most often associated with the consequences of trauma.

Because of the great variation in seriousness and need of antibiotic treatment other interventions, diagnostic criteria and expected time to healing, it has been suggested that treatment of necrotizing fasciitis and burn wounds should be studied separately from other skin and soft tissue infections. Abscesses Aneeding immediate incision and drainage may also be unsuitable for testing the effect of antibiotic treatment as the surgical procedure may be sufficient alone.

Systemic risk factors which predispose patients to severe forms of SSTI include diabetes mellitus, malnutrition, immune deficiencies, sensory neuropathies, chronic systemic illness, high age and smoking.

Studies on the effect of antibiotics need to be well defined with documentation of both local and systemic signs of infection. Infections immediately treated with incision and drainage are less suitable for studies and one or more signs of systemic infections should be required (European guidelines for clinical evaluation of anti-infective drug product 1993, European Society of Clinical Microbiology and Infectious Diseases, Stevens DL & al., 2005). Furthermore, it is important that the type of infection is well characterized. The validity of the results requires also that a significant number of each type of infection is included.

Although skin and soft tissue infections include a vast array of clinical entities, they are most often caused by two single microorganisms, *Staphylococcus aureus* and *Streptococcus pyogenes*.

A number of antimicrobial agents are available for the treatment of skin and skin structure infections, and the benefit of systemic antimicrobial therapy, accompanied by surgical intervention as necessary is clearly established. According to the clinical presentation and other patient co-morbidities treatment strategies in skin and skin structure infections include both oral therapy and an IV-to-oral switch treatment regimen. In the latter case since therapy on an outpatient basis provides for greater patient convenience and reduced healthcare costs, the switch to oral therapy generally occurs as soon as clinically indicated.

Another oxazolidinone which has both and IV and an oral formulation is increasingly utilized in the treatment of cSSTI, particularly if MRSA is considered a likely pathogen. However, its use is associated with myelosuppression, peripheral and optic neuropathies, and lactic acidosis, particularly with therapy longer than is typical for the treatment of cSSTI. These adverse effects have been linked mechanistically to mitochondrial protein synthesis (MPS) inhibition.

During the last decades, *S. aureus* has become progressively resistant to methicillin and has spread worldwide, with an increasing prevalence of community-acquired (CA) MRSA observed in many intensive care units and emergency departments, particularly in the US but also in the EU.

Furthermore, resistance to currently available MRSA drugs is increasing. There is growing concern about linezolid-resistant strains, especially due to the *cfr* gene conferring resistance to other classes of ribosome-targeting antibiotics, including clindamycin, streptogramins, phenicols, 16-C macrolides, and pleuromutilins.

New antibacterial medicinal products, especially those also available as an oral formulation, are therefore needed to treat infections due to drug-resistant Gram-positive bacteria in both hospital and community settings.

Tedizolid phosphate (TR-701 FA, the free acid form of TR-701), is a novel oxazolidinone prodrug antibiotic that is converted *in vivo* by phosphatases to the microbiologically active moiety TR-700. TR-700 is a protein synthesis inhibitor that interacts with the bacterial 23S ribosomal ribonucleic acid (rRNA) bacterial ribosome, thereby preventing the initiation of translation by inhibiting formation of the initiation complex. Tedizolid phosphate is intended for both oral and intravenous (IV) administration in the treatment of acute bacterial skin and skin structure infections (ABSSSI).

The pivotal studies supporting this application enrolled patients who complied with the definition of the term “acute bacterial skin and skin structure infections (ABSSSI)”, which practically encompasses patients with cellulitis/erysipelas, wound infections and major cutaneous abscesses with a lesion area size of at least 75 cm2 (possibly lower for areas that involve certain body surface sites, such as the face). The CHMP was of the opinion that the use of this term was more appropriate than cSSTI, as it better described the patient populations enrolled in the clinical trials. The applicant agreed with this conclusion. In this report, the two terms are however used interchangeably.

2.2. Quality aspects

2.2.1. Introduction

Two dosage forms are proposed for the drug product Sivextro: film-coated tablets and powder for concentrate for solution for infusion.

The film-coated tablets contain 200 mg of tedizolid phosphate as active substance. The other ingredients are microcrystalline cellulose, mannitol, povidone, crospovidone and magnesium stearate in the core and polyvinyl alcohol, titanium dioxide (E171), macrogol, talc and yellow iron oxide (E172) in the film-coating.

The tablets are available in aluminum foil and polyvinyl chloride (PVC)/polyvinylidene chloride (PVdC) clear film perforated unit-dose blisters.

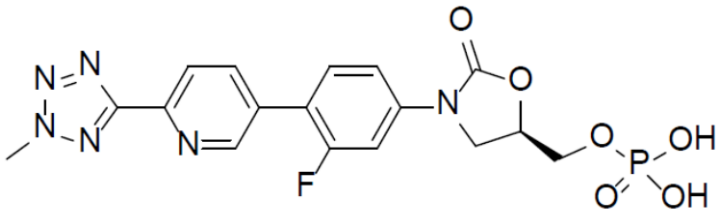
The sterile lyophilized powder for concentrate for solution for infusion also contains 200 mg of tedizolid phosphate as active substance. The other ingredients are mannitol, sodium hydroxide and hydrochloric acid.

The powder for concentrate for solution for infusion is available in Type I (10 ml) clear borosilicate tubing glass vials with a siliconised grey chlorobutyl rubber stopper.

2.2.2. Active Substance

General information

The chemical name of tedizolid phosphate is [(5*R*)-(3-{3-Fluoro-4-[6-(2-methyl-2H-tetrazol-5-yl)pyridin-3-yl]phenyl}-2-oxooxazolidin-5-yl]methyl hydrogen phosphate and has the following structure:



The chemical structure of tedizolid phosphate was inferred from the method of synthesis and confirmed using elemental analysis, phosphatase treatment, ultraviolet/visible (UV/VIS) spectroscopy, X-ray diffraction, mass spectrometry, Fourier transform infrared spectroscopy (FT-IR), and nuclear magnetic resonance (NMR) spectroscopy.

The active substance is a white to yellow crystalline non-hygroscopic anhydrous solid with a molecular mass of 450.32 Da, corresponding to the general molecular formula $C_{17}H_{16}FN_6O_6P$.

The solubility of tedizolid phosphate drug substance is highest when fully deprotonated (high pH) and lowest when fully protonated (low pH), with a steep increase in solubility between pH 4.0 and pH 6.0. Tedizolid phosphate is very soluble in dimethylsulfoxide, soluble in tetrahydrofuran, methanol and acetone and sparingly soluble in ethanol.

Tedizolid phosphate is a chiral compound. X-ray diffraction data has shown that the absolute configuration at the 5-position of the oxazolidinone ring is of the (*R*)-configuration.

Tedizolid phosphate drug substance is a crystalline solid. A polymorphism study confirmed that the polymorph resulting from the proposed manufacturing process is crystalline form A, which is the only stable identified polymorph. The other observed form, form B, is thermodynamically unstable and rapidly converts to Form A.

Tedizolid phosphate is dephosphorylated *in vivo* by alkaline phosphatase enzymes to form the highly insoluble highly permeable active moiety tedizolid.

Manufacture, characterisation and process controls

The active substance is synthesized in four main steps using commercially available well-defined starting materials with acceptable specifications.

Several iterations of the synthetic process and active substance form were used at various points during development. As mentioned above, tedizolid phosphate has 1 asymmetric centre. Its stereochemistry is controlled in the manufacturing process. It has been demonstrated that the stereocentre is not epimerisable and consequently is stable to all of the subsequent steps in the manufacturing process. Suitable analytical methods have been used over the course of development to control this stereocentre and results from this testing have indicated that there is no increase in the level of the (*S*)-enantiomer during manufacture, forced degradation studies, or on stability.

To note, the final stage of the manufacturing process involves crystallisation of purified tedizolid phosphate and consists of a series of unit operations designed to minimize the potential for endotoxin contamination. This is critical for the quality of the tedizolid phosphate injectable formulation.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

The active substance specification includes tests for appearance (visual), identity (IR, HPLC), assay (HPLC), impurities (HPLC), residual solvents (GC), heavy metals (ICP-MS), water content (KF), crystalline form (XPRD), particle size (laser diffraction), residue on ignition (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and microbial limits (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specification limits have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Analysis data on twelve batches of the active substance manufactured by the commercial manufacturer have been provided. Supportive batch analysis data from 9 batches of tedizolid disodium phosphate have also been presented.

The results are within the specifications and consistent from batch to batch.

Stability

Stability data on six pilot scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 48 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

The following parameters were tested: appearance, assay, organic impurities, chiral purity, water content, crystalline form, bacterial endotoxin and microbial limits. The analytical methods used were the same as for release. Additionally, a test for chiral purity was performed during stability testing but is not included in the proposed commercial specification since the stereocentre in question was shown to be stable.

The stability data presented indicate that there are no significant trends to any of the parameters tested for any of the batches when stored under long-term or accelerated conditions.

Photostability testing following the ICH guideline Q1B was performed on one batch, indicating that tedizolid phosphate is not photosensitive.

Forced degradation studies of tedizolid phosphate drug substance were performed on one batch to identify probable degradation products and to confirm the suitability of analytical methods. Samples were stored under the conditions of hydrolysis (acid, base), oxidation (peroxide), heat, and light. The substance is stable towards light and heat in the solid state and against acid conditions in solution. Tedizolid phosphate degrades in water, alkaline solution and under oxidative stress. The study confirmed that the analytical methods proposed are stability indicating.

Overall, the stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Two dosage forms are proposed for the drug product: film-coated tablets and powder for concentrate for solution for infusion.

Film-coated tablets

Description of the product and pharmaceutical development

Sivextro 200 mg film-coated tablets are yellow oval-shaped immediate-release, film-coated tablets, debossed with “TZD” on the obverse side and “200” on the reverse side, packed in PVC/PVdC clear film perforated unit-dose blisters.

The quality target product profile (QTPP) was defined as immediate release tablets (containing 200 mg of tedizolid phosphate) for oral administration, which can be swallowed easily and meet compendial and other relevant quality standards, in particular, rapid disintegration in the stomach and rapid dissolution in the small intestine, ease of handling and administration, and commercial acceptance. The critical quality attributes (CQAs) identified were appearance, identity, assay, degradation products, uniformity of dosage units, dissolution, water content and microbial limits.

During development different forms of the active substance and different pharmaceutical forms were studied. Tedizolid phosphate free acid was found to be the most suitable form for the manufacture of a tablet dosage form based on its physicochemical properties.

A phase 1 relative bioavailability study confirmed that the pharmacokinetics of the forms used during development were comparable and therefore formulation development progressed using only the free acid form of the drug substance.

A wet granulation process was selected in order to increase density and minimise the potential impact of drug substance content variability that can occur in early development. A non-functional film coating was incorporated to improve aesthetics.

The tedizolid phosphate film-coated tablet dosage form was designed to disintegrate in the stomach and provide rapid dissolution of the drug substance. Dissolution, which occurs readily at pH above 4, takes place within the small intestine, which is the primary site of drug absorption. Tedizolid phosphate prodrug has almost no oral absorption due to its high polarity. Intestinal alkaline phosphatase enzymes dephosphorylate tedizolid phosphate to generate the highly permeable, pharmacologically active moiety, tedizolid. The oral absolute bioavailability of the tablet formulation was found to be >90%.

The same tablet formulation evaluated in the absolute bioavailability study was used for all subsequent Phase 1 and Phase 2 clinical studies, including all pivotal Phase 3 clinical studies, and is proposed for commercial supply.

There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. The excipients selected for the core tablet formulation are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards whilst the film-coating contains pharmacopoeial excipients and is analysed according to the applicant’s in-house specifications.

Compatibility of the drug substance with the selected excipients was assessed by making binary mixtures with each excipient in a ratio based on the typical level of the excipient in a solid dosage form. These mixtures were stored in an open dish for up to 8 weeks at 40 ºC / 75% RH. Samples were tested at 0, 4 weeks, and 8 weeks for appearance, moisture, potency, and related substances. The selected excipients were found to be compatible with tedizolid phosphate.

Dissolution method development was conducted in parallel with formulation and process development of the current 200 mg drug product. The development based on evaluation and consideration of drug physicochemical properties, tablet formulation, physical properties/performance characteristics, discriminating capability, and

biopharmaceutical relevance. Several dissolution media and volumes were tested. The discriminatory power of the dissolution method was demonstrated.

The materials used in the proposed container closure system, aluminum foil and polyvinyl chloride (PVC)/polyvinylidene chloride (PVdC) clear film perforated unit-dose blisters, comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of seven main steps: sieving/pre-blending, wet granulation, drying, screening/de-lumping, blending, compression, and film coating. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process. A process-validation scheme in line with the CHMP guideline on process validation has been provided and was deemed acceptable. The applicant will validate the manufacturing process before commercialisation.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (FTIR, HPLC), assay (HPLC), degradation products (HPLC), content uniformity (Ph. Eur.), dissolution (Ph. Eur.), water content (Ph. Eur.) and microbial limits (Ph. Eur.).

Batch analysis results are provided for three pilot scale batches manufactured by the development site and one pilot and three commercial scale batches manufactured by the commercial manufacturer confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on two commercial scale and one pilot scale batches of finished product stored for 24 months under long term conditions (25 ºC / 60% RH) and intermediate conditions (30 °C / 75% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of Sivextro are identical to those proposed for marketing and were stored in both the primary packaging formats proposed for marketing.

Supportive stability data from two pilot scale batch from the manufacturer used during development stored under long-term storage conditions for 36 months and accelerated conditions for 6 months were also presented. Stability data from an open container study on one pilot scale batch stored at 25 °C / 60% RH for 6 months were also provided.

Samples were tested for appearance, dissolution, assay, degradation products, water content, microbial limits, hardness and chiral purity. The analytical procedures used are stability indicating. All values remained within the specification.

In addition, forced degradation studies and a confirmatory photostability study was performed in line with the ICH guideline on one commercial scale batch. No significant changes were observed on samples exposed to acid or oxidative conditions. Some degradation was detected under heat both in the solid state and in the presence of water, upon exposure to base, or under light exposure in the solid state. The light degradation treatments in this study are considered as worst case and not representative of intact film-coated tablets. These degradation products were not detected in the ICH confirmatory photostability studies. The results from the confirmatory

photostability indicated that tedizolid phosphate film-coated tablets are not photosensitive and consequently do not require any special labelling or packaging to mitigate exposure to light.

Based on available stability data, the shelf-life as stated in the SmPC are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

Powder for concentrate for solution for infusion

Description of the product and pharmaceutical development

Tedizolid phosphate powder for concentrate for solution for infusion, 200 mg, is supplied as a sterile, single dose lyophilised powder for reconstitution and administration by intravenous injection.

The quality target product profile (QTPP) was defined as a lyophilised powder for concentrate for solution for infusion delivering 200 mg of tedizolid phosphate that meets compendial and other relevant quality standards, and is compatible with reconstitution fluids and diluents. The critical quality attributes (CQAs) identified were appearance, identity, assay, degradation products, uniformity of dosage units, reconstitution time, pH, particulate matter, water content, sterility and bacterial endotoxins.

The active substance, tedizolid phosphate free base, has limited aqueous solubility. Therefore, a lyophilised powder formulation was selected, in which tedizolid phosphate free base is converted into the more soluble salt. Compatibility of excipients with the active substance was confirmed in stability studies.

The relative amounts of active substance and excipients were varied during development in order to minimise reconstitution time and formation of tedizolid salt whilst optimising cake appearance.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Thermal terminal sterilisation of both the reconstituted solution and drug product was investigated by both moist heat and dry heat processes. The results indicate that terminal sterilisation of tedizolid phosphate powder for concentrate for solution for infusion (drug product and reconstituted solution) using high-temperature processes negatively affects the quality of the drug product as relates to appearance, purity, and performance, and also produced several new unknown degradation products. Therefore, sterile filtration followed by aseptic filling and lyophilisation was pursued.

The drug product formulation used in the clinical studies is the same as the proposed commercial formulation.

The primary packaging for Sivextro powder for concentrate for solution is a Type I clear borosilicate tubing glass vial and siliconised grey chlorobutyl rubber stopper. An aluminum seal with a polypropylene flip-off top is applied to protect the closure. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of seven main steps: compounding of the bulk solution and pH adjustment, sterile filtration and aseptic filling; lyophilisation, stoppering, and sealing. The process is considered to be a non-standard manufacturing process.

Batch validation data from 3 consecutive commercial scale batches were provided demonstrating that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls have been duly justified and are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form appearance, identification (IR and HPLC), assay (HPLC), degradation products (HPLC), uniformity of dosage units by weight variation (Ph. Eur.), loss on drying (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.). Additional tests are carried out on the reconstituted solution: reconstitution time (visual), constituted solutions (clarity and degree of opalescence of liquids, degree of coloration of liquids, particulate contamination: visible particles) (Ph. Eur.), pH and sub-visible particles of the reconstituted solution (Ph. Eur.),

Batch analysis results are provided for four batches manufactured by the development site and five batches manufactured by the commercial manufacturer confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of five pilot scale batches of finished product stored under long term conditions (25 ºC / 60% RH) and intermediate conditions (30 ºC / 75% RH) for up to 24 months and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of finished product were manufactured at the proposed commercial site and are representative of those proposed for marketing.

Supportive stability data from 2 pilot scale batches manufactured by the site using during development stored for up to 36 months under long term conditions and 6 months at accelerated conditions were also provided.

Samples were tested for appearance, reconstitution time, constituted solutions pH, particulate matter (sub-visible particles), assay, degradation products, loss on drying and chiral purity, sterility and bacterial endotoxins. The stability data indicate that there were no significant trends or variability in the parameters tested.

In addition, forced degradation studies (under heat, light, acid, base, and oxidation conditions) and a photostability study conducted in line with the ICH Guideline on Photostability Testing of New Drug Substances and Products were conducted on one commercial scale batch. The forced degradation studies confirmed that there are only two degradation products observed in tedizolid phosphate powder for concentrate for solution for infusion in both the aqueous solution and solid state. These results indicate that the finished product is not photosensitive and consequently does not require any special labelling or packaging to mitigate exposure to light.

The in-use stability of the drug product was assessed on samples reconstituted with 4 ml of WFI. Samples were either immediately analysed, stored for 24 hours under room temperature, in a refrigerator (2-8 °C), or exposed to fluorescent light. The solutions were tested for appearance, pH, visible particulate matter, assay, organic impurities, and sub-visible particulates. No significant changes were observed for any of the parameters measured. Therefore, the data supports that the finished product is physically and chemically stable for up to 24 hours when reconstituted with WFI, and stored under the above-mentioned conditions.

Compatibility of the drug product reconstituted with 0.9% aqueous NaCl solution in IV bags was studied in combination with different IV administration sets that represent those typically found in the clinical setting. Reconstituted solutions were evaluated for up to 24 hours under both room temperature and refrigerated conditions. All samples were tested for appearance, particulate matter, assay, impurities, and pH. Results

demonstrated that the drug product solutions are physically, chemically and microbiologically stable for up to 24 hours in the IV bags and administration sets used in the study.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

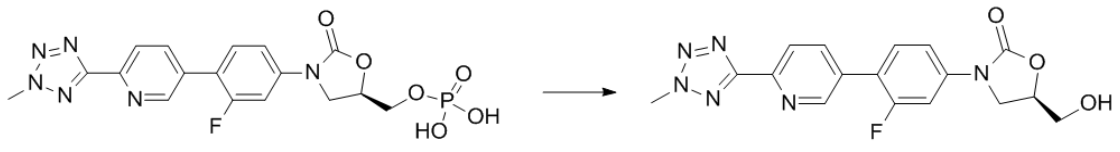
n/a

2.3. Non-clinical aspects

2.3.1. Introduction

Tedizolid phosphate (TR-701 FA) is a novel oxazolidinone prodrug antibiotic that is converted *in vivo* by phosphatases to the microbiologically active moiety tedizolid (TR-700). It has been developed for both oral (p.o) and intravenous (i.v) use. Sivextro tablets and lyophilized powder for injection are indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates. TR-701 FA is a pro-drug with a molecular weight of 450.32 and a molecular formula of $C_{17}H_{16}FN_6O_6P$. TR-701 FA has 1 asymmetric center, leading to 2 possible enantiomers. The absolute configuration at the 5-position of the oxazolidinone ring is the R optical isomer. There are no cis-trans isomers of TR-701 FA. The chemical structures of TR-701 FA and TR-700 are given in the figure below:

Figure 1 Tedizolid phosphate and tedizolid



Tedizolid phosphate
TR-701 FA

Tedizolid
TR-700

The proposed dosage regimen is 200 mg once daily (oral and intravenous (IV) routes of administration) for 6 days for the treatment of acute bacterial skin and skin structure infections (ABSSSI). The steady state geometric mean Cmax and AUC0-24 TR-700 values at the human therapeutic oral dose of 200 mg/day are 2.2 µg/mL and 24.6 µg.hr/mL, respectively.

The TR-701/FA nonclinical pharmacodynamics and safety pharmacology program included *in vitro* and *in vivo* evaluations of the TR-700 efficacy profile against pathogens relevant to cSSTIs/ABSSSI and hospital-acquired lung infections, an investigation of its potential off-target pharmacological activities, and its actions on physiological responses both *in vivo* and in isolated tissues.

GLP

Non-clinical studies on safety pharmacology, general toxicity, including reproduction and genetic toxicity studies were conducted in accordance with GLP principles. Relevant toxicokinetic/pharmacokinetic studies were also conducted according to GLP. Some other studies were not conducted to GLP but were conducted consistent with considerations of adequate scientific standards of quality and justification has been provided by the applicant.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The mechanism of action of tedizolid involves the inhibition of protein synthesis. Tedizolid binds to the peptidyl transferase centre of the 50S ribosomal subunit and inhibits the initiation phase of translation; tedizolid is 3.4-fold more potent than linezolid as a prokaryotic protein synthesis inhibitor.

Tedizolid was demonstrated *in vitro* to be active against microorganisms relevant to cSSTIs and hospital-acquired lung infections; tedizolid was 4- to 32-fold more potent than linezolid against a variety of clinical Gram-positive isolates, including vancomycin- resistant and linezolid-resistant staphylococcal and enterococcal clinical isolates.

In vivo studies were conducted in animal models of infection using linezolid as comparator. The ED_{50}s of tedizolid in systemic lethal infections induced by *S.aureus* (MRSA and MSSA) ranged from 1.5 mg/kg to 7.6 mg/kg and were generally lower than for linezolid. In mouse infected with MRCoNS, tedizolid was more effective than linezolid. In neutropenic mice infected with VRE or VSE pathogens, tedizolid was 2 to 4 fold more potent than linezolid. Lethality due to systemic infections in mice, induced by penicillin susceptible and penicillin-resistant S.pneumoniae was prevented by tedizolid at ED_{50} 3 to 6 fold lower than for linezolid using the intravenous route, but potency appeared similar using the oral route. In the neutropenic mouse infected with a *S.aureus* strain carrying the chloramphenicol-florfenicol-resistant gene encoding a 23SrRNA that confers resistance to linezolid, chloramphenicol and clindamycin, administration of tedizolid at 20 mg/kg resulted in a 100% survival. A published study (Drusano et al., Antimicrobial Agents and Chemotherapy, Nov. 2011, p. 5300–5305) in a thigh infection model showed that several fold higher intraperitoneal doses were required for stasis in granulocytopenic compared with non-granulocytopenic mouse infected with MRSA. In models of skin and soft tissue infections due to MSSA and MRSA, tedizolid was more potent than linezolid producing higher $\log_{10}$ CFU reduction. Efficacy appeared similar to linezolid at plasma exposures simulating human dosage.

Administration of tedizolid phosphate by multiple routes was effective and tedizolid was consistently more potent than linezolid against a variety of pathogens including: (i) staphylococci, including MRSA, linezolid-resistant MRSA and MRCoNS, (ii) enterococci, including VRE, and (iii) penicillin-resistant streptococci tested in a series of systemic lethal and localized animal infection models including skin and soft tissue infections and pneumonia/lung infections. Especially noteworthy was the efficacy against Gram-positive pathogens

resistant to a broad range of antibiotics commonly used in the treatment of cSSTIs, including resistant to linezolid. Additionally, in non-granulocytopenic mice which were administered tedizolid, the *in vivo* bactericidal activity against staphylococcal infections was achieved at far lower doses than in granulocytopenic mice, suggesting the substantial amplification (approximately 25-fold) of the antimicrobial efficacy due to the presence of granulocytes.

Secondary pharmacodynamic studies

Tedizolid was tested in a panel of 147 biochemical assays and 30 enzyme assays using concentrations of tedizolid (TR-700) of up to 20 µM. In this *in vitro* assessment of the potential secondary pharmacological activity of tedizolid carried out with biochemical, enzyme and radioligand binding assays, the only noteworthy finding was a weak and reversible inhibition of MAO-A and MAO-B. This inhibition of MAO is potentially associated with pressor responses resulting from the absorption of unmetabolized dietary tyramine, and with excessive serotonergic activity when co-administered with serotonin agonists and reuptake inhibitors. Focused phase 1 studies using steady-state plasma tedizolid levels found no evidence of a meaningful risk for the potentiation of the pressor response to oral pseudoephedrine or altered sensitivity to tyramine associated with the administration of tedizolid phosphate, compared with placebo (studies TR701-114, TR701-105). These results were consistent with the negative results in animal models of peripheral (rat tyramine pressor response) and central (5-HTP mouse head-twitch) MAO inhibitory activity, where no effects were observed at tedizolid plasma Cmax levels approximately 27-fold greater than the Cmax levels observed in humans at the therapeutic dose. Linezolid served as a positive control in these animal studies. This lack of activity in vivo is predicted by low circulating peak tedizolid plasma concentrations relative to the IC50 for MAO inhibition. In addition, the low brain penetration of tedizolid relative to linezolid (brain:plasma ratio of linezolid >4-fold higher than tedizolid in rats) may contribute to the lack of central MAO inhibition following the administration of tedizolid phosphate.

Safety pharmacology programme

Tedizolid was evaluated for its potential interference with the central nervous system, cardiovascular, respiratory, autonomic nervous system, the gastrointestinal and the renal organ function *in vivo* at doses of up to 200 mg/kg and *in vitro* at concentrations up to 20 µM. Both tedizolid (TR-700) and tedizolid phosphate (TR-701) were tested in *in vitro* studies. No effects on cardiovascular parameters *in vitro* and *in vivo* were reported. Exposure in an *in vivo* dog study was up to 3-fold the clinical exposure and *in vitro* margins up to 17-fold were obtained using clinical free plasma concentrations. A small, transient, but significant decrease in the body temperature was evident in mice at 100 mg/kg. Further, spontaneous locomotor activity showed a modest, but transient decrease and doses of 100 mg/kg and a 23% increase in the hexobarbital sleep time was noted in mice. This dose in mice is estimated to correspond to TR-700 exposures 20-fold greater than the exposure in humans at the recommended oral dose. In rats, the dose of 100 mg/kg caused a 40% decrease in the gastric volume secretion without affecting pH or total acidity and in the renal study moderate decreases in sodium and chloride concentrations were reported, possibly related to a trend towards an increased urine volume at the same dose. A single dose of tedizolid phosphate to rats at 100 mg/kg is associated with a TR-700 Cmax approximately 33-fold the Cmax in humans at the therapeutic dose of 200 mg/day. Taken together these findings could indicate a potential for effects on the central nervous and gastrointestinal system, but the magnitude of those effects and the margins of exposure to therapeutic levels were of limited clinical concern. The adverse reactions currently described in section 4.8 of the Sivextro SmPC include possibly related clinical effects. The CHMP agreed that from the non-clinical point of view, the primary, secondary and safety pharmacology of tedizolid is sufficiently investigated.

Pharmacodynamic drug interactions

No studies of pharmacodynamic drug interactions were conducted. The general pharmacological profiles of TR-701 and TR-700 did not suggest a potential for pharmacodynamic interactions, with the exception of the action in inhibiting MAO, which has been adequately investigated.

Conclusions

Taken together, the results of the pharmacodynamic and safety pharmacology studies show a favorable profile of TR-701/FA. *In vitro*, tedizolid is highly effective in a variety of bacterial pathogens, including against some resistant organisms. Tedizolid, administered in the form of the prodrug tedizolid phosphate, was effective in models of systemic and localized infection, with higher potency compared to linezolid. Tedizolid effects appear to undergo a dramatic amplification in the presence of granulocytes. Safety pharmacology studies of TR-700 and TR-701 examined doses resulting in plasma concentrations greatly exceeding the systemic TR-700 concentrations experienced by human patients, and did not result in findings relevant to the human safety. Overall, the results were supportive of a favorable safety and efficacy profile of TR-701/FA against ABSSSI infections in humans.

2.3.3. Pharmacokinetics

The absorption, distribution, metabolism, and excretion profiles of tedizolid and tedizolid phosphate were studied in mice, rats, rabbits, and dogs. *In vitro* evaluations assisted in exploring the distribution and metabolic profiles of TR 700 and TR 701.

Single dose pharmacokinetic (PK) parameters for TR 700 in plasma were determined after oral and intravenous (IV) administration of TR 701 in mice, rats, and dogs and after IV and oral administration of TR 700 in mice and rats. In all three species, TR 701 was rapidly and extensively metabolized to TR 700, and exposure to TR 700 was generally proportional to the administered dose of TR 701. TR 701 was reliably detectable in plasma after IV administration of TR 701, but appeared only at very low concentrations, if at all, after oral administration. Single dose administration of TR 701 FA in rats and dogs resulted in rapid exposure to TR 700 across a range of doses.

The results of pharmacokinetic and toxicokinetic studies conducted across several species indicate that the administration of TR 701 or TR 701 FA resulted in a substantial exposure to TR 700 in plasma and in the most of the tissues. Due to the rapid conversion to TR 700, the exposure to TR 701 itself was low and transient after IV administration in rats and dogs. Studies determining absolute oral bioavailability of either TR 700 or TR 701 in rodents confirmed that although the systemic exposure to the prodrug forms was extremely limited after oral administration (≤8%), the superior absorption of TR 700 from oral TR 701 versus oral TR 700 led to a significantly greater bioavailability of the active moiety (63% to 93% versus 29% to 49%). Circulating TR 701 was not detected in dogs after oral administration of TR 701. These findings are supportive of the prodrug approach to TR 700 delivery, and are concordant with human results showing essentially an equivalent exposure to TR 700 after oral or IV administration of TR 701.

Both single-dose and repeat-dose studies demonstrated a relatively orderly increase in the TR 700 exposure when the dose of TR 701/FA was increased, although some departures from dose proportionality were observed at relatively high IV and oral doses in dogs. The observed variability in the PK parameters after the oral administration of TR 701/FA in dogs may be partly explained by the appearance of emesis. In single-dose studies, noteworthy sex differences in the exposure to TR 700 after administration of the prodrug were observed only in rats, with an approximately 3-fold higher exposure in females than males. Because of these differences, doses in later rat studies were different for males and females. The clinical significance of these differences was

not further explored by the applicant and was not deemed of clinical relevance. The CHMP agreed that the submitted results of repeat-dose pharmacokinetic and toxicokinetic studies with TR 701 and TR 701 FA indicated that a sufficient exposure to TR 700 is maintained over time to facilitate an adequate evaluation of long-term safety, and that the PK profile of TR 700 supports the proposed human regimen of once-daily dose administration by oral and IV routes.

TR 700 is moderately to extensively bound to plasma proteins (>70%) across all species tested, and [14C] TR 701 derived materials are widely distributed to most tissues in both rats and dogs. However, TR 700 does not well penetrate into the red blood cells. The majority (>50%) of TR-700 binding in plasma was to serum albumin. In a subcellular distribution study, TR 700 was associated with the cytosolic fraction in macrophages and not with mitochondria or lysosomes, organelles often implicated in adverse reactions.

In Caco-2 cells, TR-700 was highly permeable with no significant efflux at concentrations up to 100 µM inferring that TR-700 will exhibit high absorption in the gastrointestinal tract. Foetuses were exposed to TR 700 in dams dosed with TR 701 FA. TR 700 was also secreted into the milk of lactating rats dosed with TR 701 FA, and therefore pups of the F1 generation were exposed to TR 700.

TR 701 is metabolically stable in animal and human liver microsomes. In contrast, TR 701 is unstable in heparinized blood and plasma samples and in rat S9 liver fractions, with the disappearance of TR 701 paralleled by the appearance of TR 700 except in the presence of a cocktail of specific phosphatase inhibitors. These findings suggest that the rapid biotransformation of TR 701/FA to TR 700 *in vivo* is not mediated by the CYP P450 system, but rather by endogenous phosphatase enzymes that are ubiquitously distributed in blood and tissues. Neither TR-701/FA nor TR-700 detectably inhibited the metabolism of selected CYP enzyme substrates, including time-dependent inhibition of CYP3A. In primary human hepatocyte cultures, TR-700 (up to 10 µM) did not induce mRNA of CYP isoforms (CYP1A2, 2B6, 2C8, 2C9, and 2C19,) with the exception of concentration dependent increase in CYP3A4 (greater than 2-fold increase in CYP3A4 mRNA was observed with tedizolid. The results from an *ex vivo* study in rats confirmed that the TR 701 administration does not result in clinically significant induction of CYP enzymes and studies using human biomaterials confirmed that TR 701 and TR 700 are not CYP inhibitors. *In vitro* studies have shown that TR-700 and TR-701/FA are unlikely to result in meaningful inhibition of P-gp, OCT1, OCT2, OAT1, OAT3, or OATP 1B3 transporters, whereas a clinical significant interaction with OATP 1B1 cannot be excluded. Inhibition of the efflux transporter BCRP (also known as ABCG2) was observed in Caco-2 cells by TR-700 (IC50=51.1 µM) and TR-701 (IC50=79.8 µM, presumably by being converted to TR-700 in vitro). The clinical relevance of this finding is unknown. While these findings in general suggest little risk for significant PK drug-drug interactions with TR 701 FA, the potential for induction of CYP3A4 needs to be further investigated.

Based on the positive results for CYP3A4 induction, the applicant is also asked to perform an *in vivo* induction study as a post-approval measure. As a first step of this measure, a suggested study setup to allow for the optimal capture a potential CYP3A induction (e.g. based on the tedizolid half-life, and the turnover rate of CYP3A4, the maximum induction effect is reached after at least 10 days of tedizolid treatment duration) should be submitted. The SmPC was updated until the results of this study will be assessed.

A study in rats confirmed that there is no evidence of an *in vivo* interconversion from the (R) enantiomer of TR-700 to the (S) enantiomer after the oral administration of (R) TR 701 FA. The principal circulating metabolite of TR 701 in rats and dogs is TR 700, with no other metabolite identified in plasma. Radioprofiling of rat urine samples after administration of [14C] TR 701 identified seven metabolites, most notably TR 700 sulfate, while in the urine of dogs, the most noteworthy peaks corresponded to N desmethyl TR 700 and TR 700 sulfate. Very small amounts of TR 700 were recovered in the urine after IV or oral administration of TR 701. Additional evidence from rats suggests that small amounts of TR 700 leave the systemic circulation through biliary

excretion. The main elimination pathway for the TR 701/FA metabolic products is through the faeces, mainly in the form of TR 700 sulfate. Nearly all of an administered dose of radiolabeled TR 701 is eliminated in faeces (approximately 90%) and in urine (approximately 10%) within 7 days after a single dose. Given that as small fraction of TR 700 is detected in the urine or in the faeces, urinary tract infections would not be expected to be optimally treated with TR 701 FA.

The drug substance used in non-clinical and clinical studies consists of approximately 99.5% of the (R)-enantiomer. No significant in vivo interconversion of (R) to (S)-TR-700 form was evident in rat given single oral doses of TR-701 FA, pure (R) enantiomer.

The major part of a dose of TR-701 in rat was excreted in faeces. Urinary excretion accounted for about 10% of dose after both oral and intravenous doses in males and females. In bile duct cannulated rats the mean amount of TR-700 recovered in bile after 4 hours was 1.76%- after a single intravenous dose of TR-701. Like in rats, the main route of elimination in dogs was the faecal excretion. After single oral or intravenous doses 83 to 107% of the 14C-TR-701 derived radioactivity was excreted in the faeces within the first 24 hours post dose. Urinary excretion accounted for approximately 10%.

After repeated oral or intravenous doses in dog systemic exposure increased greater than dose-proportional.

In humans, only tedizolid was detected in plasma. All human metabolites in plasma, urine and faeces were also present in rat and dog. CHMP agreed that the submitted pharmacokinetic data provide a sufficient characterisation of all relevant parameters.

2.3.4. Toxicology

Single dose toxicity

In single dose toxicity studies, bolus intravenous doses of 250 mg/kg resulted in deaths in mouse and rat while mortalities in dogs were noted at doses > 100 mg/kg. Likewise oral doses of 2000 mg/kg in rat were coupled to mortality (females only), while no deaths occurred in mice or males rats at comparable doses. In rodents, evidence of gastrointestinal adverse effects were evident.Dilatation of cecum, likely due to the antibiotic action of the test article against cecum microflora, was reported in both single and repeated dose toxicity studies in rodents. In dogs, hypoactivity and gastrointestinal adverse effects were noted primarily at doses ≥ 100 mg/kg.

Repeat dose toxicity

The hematopoietic and the gastrointestinal systems were the primary targets following PO and IV repeat dose administration of tedizolid phosphate, with these effects showing evidence of reversibility and occurring at multiples of the human tedizolid therapeutic exposure level.

Hematopoietic effects after oral administration in rats were characterized by mild-moderate changes in circulating RBC, WBC, and platelets, myeloid, erythroid, and megakaryocyte hypocellularity in bone marrow, and decreased splenic B cells. Changes in haematology indicative of myelosuppression were seen in rats after IV administration, although no bone marrow histological changes were reported. Consistent with the hematopoietic changes seen after PO dosing, rats also had lower immunoglobulin titres and showed a decreased ability to respond to an antigen challenge at dose levels at or near those showing haematological effects. These immunotoxicity results are consistent with findings in the 4-week general toxicity study in rats which showed a reversible decrease in splenic B-cell lymphocyte subpopulations. In dogs, hypocellularity in the bone marrow was seen in one dog after IV administration at clinically intolerant doses.

Deaths and intolerance leading to early terminations of animals were evident in both rat and dog oral and intravenous studies, although in the performed dog oral study these could have been due to gavage errors. In rats, in the oral studies of 1 and 3 months duration, doses of 100 mg/kg/day were not tolerated, but resulted in body weight loss, haematological effects, bone marrow and gastrointestinal tract atrophy, morbidity and deaths. At a non-tolerated dose of 100 mg/kg in rat, tedizolid related effects were also noted in the liver (centrilobular hepatocellular degeneration), the gastrointestinal tract (focal erosion, single cell necrosis in the colon, mucosal ulceration in the rectum), male kidney (tubular hyaline droplets, distal tubular proteinosis, inner medulla tubular necrosis),the male reproductive tract (atrophy/decreased secretion in the prostate/seminal vesicles/coagulation gland, seminiferous tubular degeneration/haemorrhage/inflammation in the testes) as well as the female reproductive tract (ovarian follicular involution and atrophy in the vagina and cervix). The dose of 100 mg/kg/day corresponded to systemic exposure ratios of 31- to 14-fold (systemic exposure decreased significantly from day 1 to day 28 in the 1 month study). Further, doses in rat of 90 mg/kg in males and 45 mg/kg in females administered via slow push injection caused mortality, while less toxicity was apparent with daily infusion over 60 minutes over a 14 day period. Clinical signs of gastrointestinal intolerance and hypoactivity tremors, gasping, pupil dilation, laboured respiration, convulsions and impaired equilibrium were noted prior to death. In a dog 2-week intravenous infusion study, body weight loss and severe local reactions including oedema, inflammation, ulceration/necrosis, hemorrhage, and vasculitis contributed to an early termination of high dose animals. At the highest dose level (100 mg/kg/2xday) bone marrow hypocellularity, atrophy of thymus, inflammation of duodenum, atrophy of oesophagus mucosa, and karyomegaly of the mucosa of the oesophagus, duodenum and jejunum were noted.

Gastrointestinal system changes in rats and dogs after oral administration included decreased food intake, reduced body weight gain, and stool effects at tolerated doses, and degeneration, necrosis, and erosion in the small/large intestine and/or stomach at clinically intolerant doses. Similar GI changes were seen after IV administration in rats and dogs, although secondary effects due to injection site toxicity complicated these changes in dogs.

Nevertheless, it should be noted that hematopoietic and GI system changes have been reported with clinical use of a wide variety of antibiotics and are seen in both animals and humans.

Other systemic toxicities seen in rats and dogs after repeat administration with tedizolid phosphate occurred at clinically intolerant dose levels that induced morbidity or moribundity. These toxicities were only seen at doses that greatly exceeded the MTD and were considered related to or exacerbated by severe physiological stress. High dose effects in the 3-month study in rats included histopathological changes in the GI tract, lymphoid and glandular tissues, mammary gland, skeletal muscle, tongue, liver, male kidney, and male and female reproductive tracts. All these changes reversed or trended toward reversal during the post-treatment recovery period. In dogs, effects secondary to the marked inflammatory changes at the IV injection sites were observed.

Considering the oral toxicity studies in rodents, the applicant was requested to further elaborate on the significant changes observed in thymus, spleen, mesenteric lymph nodes and bone marrow across the repeat dose studies described, and on the relevance and significance of these findings for the clinical safety of tedizolid in humans. The discussion took into consideration the consistent findings in the immunotoxicity studies. The applicant further clarified that the oxazolidinone class of antibiotics are coupled to effects on the haematopoietic system. Reversible myelosuppression has been reported and may result from inhibition of mitochondrial protein synthesis by oxazolidinones. Oral doses of tedizolid in rat caused mild to moderate changes in circulating RBC, WBC, and platelets, myeloid, erythroid, and megakaryocyte hypocellularity in bone marrow; and decreased splenic B cells. After intravenous doses, changes in haematology indicative of myelosuppression were seen, although no bone marrow histological changes were reported. In dogs, hypocellularity in bone marrow was seen

in one dog after IV administration at a high dose. Decreased cellularity/atrophy of lymphoid tissue was also observed and may have been associated with severe stress (body weight loss, moribund condition). Elevation in splenic T-lymphocytes in the 1-month general toxicity study in rats was consistent with a stress response contributing to thymic lymphoid depletion. Myelosuppression is an identified risk and included in the RMP.

Since peripheral and optic neuropathy were seen in both animals and humans which were administered linezolid, an extensive evaluation of the potential of tedizolid phosphate to cause peripheral and optic neuropathy was conducted in pigmented rats dosed for up to 9 months at dose levels up to 30 mg/kg/day in males and 10 mg/kg/day in females. This study showed no drug-related effects on survival, food consumption, functional observational battery assessments, locomotor activity, brain weight measurements, ocular examinations, and macroscopic and microscopic neuropathological findings (includes sciatic and optic nerves, retina and uveal tract). No evidence of peripheral and optic neuropathy was observed with tedizolid phosphate at plasma tedizolid exposures well above (approximately 8-fold) the human therapeutic exposure levels: moreover, the study involved 9 months of dosing as compared to 6 months in the study in which neuropathy findings were observed with linezolid.

In a two-week comparative oral/intravenous study in rat, the toxicity of TR-701 FA and linezolid was investigated. Overall, after oral administration clinical signs, haematological parameters and organ weight changes and histopathological changes were comparable for the two compounds, however, infusion with TR-701 FA was not tolerated based on local injection site effects from the low dose of 40 mg/kg/day whereas no adverse effects were coupled to linezolid infusion twice daily at a dose 100 mg/kg.

Qualitatively, target organs of toxicity appeared similar in rats after oral and intravenous administration with bone marrow hypocellularity and clinical as well as histopathological signs of gastrointestinal adverse effects. Tolerability of intravenous doses appeared lower than after oral and while systemic exposure generally was comparable at equal doses for both routes, Cmax ranged from 2-3 to 10-fold higher after intravenous doses. The applicant further addressed the apparent lower tolerance of intravenous doses compared with oral, noted particularly in dog. The applicant presented a thorough discussion on the possible differences in the toxicological responses following oral and intravenous dosing. Submitted data were supportive of species dependence, with rats seemingly more sensitive than dogs to the acute toxic effects of tedizolid. Higher levels of tedizolid phosphate after intravenous dosing compared with oral doses may indicate that tedizolid phosphate may have contributed to the acute effects noted. In rats, severe acute systemic effects were noted with intravenous bolus doses coupled to high C_{max} levels and severity was increased in males compared with females and related to the higher C_{max} levels in males. Acute toxicity was not evident after a 60-minute intravenous infusion.

In dog studies, tedizolid plasma levels were consistently lower after an oral dosing compared with an intravenous one, also indicating lower bioavailability in dogs compared with rat and human. Comparisons of intravenous bolus and intravenous infusion doses in dog were consistent with the fact that acute toxicity was lower after intravenous infusion and with that dogs were less sensitive than rats to acute systemic effects.

While vascular irritation after intravenous infusion was observed in rats and dogs, no observations of local non-tolerance in humans have been reported to date. The concentrations of tedizolid phosphate and infusion rate seem important determinants for vascular irritation. Studies in rabbit did not indicate any irritation potential for inadvertent perivascular, intramuscular or subcutaneous administration.

In terms of systemic exposure and maximum plasma levels, the highest levels were achieved in rat. At the proposed NOAELs in oral repeated dose toxicity studies, 30/10 mg/kg in male/female rat studies and 400/400 mg/kg in male/female dog studies margins of exposure to expected clinical values ranged from x2 to x8. These values may be considered as estimates since these are based on averages of toxicokinetic data that exhibited

marked time-dependent variability. Exposure to TR-701 was also determined in 3-month oral studies and was overall lower in dog than in rat oral studies. during 2 and 4 weeks in dogs and rats, respectively.

The oxazolidine class of antibiotics have been known to have the potential for bone marrow suppression, due to inhibition of mammalian mitochondrial protein synthesis. *In vitro* tedizolid exhibited a potency of up to 20 times that of linezolid for the inhibition of the mitochondrial protein synthesis in rat heart. Both tedizolid and linezolid thus have a potential for myelosuppression.

Genotoxicity

Tedizolid phosphate and tedizolid were tested in a battery of genotoxicity studies and, considering the overall results, the weight of evidence indicated that neither the prodrug nor the active moiety would present a genotoxic risk to humans. Because the results of genotoxicity testing did not reveal a relevant risk for humans, and since tedizolid phosphate is indicated only for short duration of therapeutic use, carcinogenicity studies were not conducted with tedizolid phosphate. Regarding studies performed on impurities, an intermediate 6 reference standard (Rx600008) and Rx600009 was considered to be positive for mutagenic activity in the Salmonella strain TA100 with metabolic activation. The applicant further elaborated on the relevance of these findings and on how the risk associated to the positive mutagenic activity of these compounds was mitigated or reduced, and this was considered resolved (being a raised 'other concern').

Carcinogenicity

No carcinogenicity studies have been conducted and are not required consistent with standard regulatory guidance.

Reproduction and Developmental Toxicity

No adverse related findings were identified in a fertility study conducted with tedizolid phosphate in rats and no toxicity to the reproductive organs was identified in a 28-day oral toxicity study conducted in rats or in 28-day and 3-month oral toxicity studies in dogs. Reproductive organ effects in the 3-month rat oral toxicity study were limited to morbid/moribund rats that did not tolerate tedizolid phosphate doses that exceeded the MTD, indicating stress to be a factor in these changes. Based on the fertility and repeat-dose toxicity studies conducted with tedizolid phosphate, there is a limited if any risk of reproductive toxicity following administration of the therapeutic dose of tedizolid phosphate to humans. In contrast to the findings with tedizolid phosphate, it is important to note that linezolid caused reversible infertility in male rats during reproductive function studies. The free acid form of tedizolid, TR-701 FA had no significant effects on fertility when tested at doses of 50 mg/kg in males and 15 mg/kg in females. These doses provided exposure multiples of approximately 4 -5 times the expected clinical exposure. A slight reduction in sperm number and epididymal weights was recorded, although the changes did not translate into any functional effects. However, considering also the effects on male reproductive organs seen at high doses (100/60 mg/kg) in 3 month repeated dose studies in rats and the known effect on male fertility of the related oxazolidinone linezolid, the potential effects of tedizolid on fertility were further discussed by the applicant and the answers provided were considered satisfactory by CHMP.

Concerning the embryo-foetal development this could not be assessed in rabbits due to dose-limiting toxicity to the GI tract, which is a common finding with antibacterial agents. Plasma tedizolid levels associated with the NOAEL in mice and rats were comparable to plasma levels at the human oral therapeutic dose. Lower mean foetal weights were noted at the high-dose level (25 mg/kg/day) and resulted in a lower mean gravid uterine weight in this group. In addition, a test article-related increase (not statistically significant) in the mean litter proportion of costal cartilage anomalies (primarily fusion);an exacerbation of the normal genetic predisposition to sternal variations in the CD-1 strain of mice) was noted in this treatment group. In rats, decreased foetal

weights and foetal developmental delay contaminant with maternal toxicity was observed at the high-dose level (15 mg/kg/day) as increased mean litter proportions of skeletal variations indicative of delayed ossification. Rib and vertebra findings that were not indicative of developmental delay were also noted for foetuses at the high-dose level (15 mg/kg/day). Taken together, these data could not exclude the possibility for tedizolid to have a teratogenic effect. The applicant was invited to further elaborate on the relevance of these findings, considering the data in the high dose groups. In its answer, the applicant explained that the effects noted in the embryofoetal development studies in mouse and rat seemed consistent with those noted for other oxazolidinones. In mouse, exposure margins for both linezolid and tedizolid were about 4-fold the expected clinical levels when considering decreased foetal body weights and increases in costal cartilage fusion. In rat decreases in foetal body weight and reduced ossification of sternebrae, vertebrae and skull occurred at about 6-fold the expected clinical levels with higher exposure levels for tedizolid compared with linezolid. CHMP agreed that the observed changes were not life-threatening and that they should not be considered as representative of teratogenic effects.

The applicant has further discussed the pre- and postnatal development (PPND) rat study. The discrepancy in the number of pups dead/missing, cannibalized in vehicle and high dose group was attributed to one litter with a high incidence (8) of pups with adverse outcomes. Pups with pale body and smaller stature seemed to correlate with a high incidence of dead and missing pups in the high dose group. The applicant indicated that on a per litter basis no statistically significant differences were apparent between control and high dose. Group survival was comparable. The high dose in the study likely represented not more than two times the exposure margin to the expected clinical, but was based on maternal effects seen in an embryotoxicity study. The CHMP considered the text included in section 5.3 of the SPC as satisfactory and reflecting the generated data.

Prenatal and postnatal development after administration of TA-701 FA was investigated in rat using doses of 1.25 to 3.75 mg/kg. No effects on either the maternal function or on the development of offspring, early behaviour, physical development, sensory functions, genital development and mating ability and fertility of offspring were evident. There were occasional statistically significant differences between groups in parameters monitored, however, due to the isolated occurrence and values similar to historical controls overall findings appeared incidental and not related to treatment of maternal animals. The number of pups found dead/missing, presumed cannibalized/euthanized between birth and PND21 amounted to 16, 16, 24, and 32 in the control, low, mid and high dose groups, respectively. There was 1 litter each in mid and high dose group with unusually high number (7 and 8) dead/missing and as the remaining 22 to 23 litters did not show higher mortality, the death of these pups were considered incidental. Pale body/small stature was noted for 12 and 11 pups, respectively, in the 3.75 mg/kg group during the period birth to PND 21 and because 4 of 7 were from the same litter overall the findings were considered incidental. The Applicant has proposed a NOAEL of 3.75 mg/kg/d for F_0 maternal systemic toxicity, F_1 neonatal/developmental toxicity, F_1 sexual maturation, systemic, neurobehavioral, and reproductive toxicity, F_2 neonatal toxicity. No test article-related effects on F_2 postnatal survival or pup body weights and body weight gains were noted. Food intake was slightly decreased in high dose maternal animals, but there was no effect on body weight. Systemic exposure at the high dose in the present study was likely not more than x2 clinical exposure.

Tedizolid exposure to foetuses and pups has shown that tedizolid is excreted in the milk of lactating rats and tedizolid plasma levels in foetuses indicated the placenta transfer of tedizolid.

No juvenile toxicity studies have been conducted, which is acceptable for the present indication.

Toxicokinetic data

Toxicokinetic data generated in rats after repeated intravenous doses, despite some interpretation difficulties, showed marked gender differences in exposure with higher exposures in females than in males were apparent.

Early toxicology studies had shown an approximate 3-fold higher plasma exposure to tedizolid in female rats versus male rats at a given dose level (due to a slower tedizolid plasma clearance in female rats), subsequent repeat-dose toxicology studies used lower doses for female versus male rats. Sex differences in pharmacokinetics were not observed in other animal species, or in humans. In all toxicology studies, plasma tedizolid AUC increased with increasing doses of tedizolid phosphate. Dose duration had no noticeable effects on tedizolid plasma levels in animals; therefore, AUC study values determined on multiple occasions were averaged when used in calculating margins relative to humans. This approach provided a more consistent and generally more conservative estimate of exposure than using the final AUC determination.

Local Tolerance

While injection site toxicity was noted with IV infusion in animals, tedizolid phosphate-related infusion site phlebitis was not detected in a venous tolerability study conducted in humans under dose administration conditions utilized for therapeutic IV administration. There also was no evidence of irritation potential for inadvertent perivascular, intramuscular, or subcutaneous administration using the therapeutic IV dose concentration with the lyophilized tedizolid phosphate drug product in rabbits. These results indicate that injection site complications are not expected with the proposed therapeutic use of tedizolid phosphate via the IV route.

In local toxicity studies in rat, dose-related acute perivasculitis and , thrombosis were evident at 5.4 mg/kg/day and perivasculitis, thrombosis, and vasculitis were evident at 18 mg/kg/day when infused over 120 minutes. In local toxicity studies in dog, dose-related microscopic findings of endothelial and subintimal vacuolation and inflammation, thrombosis, vasculitis and oedema, haemorrhage, fibrinous exudate and inflammation in the subcutis were observed at the injection site at ⩾ 6.6 mg/kg (1.1 mg/mL). Swollen forelimb(s), thrombosis, amorphous, lamellated, amphophilic material in the thrombi and vascular walls were noted at 19.8 mg/kg (3.3 mg/mL) when infused over 60 minutes. Swelling of right cephalic injection site, edematous right and left cephalic injection sites were noted at 66 mg/kg (11 mg/mL) when infused over 60 minutes. The NOAEL for vascular irritation was 3.4 mg/kg/day when infusion was over 120 minutes.

In rabbit, acute perivascular, intramuscular or subcutaneous injections did not result in any definitive tedizolid related reactions.

Other toxicity studies

In addition to conducting pivotal general toxicology studies with tedizolid phosphate, a number of special toxicity studies were conducted.

Immunotoxicity

Data from a 4 week repeated dose toxicity study in rat using oral doses of up to 100 mg/kg in males and 30 mg/kg in females showed immunosuppressive effects of tedizolid characterised at the high dose in males by decreased in splenic cell counts, decreases in T cells, B cells and double positive T cells. In females, a decrease in splenic cell counts (not statistically significant) and a slight decrease in T cells were reported. IgG titer was significantly decreased from doses of ≥30 mg/kg/day. IgG and IgM induced plaque formation was dose-dependently decreased. The clinical relevance of potential immunotoxicological effects were further discussed and considered satisfactory.

Phototoxicity

Tedizolid did not induce any relevant phototoxic reactions in a study in pigmented rat treated with a single oral dose of TA-701 FA followed by UVR exposure. The positive control 8-MOP gave expected responses.

Mechanistic Studies

These studies were undertaken to compare the capacity of tedizolid and linezolid to inhibit protein synthesis in isolated rat heart mitochondria. Both compounds inhibited mitochondrial protein synthesis in the two studies performed, with tedizolid being 20 to 25 more potent than linezolid. Assays with TR-701 in this system were consistent with a slow conversion of TR-701 to TR-700. However, the relevance of this finding to the toxicity induced by tedizolid is uncertain because tedizolid was not associated with mitochondria in incubations carried out in intact macrophages, even though substantial uptake into the cytosol occurred. Additionally, safety margins for tedizolid plasma levels at the NOAELs identified in animal toxicology studies, relative to the human therapeutic plasma exposure, were substantially and consistently greater than the safety margins derived for linezolid.

Dependence

Tedizolid was shown to inhibit MAO in in vitro studies but follow-up studies, including any potential potentiation of 5-HTP head-twitch in mice or effects on brain monoamine levels, failed to show any in vivo consequences of this activity. No CNS or withdrawal symptoms suggestive of dependency were noted in the nonclinical general toxicity and safety pharmacology studies, as well as in human clinical trials. Consequently, studies of potential dependence were not considered necessary and were therefore not conducted.

Impurities

The impurities BisRx600022, (S)-TR-701, Rx600013 and Rx600014 were qualified in 2-week rat repeated dose toxicity studies using intravenous administration. In addition, impurities were screened and tested for genotoxic potential. Positive results were reported for (R)-glycidyl butyrate, Rx600008 and Rx600009. The data have been appropriately considered in the proposed specification limits for impurities.

Further considerations

Exposure margins based on tedizolid plasma AUCs at NOAELs (averaged across study days with TK analyses) during repeat-dose toxicology studies, against plasma AUCs at the human therapeutic doses, are listed for tedizolid phosphate in the following table:

Table 1 Exposure margins based on tedizolid plasma AUCs at NOAELs during repeat-dose toxicology studies against plasma AUCs at the human therapeutic doses

Study	Sex	NOAEL Dose (mg/kg/day)	NOAEL AUC_{24} (µg•h/mL)	Exposure Margin (fold-human)[1]
Oral Repeat Dose Studies				
28-day rat (TOX-07-0701-014A)	Male	30	90.4	3.7
	Female	10	182	7.4
3-month rat (TOX-11-0701-027)	Male	30	130	5.3
	Female	10	104	4.2
9-month rat (TOX-11-0701-028)	Male	30	145	5.9
	Female	10	141	5.7
28-day dog (TOX-07-0701-013A)	Male	400	117	4.7
	Female	400	74	3.0

3-month dog (TOX-11-0701-026)	Male	400	105	4.3
	Female	400	167	6.8
Intravenous Repeat Dose Studies				
28-day rat (TOX-08-0701-009)	Male	30	122	4.3
	Female	15	93.1	3.3
14-day dog BID (TOX-08-0701-019)	Male	50	88.4[2]	3.1
	Female	50	92.4[2]	3.2
Study	**Sex**	**NOAEL Dose (mg/kg/day)**	**NOAEL AUC_{24} (µg•h/mL)**	**Exposure Margin (fold-human)[1]**
Reproductive toxicity				
Rat fertility (TOX-08-0701-026)	Male	50	>130[3]	>5.3
	Female	15	>104[3]	>4.2
Mouse embryofetal (TOX-09-0701-019)	Female	5	19	0.8
Rat embryofetal (TOX-08-0701-004)	Female	2.5	28.8	1.2
Rat pre/post-natal (TOX-11-0701-025)	Female	3.75	28.8[4]	1.2

[1] Tedizolid geometric mean AUC_{0-24} at the 200 mg/day once daily tedizolid phosphate FA therapeutic dose = 24.6 µg·hr/mL PO and 28.6 µg•hr/mL IV

[2] AUC_{0-12} x 2.

[3] AUC_{24} values for the 30 mg/kg/day male and 10 mg/kg/day female NOAELs identified in the 13-wk rat oral study utilized to calculate exposure margins as toxicokinetics not evaluated in the fertility study.

[4] AUC_{24} value for the 2.5 mg/kg/day female NOAEL identified in the rat embryofetal development study utilized to calculate exposure margins as no toxicokinetics evaluation in the pre/post-natal development study.

Although tedizolid inhibits protein synthesis in isolated rat heart mitochondria (SPH-08-0701-028), it did not distribute to the mitochondrial subcellular compartment when incubated with macrophages (murine cell line) even though substantial concentrations were taken up into the cytosolic fraction.

While NOAEL doses for oral repeat-dose studies remained constant throughout 9 months of administration in rats and 3 months of administration in dogs, exposure margins ranged from 3.7- to 7.4-fold for rats and 3.0- to 6.8 -fold for dogs. Without trends in dosage duration, these margins can be averaged across studies, generating overall exposure margins of approximately 5.4-fold in rats and 4.7-fold in dogs. Exposure margins were more consistent with IV administration of tedizolid phosphate, ranging from 3.3- to 4.3-fold in rats and 3.1- to 3.2-fold in dogs. In addition, relatively large exposure margins were identified for both males and females during fertility testing, while NOAEL doses in the embryofetal development and pre/post-natal studies were comparable to tedizolid plasma AUCs generated at the human therapeutic dose. In the mouse and rat embryofetal development studies, minor developmental findings were noted at the next highest dose above the NOAEL. These Lowest Observed Adverse Effect Level (LOAEL) doses provide plasma exposure margins of 4-fold (mice) and 2.3-fold (rats).

2.3.5. Ecotoxicity / environmental risk assessment

The applicant has submitted an environmental risk assessment in accordance with the CHMP guideline (EMEA/CHMP/SWP/4447/00 corr.1, June 2006). The studies comprised: a soil adsorption coefficient, a ready biodegradability test, a water/sediment study, chronic toxicity studies in aquatic organisms and an activated sludge respiration test. The applicant concluded that no environmental risk has been identified as a consequence of the use of tedizolid.

However, the Activated Sludge, Respiration Inhibition Test (OECD209) provided cannot be validated as the results are not clearly defined. Therefore the applicant is requested to submit a new study.

Table 2 Summary of main study results-Environmental risk assessment

Substance (INN / Invented Name): tedizolid phosphate / sivextro					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log P_{ow}	OECD117	logPow (pH 7)=1.3			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log P_{ow}	1.3			not B
	BCF	Not determined			
Persistence	DT50 or ready biodegradability	Not readily biodegradable			P
Toxicity	EC_{10} mortality	21.26 µg/L			Not T
PBT-statement :	The compound is not considered at PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	1	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					N
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Absorption-desorption	OECD 121	Koc =398.11 L/Kg			Indicative value of the binding capacity of tedizolid on organic matter
Ready Biodegradability Test	OECD 301 B	Not readily biodegradable			28 days
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT_{50}< 1 day % shifting to sediment =98-100			Distributed to the sediment
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	63.2	µg/L	*Anabaena flosaquae*
Daphnia sp. Reproduction Test	OECD 211	NOEC	600	µg/L	Reproduction and survival
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	31.75	µg/L	*Pimephales promelas*

					survival Tedizolid concentration range 13.7-220.1 µg/L
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	**Pending new study**		Lack of clear dose-response results
Phase IIb studies					
Sediment dwelling organism	OECD218	NOEC	>100	mg/kg	*Chironomus riparius*

2.3.1. Discussion on non-clinical aspects

Primary pharmacology including the antibacterial activity of tedizolid is well described. In the secondary pharmacology studies, the inhibition of MAO-A and MAO-B was shown, and tedizolid appeared *in vitro* a more potent inhibitor of MAO-A than linezolid. However, *in vivo* studies using single doses up to 300 mg/kg in mouse did not indicate any functionally significant effect of *in vitro* MAO inhibition.

Minor effects on body temperature, locomotor activity and hexobarbital sleeping time were noted in the safety pharmacology studies. Functional effects on the gastric secretion were reported in rats. The magnitude of the effects and the margins of exposure to expected therapeutic levels could indicate limited clinical concern.

Pharmacokinetic characterisation of tedizolid was consistent with rat and dog being appropriate species to use in toxicology studies. The toxicology profile after oral or intravenous administration was investigated in repeated dose studies in rat and dog. Durations of oral and intravenous toxicity studies were up to 3 months and 28 days, respectively. Haematological and gastrointestinal reactions were primary findings.

The CHMP concluded concluded that the general toxicity of tedizolid has been sufficiently investigated and characterised in studies that comply with applicable guidelines and regulatory requirements. Studies evaluating the reproduction process in mouse and rat indicated a potential for reproduction toxicity including embryotoxic effects. Data from an *in vitro* chromosomal aberration study showed positive results, while subsequent *in vivo* studies were negative and overall CHMP was in agreement that tedizolid did not appear to have any clinically significant genotoxic potential.

2.3.2. Conclusion on the non-clinical aspects

The non-clinical tests and data available for tedizolid are considered sufficient and adequate taking into account the intended indication and dosages proposed. CHMP agreed however to request the applicant to submit a new respiration inhibition test on activated sludge microorganisms as a post-authorisation measure.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were

carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study No. and Phase	Dose and Regimen	Purpose	Subjects Enrolled / Planned
Phase 1 Studies			
TR701-101	Part A: single oral placebo or 200, 400, 600, 800, or 1200 mg TR-701 Part B: oral 200, 300, or 400 mg once-daily TR-701,600 mg twice-daily linezolid, or placebo for 21 days	Safety and PK Safety, tolerability, and PK	40/40 40/50[a]
TR701-102	Single oral 600 mg TR-701	Microdialysis in subcutaneous adipose and skeletal muscle tissues	12/12
TR701-103	Single oral 600 mg TR-701 either after a high-fat meal or in fasting conditions	Food effect	12/12
TR701-105	Multiple oral 200 mg TR-701 FA or placebo and tyramine HCl (25 mg then escalated in 50-mg increments until TYR_{30} reached)	Safety, tolerability, and blood pressure response of TR-701 FA in combination with tyramine	39/30
TR701-106	Single oral 204 mg [^{14}C]-TR-701 FA containing 100 µCi ^{14}C	Safety, tolerability, PK, route of TR-701 excretion, TR-700 metabolic profile	6/6
TR701-107	A. Single ascending IV dose, placebo or 50 to 400 mg TR-701 FA B. Multiple ascending IV dose, placebo or 200 or 300 mg TR-701 FA once daily for 7 days C. Open-label bioavailability, 200 mg TR-701 FA oral and IV D. Venous tolerability, placebo or 200 mg TR-701 FA IV once daily for 3 days	Safety, tolerability, PK, absolute bioavailability, venous tolerability	A. 51/52 B. 21/20 C. 8/8 D. 10/10
TR701-108	Single oral TR-701 FA or TR-701 (disodium salt of TR-701) equivalent to 150 mg of TR-700	Relative bioavailability, PK, safety, and tolerability	12/12
TR701-109	Single oral 200 mg TR-701 FA	Safety, tolerability, PK in elderly	28/28
TR701-110	Multiple oral 200 mg TR-701 FA once daily for 10 days	Safety and ophthalmic neurologic assessment	72/72
TR701-111	Single oral or IV 200mg TR-701 FA	Safety, tolerability, PK in adolescents	20/20
TR701-114	Multiple oral 200 mg TR-701 FA or placebo once daily for 5 days and 60 mg PSE on Day 5	Safety and blood pressure response of TR-701 FA in combination with PSE	18/18
TR701-115	Single oral 200 mg or 1200 mg TR-701 FA, 400 mg moxifloxacin, or placebo	Potential QTcF effects	48/48
TR701-119	Oral 200 mg TR-701 FA once daily for 3 days	Safety, PK, and disposition of TR-700 into pulmonary	20/20

Study No. and Phase	Dose and Regimen	Purpose	Subjects Enrolled / Planned
		epithelial lining fluid and alveolar macrophages	
TR701-123	Single IV 200 mg TR-701 FA	Safety and PK in advanced renal impairment with or without hemodialysis	24/24
TR701-124	Single oral 200 mg TR-701 FA	Safety and PK in moderate or severe hepatic impairment	32/32
Phase 2 Studies			
TR701-104	Oral 200, 300, or 400 mg TR-701 once daily; for 5-7 days	Clinical and microbiological response, safety, popPK	192/180
TR701-126	Oral 200 mg TR-701 FA once daily for 6 days	Safety and exploratory skin lesion measurement	200/200
Phase 3 Studies			
TR701-112	Oral 200 mg TR-701 FA once daily for 6 days or 600 mg linezolid twice daily for 10 days	Efficacy, safety, popPK in the treatment of ABSSSI	667/658
TR701-113	IV to oral 200 mg TR-701 FA once daily for 6 days or IV to oral 600 mg linezolid twice daily for 10 days	Efficacy and safety in the treatment of ABSSSI	666/658
Studies Performed in Japan			
16101	Single escalating dose 50 or 100 mg TR-701 FA IV, placebo control; 200 mg TR-701 FA IV or oral, placebo control	Safety, tolerability, PK, and absolute bioavailability	36/36
16102	IV or oral 200 mg TR-701 FA or placebo once daily for 7 days	Safety, tolerability, PK and intestinal flora evaluation	24/24

Abbreviations: ABSSSI=acute bacterial skin and skin structure infection; IV=intravenous; PK=pharmacokinetics; popPK=population pharmacokinetics; PSE=pseudoephedrine; QTcF=QT interval corrected for heart rate using Fridericia's formula
Note: TYR30=the dose of tyramine required to raise systolic blood pressure by 30 mmHg.

2.4.2. Pharmacokinetics

Tedizolid phosphate (TR-701 FA) is a novel oxazolidinone prodrug antibiotic developed for the treatment of acute bacterial skin and skin structure infections by both intravenous (IV) and oral routes of administration. The proposed commercial drug product dosage forms are tedizolid phosphate formulated as a 200 mg tablet and a lyophilised powder for reconstitution for intravenous (IV) use.

Tedizolid phosphate and tedizolid has one asymmetric center, leading to two possible enantiomers. Tedizolid phosphate is administered as the R isomer. At least in the rat, no significant *in vivo* inter-conversion from R-tedizolid to S-tedizolid occurs. *In vitro* stability data, showing high stability of the R-isomer, also support the assumption of a low risk for *in vivo* inter-conversion in humans.

After dissolution in the GI tract, TR-701 FA is rapidly converted by phosphatases to tedizolid (TR-700), the microbiologically active moiety. As an inactive and short-lived prodrug, pharmacokinetics of *tedizolid phosphate* are relatively unimportant.

The PK of tedizolid has been evaluated by the applicant in 9 phase 1 studies, 1 phase 2 study and 2 phase 3 studies. Two further phase 1 studies were conducted independently in Japanese patients.

The PK evaluation was thorough, including studies in healthy subjects and in patients with cSSTI, and evaluations of the effect of age (elderly and adolescent subjects), renal and hepatic impairment, sex and ethnicity on the PK of tedizolid. The specific phase 1 PK studies were complemented by population PK analyses that incorporated data from the phase 2 study TR701-104 and both phase 3 clinical studies (*TR701-112* and *TR701-113*).

In most of the PK clinical studies, the usual PK parameters (AUC_{0-t}, AUC_{0-inf}, C_{max}, $t_{½}$, λ_z, Cl/F, V_z/F) were calculated based on the plasma concentrations of TR-700, the active metabolite of TR-701, using a model independent approach. The statistical analysis of primary PK parameters (usually, AUC_{0-t}, AUC_{0-inf}, C_{max}) was performed using conventional methods recommended in bioequivalence studies (ANOVA, CI 90%).

Pharmacokinetics of TR-701

Following ***IV infusion*** of TR-701 FA, TR-701 does not appear to enter into tissues significantly (*V*ss of approximately 10 L, a volume slightly smaller than extracellular body fluid), is rapidly converted to TR-700 (half-life of approximately 10 minutes) presumably by alkaline phosphatases in the circulation, and is generally present at detectable concentrations in plasma for approximately 1 hour (TR701-107).

Following ***oral administration***, trace concentrations of TR-701 in plasma have been detected only at the highest administered supratherapeutic dose of 1200 mg TR-701/FA (*TR701-101* and *TR701-115*). Absolute oral bioavailability of TR-701 is <1%. Activation, by formation of TR-700, would occur during absorption process extensively through the first passage in the intestinal wall and liver prior to reaching the systemic circulation.

TR-701/FA is inactive in most *in vitro* systems. Results where biological activity has been demonstrated are believed to be due to formation of TR-700 within the test systems. Metabolism of TR-701 in human liver microsomes is limited to formation of TR-700.

For the reasons described above, the assessment was focused on the active moiety, TR-700.

Pharmacokinetics of TR-700

The PK of TR-700 was similar following administration of either TR-701 or TR-701 FA.

The mean TR-700 plasma concentrations and PK parameters in healthy adult subjects after single and multiple oral and IV doses are similar. Mean $t_{½}$ values ranged from 9 to 13 hour.

Following multiple once-daily oral or IV administration, steady-state plasma concentrations are attained within 3 days with modest drug accumulation (approximately 28%). Tedizolid exposure seems to be dose-proportional and not time-dependent. Steady state PK results are reasonably well predicted from single dose data.

Absorption

Following oral administration, peak plasma TR-700 concentrations are achieved within approximately 3 hours after dosing and the absolute bioavailability is 91%. Given the high value of absolute bioavailability no dosage adjustment is required between IV and oral administration.

In vitro dissolution testing and *in vivo* absorption data shows that dissolution is not rate limiting to absorption. Since the tablet formulation was used in all Phase 3 (and most Phase 1) studies, no bridging BE study was considered necessary.

Oral TR-701 FA may be given without regard to timing of meals, as the total exposure [AUC0-∞] is unchanged between fasted or fed (high-fat, high-calorie meal) conditions (*TR-701-103*). The rate of absorption was

decreased (C_{max} was 26% lower and time to maximum concentration [t_{max}] was 6 hours later), but these differences are not considered clinically meaningful given that the AUC/MIC is the critical factor for efficacy.

Extrapolation of food-effect results to TR-701 tablet is acceptable given the rapid dissolution rate of tedizolid phosphate from both capsule and tablet formulations and the high oral bioavailability of tedizolid phosphate.

Distribution

Pharmacokinetic studies have demonstrated that TR-700 rapidly distributes into tissues, with mean Vss values ranging from approximately 67 to 80 L after a single IV dose of 200 mg (*TR701-107*). TR-700 is moderately protein bound in human plasma (70% to 90%, primarily to albumin), and binding appears to be independent of concentration.

TR-700 rapidly penetrated into the interstitial space fluid of adipose and skeletal muscle tissue, resulting in TR-700 exposures in these compartments that were similar to free drug exposure in plasma (*TR-701-102*). Furthermore, TR-700 concentrates highly in the pulmonary epithelial lining fluid and alveolar macrophages (*TR-107-119*).

Elimination (metabolism/excretion):

The specific enzymes responsible for the metabolism of tedizolid phosphate to tedizolid, by dephosphorylation, and further metabolism of tedizolid to tedizolid sulfate, by sulfation, were further investigated by the applicant in order to identify the specific enzymes governing these metabolic steps together with their localisation and potential polymorphism.

The metabolism of tedizolid phosphate (TP) to tedizolid is governed by phosphatases ubiquitously expressed both in the liver and intestine. Polymorphism of phosphatase enzymes is not known.

An *in vitro* study of the specific sulfotransferase (SULT) enzymes involved in the metabolism of tedizolid was performed. Both recombinant SULT and pooled human liver and intestinal cytosol were incubated with tedizolid as well as positive and negative controls. All different human liver cytosol pools revealed a better (at least 2-fold higher) sulfonation activity of tedizolid in comparison to the human intestinal cytosol pool. Overall, both tissues liver and intestine may contribute to sulfonation of tedizolid in humans. The results of this study showed involvement of multiple SULTs (SULT1A1, SULT1A2, and SULT2A1) in the biotransformation of tedizolid which suggests that no single isozyme is critical to the clearance of tedizolid.

The results from a single oral administration of 204 mg [^{14}C]-TR-701 FA (containing 100 µCi [^{14}C]-TR-701 FA) under fasted conditions (*TR701-106*) indicated that the majority of elimination occurs via the liver, with 81.5% of the radioactive dose recovered in feces and 18.0% in urine. TR-700 accounts for most if not all of circulating radiocarbon in plasma (95%), but is excreted in low levels in urine and faeces (≈3%). The majority of excreted radioactivity was identified to be the sulfate conjugate of TR-700. None of the 3 non-circulating TR-700 metabolites (desmethyl TR-700, TR-700 sulfate, and TR-700 carboxylate) has significant antimicrobial activity.

Inter-subject variability (as determined by *coefficient of variation for AUC* in noncompartmental studies, or *CL* in the popPK analysis) ranged from approximately 20% to 30% across the studies and was generally higher following oral than IV administration, as expected.

Intra-individual variability was not formally assessed in clinical studies, but is expected to be small based on the repeat measure data available (*TR701-101, TR701-107, and TR701-114*). PopPK analysis results regarding the drug variability are in agreement with this expected low intra-subject variability.

The PopPK analysis estimated inter-individual variability in clearance (31 %CV) and volume of distribution (13.4 %CV) to be small and indicated that relatively consistent PK will be observed across a wide range of patient intrinsic factors. Minor increases in clearance with increasing ideal body weight (IBW), decreases in clearance with increasing total bilirubin, and increases in volume of distribution with increasing IBW were noted in the population analysis. The effects of age, weight, BMI, sex, race, ethnicity, renal function, ALT, AST, and indirect bilirubin were not found to have statistically significant influences on k_a, CL, or V_c.

In the popPK analysis, the residual variability for the phase 2/3 data was found modest. Residual variability for the phase 1 data was also relatively small.

The pharmacokinetics of tedizolid has been documented in subjects with severe renal impairment with or without haemodialysis, subjects with moderate or severe hepatic impairment, elderly and adolescent subjects. No studies in children (<12 years old) were performed. Influence of other intrinsic factors (such as gender, race and weight) was also addressed based on the performed clinical studies and based on the population PK analysis.

As a result of the minor variations in drug exposure, no dose adjustments from the proposed 200 mg once daily dosing regimen are considered necessary in any of these special populations. Given the PK/PD relationship for tedizolid, the CHMP agreed with this approach. The Sivextro SmPC is in accordance with this conclusion and no dose adjustment is recommended.

The **drug-drug interaction potential** of tedizolid phosphate and tedizolid on CYP enzymes and transporters was investigated in a number of *in vitro* studies. *In vitro,* no consistent inhibition of important drug uptake (OAT1, OAT3, OATP1B3, OCT1, and OCT2) and efflux transporters (P-gp and BCRP) was observed with the exception of BCRP and OATP1B1, which was inhibited by tedizolid. High levels of tedizolid phosphate in the gastrointestinal tract following oral administration and conversion to tedizolid by phosphatase enzymes in the intestinal microvilli could result in interactions with other orally administered drugs that are substrates of BCRP (including methotrexate, pitavastatin, rosuvastatin, sulfasalazine and topotecan). The clinical relevance of this possible interaction is unknown, but cannot be excluded.

Some *in vitro* inhibitors of SULT are described in the medical literature, such as non-steroidal anti-inflammatories (NSAIDs: mefenamic acid, etc.), oral contraceptives (19-norethindrone acetate, ethynodiol diacetate, and mifepristone, 17α-ethynylestradiol), antiestrogens (clomiphen), antiandrogen (cyproterone). However, whether these are active *in vivo* is at present unknown.

As sulfotransferase substrates are sometimes inhibitors, it is reasonable to assume that *in vitro* inhibition of one or more SULTs by tedizolid may occur. Inhibition studies were not conducted and the applicant is encouraged to investigate whether tedizolid is an inhibitor of SULTs *in vitro*.

Based on the positive *in vitro* results for CYP3A4 induction the applicant is also asked to perform an *in vivo* induction study as post-approval measure. As a first step of the measure, a suggested study setup to allow for an optimal capture of a potential CYP3A induction (e.g. based on the tedizolid half-life, and the turnover rate of CYP3A4, the maximum induction effect is reached after at least 10 days of tedizolid treatment duration) should be submitted. The SmPC was updated until the final results of the study will be assessed.

Two in vivo DDI studies, investigating the PD and PK drug-drug or drug-dietary interactions have been submitted, pseudoephedrine (Study TR701-114) and dietary tyramine (Study TR701-105). No PK interaction was seen in these studies.

2.4.3. Pharmacodynamics

Mechanism of action

TR700, as other oxazolidinone antibiotics, acts by inhibiting protein biosynthesis in the bacterial cell, by binding to the 50S ribosomal subunit and, therefore, prevent the formation of the translation initiation complex by blocking the combinations of the 50S and the 30S ribosomal subunits, resulting in lack of protein expression by the bacterial cell and, eventually, in cell death. A dose-dependent effect upon protein synthesis, consistent with the proposed mechanism of action via interaction with the 23S rRNA subunit was demonstrated in study PHA-08-070 1-034, supporting this mode of action. No adverse effects were seen against the other major synthetic pathways indicating that antibacterial activity is selectively due to this mechanism.

Primary and Secondary pharmacology

The applicant submitted the results of a comprehensive program to evaluate the potential for the development of resistant mutants, either to tedizolid or to linezolid, upon serial passages in culture medium.

In vitro studies demonstrated a relatively low potential for the emergence of resistance to tedizolid in staphylococci, enterococci and beta-haemolytic streptococci, which did generally not occur at concentrations at which resistance to linezolid has emerged. The potential for the emergence of resistance, however, might by higher for MRSA strains. Exposure of MRSA DR1 strain to either tedizolid or linezolid increased the MIC for the other oxazolidinone. The emergence of resistance was related to the G2576T mutation at the level of the gene encoding for 23S ribosomal subunit, a mutation that also conferred resistance to linezolid. Activity against SA strains with genetic resistance to quinolones (efflux pump genes NorA and MepA), VISA, tetracyclines and lincomycin was tested.

The presence of NorA or MepA genes among *S. aureus*, related to the overexpression of the NorA efflux pump (*S. aureus* 4642) or the MepA efflux pump (*S. aureus* 4641) did not affect the *in vitro* activity of either oxazolidinone. Tedizolid and linezolid maintained activity against a homogenous vancomycin-intermediate strain of *S. aureus* (VISA) that also carried *tetM*, and was thus resistant to tetracycline as well as to fluoroquinolones. Both tedizolid and linezolid maintained activity against the evaluated *Enterococcus faecalis* and *Enterococcus faecium* isolates, which both possessed the lincomycin resistance gene *lmrB.*

In summary, with regard to the studies with serial passage in culture medium, MICs for TR700 were generally lower than the MICs observed for linezolid for the key bacterial strains for the current application, with a low potential for the emergence of spontaneous resistance by serial passages in culture medium. An impact has been observed, however, for previous exposure to either oxazolidinone in *S.aureus*, conferring decreased susceptibility to the other compound in the group, and documentation of the emergence of specific mutants at the level of the 23S ribosomal subunit (G2576T).

The *in vitro* activity of TR700 against *S.aureus* strains carrying the *cfr* gene, which confers resistance to linezolid, seems to have been retained, while the epidemiologic relevance of this potential advantage may be low.

There was no sign of any microbial flora substitution after multiple IV or oral tedizolid phosphate doses of 200 mg once daily over 7 days in Japanese healthy male subjects. This study was however small and only a low risk population for post-antibiotic gastro-intestinal complications including C. difficile-associated diarrhea (CDAD) was included.

<u>In vitro microbiology studies</u>

The *in vitro* spectrum and potency of TR700 against clinical isolates were determined in a variety of studies conducted during the preclinical and clinical development, including an extensive panel of key bacterial strains.

Microbiology susceptibility testing of the main target bacterial species have been obtained from profiling and surveillance studies including a large recent surveillance study conducted in the US and a similar surveillance study conducted in Europe.

Overall, as expected, the microbiologic activity spectrum of TR700 was largely limited to Gram-positive organisms and overlapped that of linezolid. TR700 demonstrated relevant activity against staphylococci (*S. aureus*, *S. epidermidis*, other coagulase-negative staphylococci), enterococci (*E. faecium*, *E. faecalis* and other enterococci), streptococci (*S. pyogenes*, *S. agalactiae*, Group C/F/G streptococci, *S. anginosus* group streptococci, *S. pneumoniae)*, *Corynebacterium jeikeium*, *Listeria monocytogenes*, some atypical respiratory pathogens (*Legionella pneumophila*, *Chlamydophila pneumoniae)*, mycobacteria (*Mycobacterium* spp. including *M. tuberculosis, M. avium, and M. kansasii*), *Nocardia brasiliensis*, Gram-positive anaerobes (*Clostridium* spp. including *C. difficile* and *C. perfringens*, and *Peptostreptococcus* spp. including *P. micros* and *P. anaerobius*).

TR700 was only moderately active (minimum inhibitory concentration (MIC) values or minimum inhibitory concentration values against 90% of the isolates (MIC90) of 1 to 4 µg/mL) against the fastidious Gram-negative respiratory pathogen *Moraxella catarrhalis*, and against *Neisseria gonorrhoeae*, *Chlamydophila psittaci*, and *Chlamydia trachomatis*.

TR700 was inactive (MIC90 values ≥8 µg/mL) against *Mycoplasma pneumoniae* and the majority of *Haemophilus influenzae.*

The main results for the *in vitro* microbiologic program are summarized in the tables below:

Table 3 Main results of the in vitro microbiologic studies

Report MCR-08-0701-016	**N**	**MIC50**	**MIC90**	**N**	**MBC50**	**MBC90**
All *Staphylococcus spp.*	336	0.25	0.5	112	8	32
All *S. aureus* combined	234	0.5	0.5	82	4	16
MSSA	105	0.25	0.5	25	16	32
MRSA	129	0.5	1	57	2	16
S. aureus linezolid-R	13	4	8	2	16	>32
VnSSA	32	0.25	1	4	0,5	1
All coagulase-negative staphylococci (CoNS) combined	104	0.25	0.5	32	16	32
All Methicillin-Resistant CoNS	58	0.25	0.5	21	16	32
All Methicillin-Susceptible CoNS	46	0.25	0.5	11	16	32
All enterococci Combined	203	0.5	0.5	70	32	32
VREfcl	45	0.5	0.5	20	32	>32
VSEfcl	54	0.5	0.5	15	32	32
VREfcm	52	0.5	0.5	20	32	32
VSEfcm	52	0.5	0.5	15	32	32
All streptococcal spp. combined	361	0.25	0.25	53	1	16
All *Streptococcus pneumoniae* strains combined	133	0.25	0.25	33	1	2
SPPS	53	0.25	0.25	12	1	2
SPPI	26	0.25	0.25	10	1	1
SPPR	54	0.25	0.25	11	1	2
All ß-hemolytic streptococcal strains	202	0.25	0.25	22	16	32
S. viridans group	30	0.25	0.25	30	0,12	0,5
C. jeikeium	12	0.25	0.25	12	32	32

L. monocytogenes	33	0.25	0.25	33	32	32

MCR-12-0701-067A	Year: 2011		
	N	MIC50	MIC90
S. aureus	2324	0.25	0.5
S. epidermidis	161	0.12	0.25
Other CNS	89	0.12	0.5
E. faecalis	344	0.25	0.5
E. faecium	114	0.25	0.5
Other *Enterococcus spp*	11	0.25	0.5
S. agalactiae	248	0.25	0.25
S. pyogenes	214	0.12	0.25
Other BHS	14	0.25	0.25
MCR-13-0701-096	Year: 2012		
	N	MIC50	MIC90
S. aureus	2175	0.25	0.5
S. epidermidis	190	0.12	0.25
Other CNS	97	0.25	0.5
E. faecalis	290	0.25	0.5
E. faecium	107	0.25	0.25
Other *Enterococcus spp*	7	0.12	NA
S. agalactiae	282	0.25	0.25
S. pyogenes	193	0.12	0.25
Other BHS	24	0.12	0.25
Combined 067A and 096 (2011+2012 data)			
	N	MIC50	MIC90
S. aureus	4499	0.25	0.5
S. epidermidis	351	0.12	0.25
Other CNS	196	0.25	0.5
E. faecalis	634	0.25	0.5
E. faecium	221	0.25	0.5
Other *Enterococcus spp*	18	0.25	0.5
S. agalactiae	530	0.25	0.25
S. pyogenes	407	0.12	0.25
Other BHS	38	0.12	0.25

Microbiologic activity against a comprehensive panel of different relevant MRSA genotypes associated with either community-acquired (CA) or health-care associated (HA) infections (ST5-MRSA-II (USA100), ST36-MRSA-II (USA200/EMRSA16), ST8-MRSA-IV (USA300), ST1-MRSA-IV (USA400), ST8-MRSA-IV (USA500) -MRSA-IV (USA800), ST22-MRSA-IV (EMRSA15), ST80-MRSA-IV (European community associated), ST247-MRSA-I (Iberian clone), ST239-MRSA-III (Brazilian clone)) was assessed and the results indicated that MIC90 values are consistently ≤ 0.5 mg/l for tedizolid, generally similar to MIC50 values, while MIC90 values are between 2-4 mg/l for linezolid.

The data regarding different genotypes of MRSA may be considered particularly relevant for the procedure, as the added value of tedizolid may be along this specific activity profile. Overall, the panel may be regarded as comprehensive and reasonably representative of the most relevant epidemiologic genotypes described in Europe and the observed MIC values may be considered consistent with the overall *in vitro* microbiologic activity described in the studies submitted by the applicant.

The *in vitro* microbiologic activity of the main metabolites of tedizolid was adequately evaluated. Considering the trace plasma expression of the identified M1, M2 and M4 metabolites and the shown reduced microbiologic activity, no clinical significant contribute to the compound's primary effect is expected from these metabolites.

For tedizolid, there was a moderate inoculum effect in that the MICs of both study strains increased approximately 4- to 8-fold over a range of inoculum density of 103 through 107 CFU/ml and 2-fold over a range of inoculum density of 104 through 105 CFU/ml.

In study PHA-07-0701-061, a negligible post-antibiotic effect 0.05 to 0. 7 hours for staphylococci and of 0.15 to 1.05 hours for enterococci has been observed, and it is unlikely that it may impact on the clinical outcome.

Microbiology studies in the animal model

The *in vivo* characterization of the microbiologic activity of tedizolid was evaluated in a series of comprehensive animal model studies. Throughout these studies:

- the protective efficacy of TR701 against staphylococcal systemic infections in mice, namely against infections caused by coagulase-negative staphylococci, was shown;
- The efficacy against enterococcal systemic infections in immunocompromised mice was shown.
- The efficacy against systemic infections caused by *S. pneumoniae* was shown.
- The efficacy against MRSA infection in mouse SSTIs was shown.
- A series of well conducted published experiments evaluated the in vivo pharmacodynamics of TR701 against methicillin-susceptible and methicillin-resistant *S. aureus* strains in a mouse thigh infection model. The results have indicated that the area under the concentration-time curve over 24 hours divided by the MIC (AUC/MIC ratio) was the PD index for TR701/TR700 that was linked with efficacy. The target total and free drug AUC/MIC ratios were calculated as 250 and approximately 50, respectively.
- A published study by Keel (Keel 2012) evaluated the efficacy of TR701 and linezolid against MSSA and MRSA pathogens in a mouse thigh infection model in order to establish the efficacy profile of the two drugs at plasma exposures simulating those associated with TR700 and linezolid administration in humans. Four MRSA strains (3 hospital-associated MRSA [HA-MRSA] including one vancomycin-resistant [VRSA], one CA-MRSA) and one MSSA strain were studied. MIC values ranged from 0.25 to 0.5µg/mL for TR700 and from 2 to 4 µg/mL for linezolid. The results of the pharmacokinetic determinations indicated that the dosage regimens for TR701 FA and linezolid in mice targeted exposures that approximated the intended human

*f*AUC$_{0-24}$ values, although the actual *f*AUC$_{0-24}$ values from the study were low for TR700 and high for linezolid. For TR700, the actual *f*AUC$_{0-24}$ was 2.99 µg•hr/mL (under the target of 5.2 µg•hr/mL) and for linezolid the actual *f*AUC$_{0-24}$ was 144 µg•hr/mL (above the target of 96.6 µg•hr/mL). The human simulated regimens for TR700 and linezolid produced reductions against all isolates. The human simulated regimen of TR700 exposure resulted in mean total drug AUC$_{0-24}$/MIC ratios of 79.7 and 39.8 for isolates with MIC values of 0.25 µg/mL and 0.5 µg/mL, respectively.

- A dose-dependent response to TR701 treatment was observed in both granulocytopenic and nongranulocytopenic mice. In granulocytopenic mice, stasis was achieved at human-equivalent dose of slightly less than 2300 mg/day at 24 hours, slightly less than 2100 mg/day at 48 hours and slightly less than 2000 mg/day at 72 hours. In nongranulocytopenic mice, stasis was achieved at human-equivalent dose of slightly greater than 100 mg/day at 24 hours and less than 100 mg/day at 48 hours and 72 hours. These data suggest that the activity of tedizolid may be significantly reduced in the presence of neutropenia. In a study conducted in **non-neutropenic** animals, TR701 treatment of MRSA infection was administered at dosages to simulate achievable human plasma levels. The results of PK determinations indicated that the dose regimens for TR701 in mice resulted in exposures that approximated the intended human fAUC0-24 values. In this study, the effect of neutrophils on in vivo killing by TR701 was investigated. Massive amplification of bacterial cell kill was seen in the non-neutropenic mice; the MRSA kill mediated through granulocytes enhanced TR700 activity by a factor of 16-, 25-, and 35-fold (on average, 25-fold) for non-neutropenic versus neutropenic animals at the 24, 48 , and 72 hour time points, respectively (Drusano 2011).

The activity of tedizolid seems to be significantly dependent upon the neutrophil count, as the magnitude of the microbiologic effect was greatly amplified in the presence of neutrophils and the concentrations needed to achieve bacterial stasis in the neutropenic model were apparently not compatible with the expected AUC values estimated for the proposed dose for human studies. The CHMP requested the applicant to include a specific warning in the Sivextro SmPC regarding the neutropenic population. This was agreed upon by the applicant.

The pharmacokinetic/pharmacodynamic relationship against staphylococci was tested for TR701 FA in a neutropenic mouse thigh model of systemic infection (which is predictive for human efficacy in ABSSSI) and determined that the fAUC/MIC ratio explained more of the variance in the exposure-response relationship than did the other candidate pharmacodynamic indices (fCmax/MIC and fTime> MIC ratio, published data by Louie et al. already described above).

The fAUC/MIC ratio to achieve stasis in this study conducted in neutropenic mice was ~50, which would correspond to a total AUC/MIC ratio of ~250 for protein binding of 80%.

In a study of TR701 FA in neutropenic versus non-neutropenic animals, dose-response enhancement was approximately 16-, 25-, and 35-fold (on average, 25-fold) greater for non-neutropenic versus neutropenic animals at the 24-hour, 48-hour, and 72-hour time points, respectively. Although not determined in the comparative study, adjusting previously obtained fAUC/MIC ratio from neutropenic mice by the most conservative enhancement factor of 16-fold at the 24 hour time point, the target fAUC/MIC ratio would be 3 (based upon a total AUC/MIC ratio of 15 and 80% protein binding factor).

Based on these assumptions, an estimated AUC value between 24 (single dose) and 26 (SS) µg*h/mL for the oral formulation, 200 mg, and 27 (single dose) and 29 (SS) µg*h/mL for the IV formulation, 200 mg, would be, in principle, acceptable for the treatment of bacterial phenotypes with MIC values up to 8 mg/l. This may be considered adequate for the treatment of most target bacterial phenotypes evaluated within the *in vitro* microbiologic efficacy program.

A published study characterized and compared the in vivo antimicrobial characteristics of TR700 and linezolid against MSSA and MRSA pathogens in a neutropenic mouse pneumonia model, and identified by PK/PD modeling the pharmacodynamic target value (AUC/MIC) for each compound. The mean 24 hour total drug AUC/MIC values associated with a static endpoint were 133 and 27.2 for TR700 and linezolid, respectively. When protein binding was considered, the mean *f*AUC/MIC values for TR700 and linezolid were similar at 20 and 19, respectively. The mean 24 hour *f*AUC/MIC values associated with 1 $\log_{10}$ kill reduction were roughly 2-fold higher than that needed for stasis (34.6 for TR700 and 46.1 for linezolid). The plasma 24 hour *f*AUC/MIC values associated with net stasis and 1-$\log_{10}$ kill were not, however, significantly different among the 4 MSSA strains and 7 MRSA strains tested. Overall, the results suggest similar antibacterial efficacy for TR701 and linezolid and support the proposed PK/PD target as the AUC/MIC ratio as proposed by Louie et al.

Relation between plasma concentration and effect

In the only clinical dose-response study in patients with cSSTI that received 200, 300 and 400 mg tedizolid phosphate for 5-7 days, there was no relationship found between the plasma concentration and efficacy. The dose range tested was however limited. The probability of TEAE increased with approximately 30% from the lowest to the highest dose. No trends were observed in this study in the relationships between neutrophil or platelet counts and exposure. It should however be noted that the study duration was only 5 to 7 days.

The applicant has presented a rationale for the proposed MIC and zone diameter interpretive breakpoints and has approached EUCAST to set interpretive breakpoints for tedizolid in the EU.

The final susceptibility testing breakpoints established by the EUCAST were:

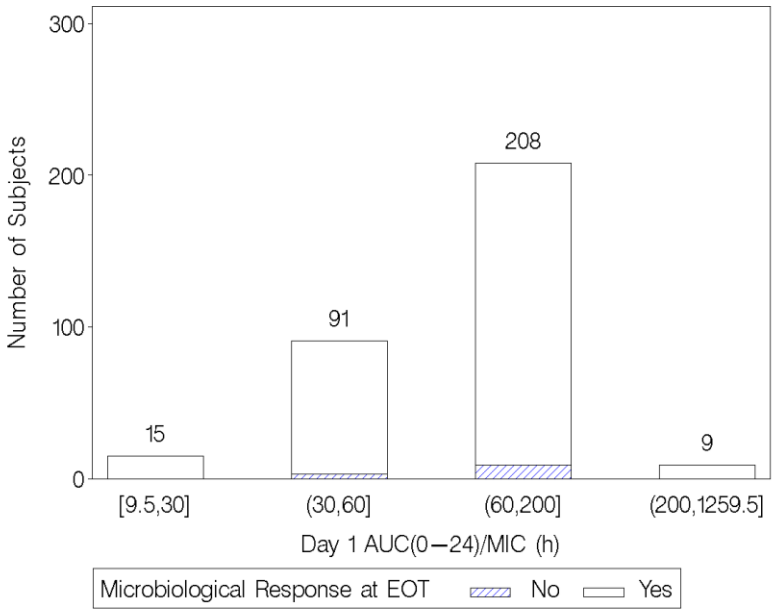
Organisms	**Minimum Inhibitory Concentrations (mg/L)**	
	Susceptible (≤S)	**Resistant (R>)**
Staphylococcus spp.	0.5	0.5
Beta haemolytic streptococci of Groups A,B,C,G	0.5	0.5
Viridans group streptococci (*Streptococcus anginosus* group only)	0.25	0.25

and are reflected in section 5.1.

Animal model PK/PD data demonstrated that fAUC/MIC ratio was the pharmacodynamic parameter best correlated with response. The fAUC/MIC ratio to achieve stasis in a study with neutropenic mice was approximately 50, which would correspond to a total AUC/MIC ratio of approximately 250 for protein binding of 80%. To achieve stasis in immunocompetent mice the target fAUC/MIC was at least 16-fold less and a fAUC/MIC target of 3 or AUC/MIC target of 15 (80% protein binding).

Target attainment analysis was performed to estimate the probability of attaining the PK/PD target measure (AUC_{0-24}/MIC ratio) associated with the efficacy of tedizolid phosphate to determine MIC susceptibility breakpoints. The majority of patients had an AUC/MIC above the target of 15 and there was no apparent drop in efficacy across a wide range of AUC/MIC ratios observed in studies TR701-112 and TR701-113 (see below figure).

Figure 2 Frequency distribution of grouped day 1 AUC_{0-24}/MIC ratio, by microbiological response at end of treatment



The number above each bar represents the number of subjects in each bar.

Parentheses indicate the respective endpoint is not included in the interval. Brackets indicate that the respective endpoint is included in the interval.

The applicant submitted the results of an analysis of the correlation between MIC values and clinical outcomes, based on the outcomes of the clinical efficacy studies. A positive clinical response was observed for staphylococci, streptococci, and enterococci for MIC values up to 0.5, 0.25, and 0.5 µg/mL, respectively. Virtually identical results were observed for the favourable microbiologic outcome as for the clinical outcome.

Virtually identical results were observed when analysing the favourable microbiologic response and the clinical outcome for zone diameter.

In vivo studies to evaluate the potential for drug interactions

The potential for peripheral inhibition of MAO-A was evaluated using tyramine in Study TR701-105, and pseudoephedrine in Study TR701-114.

Tyramine is an indirectly acting sympathomimetic drug, displacing neurotransmitter from adrenergic axonal terminals, resulting in an increase in systolic blood pressure (SBP) when administered intravenously and/or in the presence of monoamine oxidase inhibitors (MAOIs). Co-administration of tyramine with MAOIs has been used to determine the potential for clinically significant drug interactions. In the performed study TR701-105, all subjects (24/24) receiving tedizolid phosphate had increases in SBP of ≥30 mmHg when co-administered with tyramine (148-549 mg) in contrast to 7 subjects (7/24) in the placebo group when co-administered with tyramine (249-549 mg).

Of the 7 subjects who reached TYR30 in both treatment periods (PP analysis set), 1 subject had a tyramine sensitivity factor (TSF) ≥2 which is considered to indicate a clinically relevant mean difference to detect a meaningful pharmacological effect. The geometric mean TSF value was 1.36 with a confidence interval between 1.05 to 1.76.

Study TR701-114 was performed to assess if tedizolid phosphate potentiates the pressor response to pseudoephedrine (PSE), a sympathomimetic drug. According to the applicant, the mean (SD) maximum change

in SBP was 11.4 (5.55) mmHg with tedizolid phosphate and PSE and 12.3 (5.95) mmHg with placebo and PSE. Although in study TR701-114, the mean maximum change in SBP (measured at day 5, 3 hours after dose vs. predose at day 5) was 7.6 mmHg with tedizolid phosphate and PSE and 8.1 mmHg with placebo and PSE. In the study by Hendershot et al. (J Clin. Pharmacol. 2001;41:563-572), the mean maximum increase from baseline in SBP was 18 mmHg with pseudoephedrine (60 mg). In the same study SBP was reported to be 15 mmHg with the co-administration of linezolid with placebo, and it was 32 mmHg with co-administration of linezolid and pseudoephedrine.

Overall, a potential peripheral inhibition of MAO-A cannot be excluded. At the request of CHMP, the applicant included an appropriate warning regarding monoamine oxidase inhibitors in SmPC section 4.4.

With regard to the potential interaction with other antimicrobial agents that may be used concomitantly, and specifically addressing the potential for synergy/antagonism with other anti-infective agents, TR700 demonstrated no interaction when assessed in combination with 12 other antibacterial agents against the Gram-positive test strains of S. *aureus, E.faecalis,* S. *pyogenes,* and S. *pneumoniae.* Against the Gram-negative organism *E. coli,* TR700 lacked inherent antibacterial activity, and yielded a result of no interaction when tested in combination with 8 gram-negative-active agents. Under the conditions of this study, TR700 in combination with other antibacterial agents does not result in antagonistic interactions.

Also, TR700 demonstrated no interaction when assessed in combination with high concentrations of the 3 antifungal agents, amphotericin B, terbinafine HCI, and ketoconazole, against the Gram-positive test strains of S. *aureus, E. faecalis, S. pyogenes,* and S. *pneumoniae.* The presence of these agents at therapeutically relevant concentrations under clinical circumstances is therefore not expected to impair the antibacterial activity ofTR700 where the use of antibacterial and antifungal combination therapy is indicated.

2.4.4. Discussion on clinical pharmacology

Regarding pharmacokinetics, the expected tedizolid systemic exposure in adults is well supported by the PK studies submitted (including the population PK analysis). No significant differences are expected in any adult sub-population. The PK of tedizolid supports a once-daily administration regimen. In addition, the same dosing schedule can be used in all patient populations and in hepatic and renal impairment.

The *in vitro* drug interaction programme submitted was nevertheless considered not complete. The presented *in vitro* data indicated that tedizolid may be a clinically relevant CYP3A4 inducer *in vivo* and therefore the applicant should investigate the CYP3A4 induction potential of tedizolid in an *in vivo* interaction study post-approval. An *in vivo* midazolam induction study should be performed as a MEA. As a first step, a suggested study setup to allow for optimal study setup to capture a potential CYP3A induction (*e.g*. based on the tedizolid half-life, and the turnover rate of CYP3A4, the maximum induction effect is reached after at least 10 days of tedizolid treatment duration) should be submitted.

Overall, CHMP concluded that the clinical PK program for *Sivextro* development is comprehensive and well conducted.

The *in vitro* and *in vivo* microbiologic activity of TR700 were adequately evaluated with regard to the clinical efficacy program, and the results of the different studies and analyses are consistent with the expectation of an overall good activity against the key pathogens for the claimed indication. The activity against MRSA (and VRE) was overall good with MIC values that are compatible with the estimated concentrations that were achieved with the proposed 200 mg OD dose for TR700 in human PK studies. However, the potential for the emergence of resistance may be higher for MRSA than for MSSA and the potential for cross resistance between the two

oxazolidinones may be significant. The studies in animal infection models are comprehensive and also demonstrated good overall activity in the models that may be considered useful for the indication. The microbiologic activity in the animal model seemed to be significantly affected by the presence or absence of neutrophils, a finding that was further discussed by the applicant in the light of the need for specific warning in the neutropenic human population, which was included in section 4.4 of the SmPC.

Where the MIC values were considered, the activity of TR700, when compared to the activity of linezolid across *in vitro* and *in vivo* animal studies was generally superior for the relevant key pathogens.

Animal PK/PD studies indicate that the AUC/MIC ratio may be the relevant PK/PD parameter for the prediction of clinical effect, and indicate that the PK values achieved with the 200 mg dose, either administered orally or IV, are expected to achieve AUC/MIC values consistent with adequate clinical response for the key pathogens. Therefore, the overall assessment of the PK/PD relationship gave reasonable confidence that the dose proposed for human studies in ABSSSI would show clinical meaningful activity against key pathogens, while it would benefit from further exploring in clinical dose-ranging studies.

Human pharmacodynamic studies relative to safety did not show the occurrence of neurologic events after a 10 day exposure to the 200 mg dose intended for the clinical efficacy and safety program.

The AUC/MIC ratio to achieve stasis in neutropenic mice was at least 16 times that of immunocompetent animals. The applicant explained the large difference in the PK/PD target in neutropenic mice compared to immunocompetent animals as a phenomenon which was not seen with other antibacterial agents. Additional data from other animal model studies were provided, in which tedizolid and linezolid ED50 did not differ substantially in neutropenic animals, indicating that the effect seen with tedizolid may not only be applicable to tedizolid but also linezolid.

Neutropenic patients were excluded from the pivotal trials. Information of lack of data in neutropenic patients is currently stated in section 4.4 of the SmPC. A potential peripheral inhibition of MAO-A cannot be excluded. The applicant included a warning regarding monoamine oxidase inhibitors in SmPC section 4.4.

Regarding pharmacodynamics, the *in vitro* and *in vivo* microbiologic activity of TR700 was adequately evaluated with regard to the clinical efficacy program. The activity against MRSA (and VRE) was overall good with MIC values that are compatible with the estimated concentrations that were achieved with the proposed 200 mg OD dose for TR700 in human PK studies.

Where the MIC values were considered, the activity of TR700, when compared to the activity of linezolid across in vitro and in vivo animal studies was generally superior for the relevant key pathogens.

Human pharmacodynamic studies relative to safety did not show the occurrence of neurologic events after a 10 day exposure to the 200 mg dose intended for the clinical efficacy and safety program.

The AUC/MIC ratio to achieve stasis in neutropenic mice was at least 16 times that of immunocompetent animals. The large difference in the pharmacodynamic target in neutropenic mice compared to immunocompetent animals is a phenomenon not seen with other antibacterial agents. However, the applicant has provided data from other animal model studies in which tedizolid and linezolid ED50 did not differ substantially in neutropenic animals indicating that the effect seen with tedizolid may not only be applicable to tedizolid but also linezolid. An extrapolation of animal model data to humans raises concerns that a 200 mg once daily dose of tedizolid phosphate would be too low to achieve target attainment in a large number of neutropenic patients (with an AUC/MIC target of 250) provided that the PK is the same as in immunocompetent patients. This is in line with the fact that tedizolid is a bacteriostatic antibacterial.

Based on the additional data provided by the applicant, the CHMP further discussed the importance of these experimental findings. As neutropenic patients were excluded from the pivotal trials, information of lack of data in neutropenic patients was included in section 4.4 of the SmPC. A potential peripheral inhibition of MAO-A cannot be excluded and the applicant included an appropriate warning regarding monoamine oxidase inhibitors in SmPC section 4.4. Conclusions on clinical pharmacology

In vitro data, animal model data and the outcome of clinical studies have shown that tedizolid phosphate exerts potent activity against the major pathogens causing ABSSSI.

2.5. Clinical efficacy

The initially claimed indication for tedizolid was the treatment of complicated skin and soft tissue infections in adults. The CHMP requested and the applicant has agreed that the indication "treatment of acute bacterial skin and skin structure infections" is more appropriate and should be used instead.

Prior to the initiation of definitive safety and efficacy studies (phase 3), clinical studies were conducted using a disodium salt amorphous form of TR701. Subsequently, a free acid crystalline form of TR701 (TR701 FA) was found to be a superior drug substance as it is a stable, non-hygroscopic, crystalline form. TR701 FA demonstrated comparable bioavailability to TR701 (protocol TR701-108). All subsequent studies including the two Phase III studies and a Phase 2 open-label study that gathered additional safety and skin lesion size measurement data (TR701-126), have used TR701 FA which is the intended commercial drug product for both oral and IV administration in the treatment of cSSTI/ABSSSI and future clinical indications.

In order to comply with the EMA-CHMP recommended primary endpoint to establish efficacy, which was the test-of-cure assessment of the clinical response by the investigator at a post-therapy evaluation (PTE) as the primary endpoint, a hybrid approach was developed for the phase 3 studies, which meant that the studies were to be powered appropriately for both the FDA and the EMA endpoints, and would collected data supporting registration in both regions, as suggested in the CHMP guidance (Committee for Medicinal Products for Human Use: Guideline on the Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections [CPMP/EWP/558/95 rev 2; EMA guidance 2011]). The resulting proposed endpoints are summarized in the following table:

Table 3 Overview of Different Efficacy Endpoints for EMA and FDA in Pivotal Studies

	Regulatory Guidance	Primary Efficacy Endpoint	Key Secondary Efficacy Endpoint	Key Sensitivity Analyses
TR701-112	EMA	Investigator's Assessment of Clinical Response at PTE	Investigator's Assessment of Clinical Response at End of Therapy (EOT)	Not applicable
	FDA	Early clinical response (cessation of spread + absence of fever) at 48-72 hour after start of treatment	Programmatic Sustained Clinical Response at EOT	≥20% decrease in lesion area at 48-72 hour after start of treatment Programmatic Clinical Response at EOT
TR701-113	EMA	Investigator's Assessment of Clinical Response at PTE	Investigator's Assessment of Clinical Response at EOT	Not applicable
	FDA	≥20% decrease in lesion area at 48-72 hour after start of treatment	Programmatic Clinical Response at EOT	Early clinical response (cessation of spread + absence of fever) at 48-72 hour after start of treatment

2.5.1. Dose response studies

Two **phase 2 studies** were conducted:

- TR701-104, a multicentre, randomized, double-blind dose-ranging, non-comparative study evaluating the clinical and microbiological response, safety, and population PK in adult patients with cSSTI and
- TR701-126, a phase 2, open-label, multicentre study designed to further assess the safety of oral TR701 FA 200 mg once daily for 6 days for the treatment of major cutaneous abscess or cellulitis/erysipelas (200 patients).

The later study was conducted to assess the validity of the primary efficacy endpoint used by the FDA, for which various lesion area measurement methods were tested and the reliability of measuring the lesion area was assessed using two different observers.

Study TR701-104 was the only formal dose-response study, which evaluated the effect of TR701FA for the treatment of a spectrum of skin and soft tissue infections in three groups of patients at three oral dose levels: 200 mg (N=63), 300 mg (N=63) and 400 mg (N=62). The treatments were administered only by the oral route and the treatment duration was for at least 5 consecutive days, but no more than 7 days. No dose adjustments were allowed and the study which, as said, did not use a comparator. The schedule for the study visits was quite similar to the one chosen for the two main studies, as were the definitions for the ITT and PP population. The TOC visit was scheduled for 7-14 days post-treatment, as per the European guidance. The final disposition of enrolled

subjects differed from the population enrolled in the two main studies with regard to the percentage of patients with abscesses at baseline, ranging from 73% to 79% across the three dose groups, outside the range recommended by European guidance (up to approximately 30% of the patients). Of note, the recommended range was subsequently observed in studies TR112 and TR113. Also, the remaining infections were deep/extensive wound infections, while the numbers were small across the three dose arms (15 for each arm). The large majority of the isolates were MRSA, in line with the type of lesions that were to be included. With regard to the baseline susceptibility to T-701, all strains had MICs ≤ 0.5 mg/ml with only 6/108 MRSA strains and 3/27 MSSA strains having MICs =0.5 mg/ml.

A total of 152 (80.9%) patients had incision and drainage performed at the primary infection site between 2 days prior to treatment through 7 days after the initiation of treatment; 151 (80.3%) had the procedure performed at baseline (Day -2 to Day 2). Incidence was similar across dose groups.

The results from this dose-ranging study indicated that the clinical cure rates were uniformly high across all 3 TR701 dose groups (200, 300, and 400 mg) at the TOC visit (98.2%, 94.4%, and 94.4% in the CE population; 88.9%, 88.9%, and 85.5% in the cMITT population, respectively) and at the EOT visit (98.3%, 94.9%, and 96.6% in the CE population; 93.7%, 90.5%, and 91.9% in the cMITT population, respectively).

Microbiological response rates based on a satisfactory response (eradication or presumed eradication) were uniformly high across all three TR701 dose groups (200, 300, and 400 mg) at the TOC visit (100%, 93.2%, and 100% in the ME population, respectively). No clinical relapse or microbiological recurrence was reported at the LFU visit in the cMITT, CE, or ME populations.

Clinical cure rates were similar for subgroups based on baseline infection characteristics of lesion type (abscess, cellulitis, wound), lesion size, and when systemic signs of infection were present at baseline. Microbiological response rates in patients with *S. aureus* isolated at baseline (N=119, ME population) was 97.5%. Microbiological success rate was 97.9% for patients with MRSA (92/94 patients) and 95.7% for patients with MSSA (22/23 patients).

In the cMITT population, clinical cure rates at the TOC visit were similar between types of infection (abscess, cellulitis, and wound) and ranged from 81.8% to 90.9%. For each type of infection, no clinically meaningful differences were noted between dose groups.

Analysis of efficacy results by lesion size and by baseline signs of infection were not suggestive of clinically significant differences between dose arms. At the TOC visit in the ME population, microbiological response for patients with *S. aureus* was satisfactory for 97.5% (116/133 patients) of patients and rates ranged from 91.7% to 100% across dose groups. For patients with MRSA or methicillin-susceptible *S. aureus* (MSSA) pathogens, a satisfactory response was noted in 97.9% and 95.7% of patients, respectively, and differences between dose groups were not clinically meaningful. For patients with MRSA or MSSA pathogens, clinical cure rates were 96.8% and 95.7%, respectively. In the MITT population, 7 patients (3.7%) were assessed as clinical failures. The failures were identified in 1 patient with cellulitis (3% of those with cellulitis), in 1 with a wound infection (10% of those with wound infection), and in 5 patients with large abscesses (4% of those with large abscesses). No clinical relapse or microbiological recurrence was reported at the LFU visit in the cMITT, CE, or ME populations.

Therefore, efficacy and safety (see below, as the safety profiles were similar for the three doses) the results of this study support the choice of the 200 mg OD dose for a period of 5 to 7 days of treatment to be further developed in the main studies.

2.5.2. Main studies

The **Phase 3 studies (TR701-112 and TR701-113)** were both non-inferiority, global, multicentre, randomized, double-blind, double-dummy efficacy and safety studies in patients with ABSSSI.

Study TR701-112: A Phase 3 Randomized, Double-Blind, Multicentre Study Comparing the Efficacy and Safety of 6-Day Oral TR-701 Free Acid and 10-Day Oral Linezolid for the Treatment of Acute Bacterial Skin and Skin Structure Infections

Methods

Study Participants

Patients were required to have cellulitis/erysipelas, major cutaneous abscess or wound infection with a minimum total lesion surface area of 75 cm^2 and at least one regional or systemic sign of infection (lymphadenopathy, fever, >10% immature neutrophils, abnormal WBC count).

Eligible subjects in study TR701-112 were randomised 1:1 to receive treatment with PO tedizolid phosphate 200 mg once daily for 6 days or PO linezolid 600 mg every 12 h for 10 days Patients were to start treatment with at least 1 IV dose of tedizolid phosphate or 2 IV doses of linezolid before considering the option to switch to oral therapy. Switching from IV to oral study drug required that 2 of the 4 following criteria be met:

- The primary skin lesion has not increased in area, length, or width from baseline
- Temperature is <37.7°C at last measurement
- No local signs or symptoms of the primary ABSSSI site are worsening since previous visit
- Improvement of at least 1 local sign or symptom of the primary ABSSSI site since previous visit

Exclusion of entities like diabetic foot infection and infected burns were acceptable, as these often are associated with Gram-negative pathogens.

Treatments

Adjunctive antibacterial therapy was to be prohibited in both studies in patients with cellulitis/erysipelas or major cutaneous abscess. However, patients with wound infections could be treated with adjunctive aztreonam and/or metronidazole, if a Gram-negative pathogen was suspected (e.g. Gram stain) or confirmed by culture. A patient with a wound infection found to have a gram-negative pathogen after randomization, but no gram-positive pathogen, was to discontinue study drug and complete assessments for safety.

Objectives

The primary objective was to determine the non-inferiority in the rate of the investigator's assessment of clinical success of 6-day tedizolid phosphate oral compared with that of 10-day linezolid treatment oral at the PTE visit (7 to 14 days after the EOT visit) in the Intent-to-Treat (ITT) and Clinically Evaluable at PTE (CE-PTE) populations.

The secondary efficacy objectives were as follows:

- To compare the per-patient favourable microbiological response rate at the PTE Visit in the microbiological ITT (MITT) and microbiologically evaluable (ME) analysis sets

- To compare the Investigator's assessment of clinical response at the 48-72 Hour, Day 7, and EOT Visits in the ITT and Clinically Evaluable at EOT (CE-EOT) analysis sets (for the EOT Visit only)

- To compare the per-pathogen favourable microbiological response rates at the PTE Visit in the MITT and ME analysis sets

- To compare the per-patient and per-pathogen favourable microbiological response rates at the EOT Visit in the MITT analysis set.

Outcomes/endpoints

The co-primary efficacy endpoints were the investigator's assessment of clinical success at the PTE visit in the Intent-to-Treat (ITT) and Clinically Evaluable at PTE (CE-PTE) populations.

Clinical success was defined as a subject having (all of the following):

- Resolution or near resolution of most disease-specific signs and symptoms
- Absence or near resolution of systemic signs of infection (lymphadenopathy, fever, >10% immature neutrophils, abnormal WBC count), if present at baseline
- No new signs, symptoms, or complications attributable to the ABSSSI so no further antibiotic therapy is required for the treatment of the primary lesion

Clinical failure was defined as a subject having (any of the following):

- Required additional antibiotic therapy for treatment of the primary lesion.
- Unplanned major surgical intervention (e.g., amputation) required due to failure of study drug
- Developed osteomyelitis after baseline
- Persistent Gram-positive pathogen bacteraemia
- TEAE led to discontinuation of study drug and patient required additional antibiotic therapy to treat the ABSSSI
- Death (all-cause mortality) within 28 days of first administration of study drug.

Indeterminate was defined as a subject having study data not available for the evaluation of efficacy for any reason including:

- Osteomyelitis present at baseline;
- Lost to follow-up;
- Extenuating circumstances that precluded the classification of a clinical success or failure;
- For patients with cellulitis/erysipelas or major cutaneous abscess: Gram-negative organism isolated at baseline that required a different antibiotic therapy;
- For patients with wound infections: Gram-negative organism isolated at baseline that required a different antibiotic therapy other than aztreonam or metronidazole;
- Patient withdrew consent;
- Treatment change before completing at least 48 hours of study drug, excluding treatment-related AEs.

Sample size

The study was designed to show non-inferiority (NI) in the primary outcome measure after initiation of treatment of TR-701 FA 200 mg once daily × 6 days compared with linezolid 600 mg every 12 hours × 10 days in the ITT and CE-PTE analysis set. A NI margin of 10% was used based on analyses of historical data regarding the treatment effect of antibiotics as well as the contemporary data of the efficacy of linezolid. Approximately 658 patients were to be randomized with 329 patients assigned to each treatment group.

Randomisation

Eligible subjects were randomised 1:1 to receive treatment with PO tedizolid phosphate 200 mg once daily for 6 days or PO linezolid 600 mg every 12 h for 10 days. A total of 667 patients were randomized; 332 to receive TR-701 FA and 335 to receive linezolid.

Blinding (masking)

This is a double-dummy study, with placebo unique to each active treatment (placebo for TR-701 FA and placebo for linezolid).

Statistical methods

The primary efficacy outcome was analysed by determining a 2-sided 95% confidence interval (CI) for the observed difference in the sustained clinical response rate at the EOT Visit and the Investigator's assessment of clinical success at the PTE Visit between the TR-701 FA group and the linezolid group. Safety analyses include summaries of treatment-emergent AEs, descriptive statistics of laboratory values, frequency distributions of laboratory values classified based on toxicity grades, descriptive statistics of vital signs and ECG parameters, and frequency distributions of abnormal physical examinations.

Seven analysis sets were defined and are summarized in the table below:

Table 4 Analysis sets used

Analysis Set	***Definitions***
Intent-to-Treat (ITT)	*All randomized patients*
Safety Analysis Set	*All patients in the ITT Analysis Set who received at least 1 dose of drug during the study*
Microbiological ITT (MITT)	*All ITT Analysis Set patients who had a baseline gram-positive bacterial pathogen known to cause ABSSSI. This included bacterial pathogens known to cause ABSSSI identified in an appropriate specimen from the primary skin lesion or blood.*
Clinically Evaluable (CE): CE-EOT, CE-PTE, and CE-EOTSUS	*Three CE analysis sets are defined; the CE-EOT and the CE-PTE, used for the analysis of the Investigators assessment of clinical response, and the CE-EOTSUS, used for the analysis of the programmatic determination of sustained clinical response. A separate analysis set is required for the analysis of the programmatic determination of sustained clinical response since this outcome measure carries forward failures from the 48-72 Hour Visit (early clinical response) whereas this is not the case for the Investigator's assessment of clinical response at EOT.* *All patients in the ITT Analysis Set who complied with the protocol with no major violations, as defined in the SAP, and who meet the following criteria:* *To be included in the CE-EOT Analysis Set, patients must also have met the following*

	criteria: *Completed the Investigator's assessment of clinical response (i.e., was not deemed an indeterminate outcome) at the EOT Visit* *The EOT Visit occurred on Day 11 (+2 days) or within 2 days of the last dose of study drug* *To be included in the CE-PTE Analysis Set, patients must also have meet the following criteria:* *Completed the Investigator's assessment of clinical response (ie, was not deemed an indeterminate outcome) at the PTE Visit, unless the patient was classified as a clinical failure at the EOT Visit* *The PTE Visit occurred 7 to 14 days after the EOT Visit, unless the patient was considered to be a clinical failure based on the Investigator's assessment at the EOT Visit. If the patient did not have an EOT Visit, the PTE Visit must occur within 7 to 14 days of Day 11 (the protocol specified time point for the EOT Visit)* *To be included in the CE-EOTSUS Analysis Set, patients must also have meet the following criteria:* *Completed the outcome assessment at the 48-72 Hour Visit, unless the patient was a failure (for programmatic determination of sustained clinical response) at the EOT Visit* *Completed the sustained clinical response outcome assessment at the EOT Visit (i.e., was not programmatically determined to be an indeterminate response), unless defined as a non-responder at the 48-72 Hour Visit* *The 48-72 Hour Visit occurred no later than 72 hours (i.e., <73 hours) after the first dose of study drug and the EOT Visit occurred on Day 11 (+2 days) or within 2 days after the last dose of study drug unless the patient was defined as a non-responder (for the programmatic determination of early clinical response) or a failure (for the programmatic determination of sustained clinical response). Patients who are defined as a failure for the programmatic determination of sustained clinical response at EOT will be included in the CE analysis set if the EOT Visit is within 7 days of the allowable window (Day 11 [+2 days] or within 2 days after the last dose of study drug)*
Microbiologically Evaluable (ME)	*All patients in the MITT Analysis Set who also are in the CE-PTE Analysis Set*

Abbreviations: ABSSSI=acute bacterial skin and skin structure infection; CE-EOT=clinically evaluable at end of therapy; CE-EOTSUS=CE-EOT for sustained response; CE-PTE=CE at post-therapy evaluation; EOT=end of therapy; ITT=intent-to-treat; ME=microbiologically evaluable; MITT=microbiological intent-to-treat; SAP=statistical analysis plan

Analysis Sets

1. ITT: All randomized patients (N=667; 332 TR-701 FA, 335 linezolid)

2. Safety: All treated patients (N=666; 331, 335)

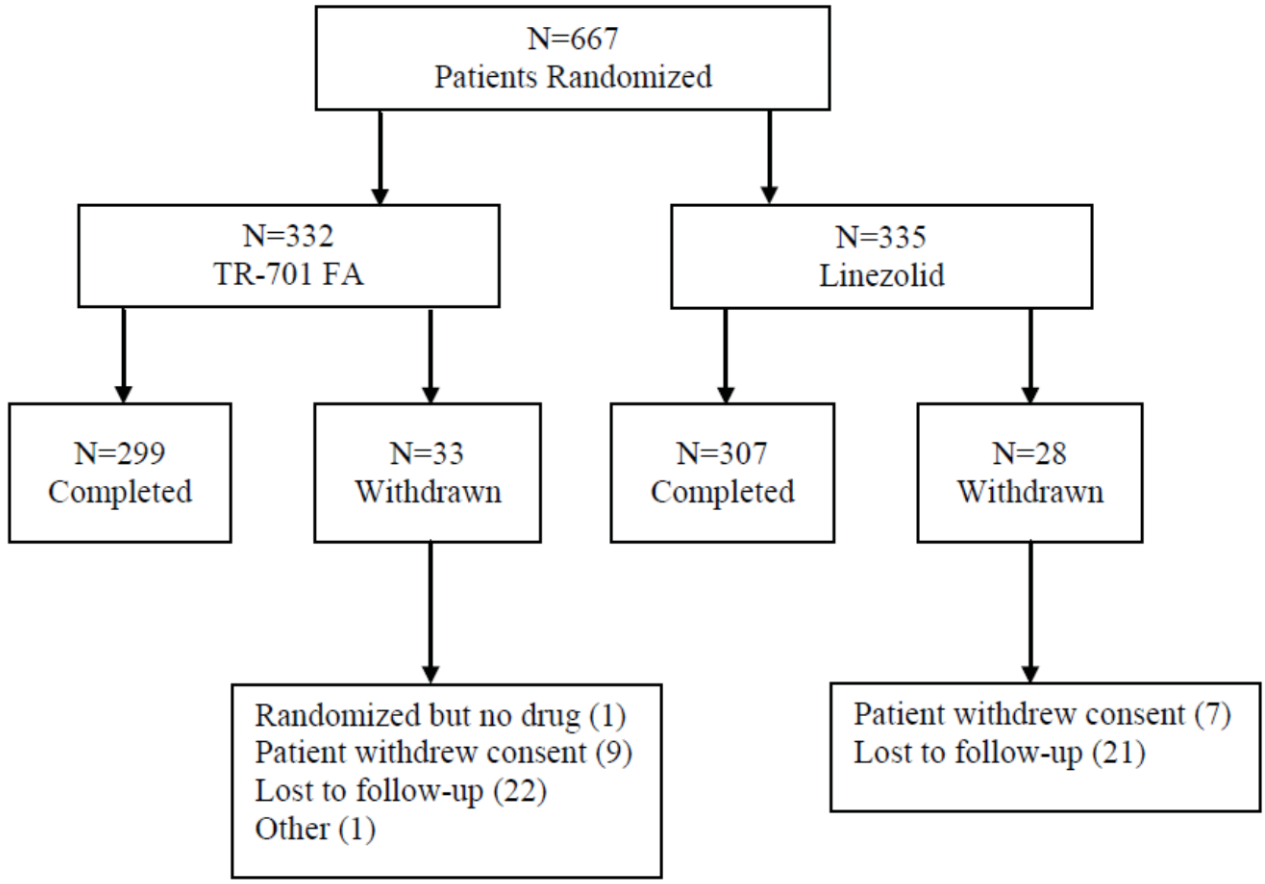
3. MITT: All randomized patients who have a baseline gram-positive bacterial pathogen known to cause ABSSSI (N=418; 209, 209)

4. CE-EOT: All randomized patients receiving at least 1 dose of study therapy, completed the 48-72 Hour and EOT assessments, no concomitant systemic antibiotic therapy through EOT, and no confounding events or factors (N=559; 273, 286)

5. CE-PTE: All randomized patients receiving at least 1 dose of study therapy, completed EOT and PTE Investigator's assessments, no concomitant systemic antibiotic therapy through PTE, and no confounding events or factors (N=559; 279, 280)

6. ME: Patients in the MITT Analysis Set who are also in the CE-PTE Analysis Set (N=342; 171, 171)

Participant flow



Abbreviation: FA=free acid.

Study TR701-113: A Phase 3 Randomized, Double-Blind, Multicentre Study Comparing the Efficacy and Safety of Intravenous to Oral 6-Day TR-701 Free Acid and Intravenous to Oral 10-Day Linezolid for the Treatment of Acute Bacterial Skin and Skin Structure Infections

Methods

Study Participants

In this randomized, double-blind, double-dummy, multicentre, global phase 3 study, adults with ABSSSI were randomized 1:1 to receive IV to oral TR-701 FA 200 mg once daily for 6 days OR IV to oral linezolid 600 mg every 12 hours for 10 days. Randomization was to be stratified by geographic region and clinical syndrome (major cutaneous abscess [maximum of 30% of the study population, of which not more than approximately half were to originate from the North American study population], cellulitis/erysipelas, and wound infection). Patients were to start treatment with at least 2 IV doses of study drug; patients could have received IV therapy for the entire treatment duration.

Subjects could then be switched from IV to oral study drug provided 2 of the 4 following criteria were met:

• The primary skin lesion had not increased in area, length, or width from baseline

• Temperature was <37.7°C at last measurement

• No local signs or symptoms of the primary ABSSSI site worsened since previous visit

• Improvement of at least 1 local sign or symptom of the primary ABSSSI site since previous visit

Patients with cellulitis/erysipelas or major cutaneous abscess caused by Gram-negative pathogens were excluded from enrolment.

Treatments

Adjunctive antibacterial therapy was prohibited in patients with cellulitis/erysipelas or major cutaneous abscess. Adjunctive aztreonam and/or metronidazole could have been initiated in patients with wound infection provided a gram-negative pathogen was suspected or confirmed. The study drug was discontinued in patients later found to have a Gram-negative pathogen, but no Gram-positive pathogen.

Objectives

The primary objective was to determine the non-inferiority in the rate of the investigator's assessment of clinical success rate of intravenous (IV) to oral 6-day TR-701 free acid (FA) compared with that of 10-day linezolid treatment (IV to oral) at the PTE Visit (7 to 14 days after the EOT Visit) in the Intent-to-Treat (ITT) and Clinically Evaluable at PTE (CE-PTE) populations.

The secondary objectives were as follows:

The secondary efficacy objectives were as follows:

- To compare the per-patient favourable microbiological response rate at the PTE visit in the microbiological ITT (MITT) and microbiologically evaluable (ME) analysis sets

- To compare the Investigator's assessment of clinical response at the 48-72 Hour, Day 7, and EOT visits in the ITT and clinically evaluable at EOT (CE-EOT) analysis sets (for the EOT visit only)

- To compare the per-pathogen favourable microbiological response rates at the PTE visit in the MITT and ME analysis sets

- To compare the per-patient and per-pathogen favourable microbiological response rates at the EOT visit in the MITT analysis set.

Outcomes / endpoints

The co-primary efficacy endpoints were the Investigator's assessment of clinical success at the PTE Visit in the Intent-to-Treat (ITT) and Clinically Evaluable at PTE (CE-PTE) populations.

Sample size

The study was designed to show NI in the primary outcome measure after initiation of treatment of TR-701 FA 200 mg once daily × 6 days compared with linezolid 600 mg every 12 hours × 10 days in the ITT and CE-PTE analysis set. A NI margin of 10% was used based on analyses of historical data regarding the treatment effect of antibiotics as well as the contemporary data of the efficacy of linezolid. Approximately 658 patients were to be randomized with 329 patients assigned to each treatment group.

Randomisation

In this randomized, double-blind, double-dummy, multicentre, global Phase 3 study, adults with ABSSSI were randomized 1:1 to receive IV to oral TR-701 FA 200 mg once daily for 6 days OR IV to oral linezolid 600 mg every 12 hours for 10 days. Randomization was stratified by geographic region and clinical syndrome (major cutaneous abscess [maximum of 30% of the study population, of which not more than approximately half were to originate from the North American study population], cellulitis/erysipelas, and wound infection). A total of 666 patients were randomized; 332 to receive TR-701 FA and 334 to receive linezolid.

Blinding (masking)

A double-dummy approach was chosen with placebo unique to each active treatment (placebo for TR-701 FA and placebo for linezolid for both IV and oral formulations) to maintain the treatment blind.

Statistical methods

The primary efficacy outcome was analysed by determining a 2-sided 95% confidence interval (CI) for the observed difference in the sustained clinical response rate at the EOT Visit and the Investigator's assessment of clinical success at the PTE Visit between the TR-701 FA group and the linezolid group. Safety analyses include summaries of treatment-emergent AEs, descriptive statistics of laboratory values, frequency distributions of laboratory values classified based on toxicity grades, descriptive statistics of vital signs and ECG parameters, and frequency distributions of abnormal physical examinations.

Main efficacy results

In the two pivotal trials, approximately 90% of patients completed the study. In study TR701-112 there were some imbalances in the reasons for discontinuing the study drug (treatment failure and Gram-negative infection), disfavouring the linezolid group. In study TR701-113, some of the imbalances in the reasons (treatment failure) for discontinuing the study drug were disfavouring the tedizolid phosphate group, while others (several subjects randomized but not receiving the study drug) were disfavouring the linezolid group. Other reasons for subjects either prematurely discontinued from the studies or discontinued study drug were relatively well balanced across treatment groups within each study. The subject disposition and the reasons for discontinuation are depicted in the below tables for study TR701-112 and TR701-113, respectively.

Table 5 Subject disposition and reasons for discontinuation in study TR701-112

	TR-701 FA (N=332) n (%)	Linezolid (N=335) n (%)	Total (N=667) n (%)
Patients completed study drug	**304 (91.6)**	**297 (88.7)**	**601 (90.1)**
Patients prematurely discontinued study drug	27 (8.1)	38 (11.3)	65 (9.7)
Primary reason for study drug discontinuation			
Adverse Event	1 (0.3)	2 (0.6)	3 (0.4)
Treatment failure	2 (0.6)	7 (2.1)	9 (1.3)
Patient withdrew consent	7 (2.1)	5 (1.5)	12 (1.8)
Patient lost to follow-up	12 (3.6)	13 (3.9)	25 (3.7)
At request of sponsor or Investigator	2 (0.6)	4 (1.2)	6 (0.9)
Staphylococcus aureus bacteremia	0	0	0
Patient requires prohibited medication	0	1 (0.3)	1 (0.1)
Abnormal liver function tests	0	0	0
Gram-negative infection	2 (0.6)	5 (1.5)	7 (1.0)
Other	1 (0.3)	1 (0.3)	2 (0.3)
Patients completed study	**299 (90.1)**	**307 (91.6)**	**606 (90.9)**
Patients prematurely discontinued from the study	33 (9.9)	28 (8.4)	61 (9.1)
Primary reason for study discontinuation			
Patient randomized but did not receive study drug	1 (0.3)	0	1 (0.1)
Patient withdrew consent	9 (2.7)	7 (2.1)	16 (2.4)
Patient lost to follow-up	22 (6.6)	21 (6.3)	43 (6.4)
At request of sponsor or Investigator	0	0	0
Other	1 (0.3)	0	1 (0.1)

Table 6 Subject disposition and reasons for discontinuation in study TR701-113

	TR-701 FA (N=332) n (%)	Linezolid (N=334) n (%)	Total (N=666) n (%)
Patients randomized but did not receive drug	1 (0.3)	7 (2.1)	8 (1.2)
Patients completed study drug	307 (92.5)	304 (91.0)	611 (91.7)
Patients prematurely discontinued study drug	24 (7.2)	23 (6.9)	47 (7.1)
Primary reason for study drug discontinuation			
Adverse event	1 (0.3)	4 (1.2)	5 (0.8)
Treatment failure	9 (2.7)	2 (0.6)	11 (1.7)
Patient withdrew consent	4 (1.2)	5 (1.5)	9 (1.4)
Patient lost to follow-up	5 (1.5)	9 (2.7)	14 (2.1)
At request of Sponsor or Investigator	2 (0.6)	1 (0.3)	3 (0.5)
Staphylococcus aureus bacteremia	0	0	0
Patient requires prohibited medication	0	2 (0.6)	2 (0.3)
Abnormal liver function tests	0	0	0
Gram-negative infection	0	0	0
Other	3 (0.9)	0	3 (0.5)
Patients completed study	**313 (94.3)**	**306 (91.6)**	**619 (92.9)**
Patients prematurely discontinued from the study	19 (5.7)	28 (8.4)	47 (7.1)
Primary reason for study discontinuation			
Patient randomized but did not receive study drug	1 (0.3)	7 (2.1)	8 (1.2)
Patient withdrew consent	6 (1.8)	5 (1.5)	11 (1.7)
Patient lost to follow-up	11 (3.3)	14 (4.2)	25 (3.8)
At request of Sponsor or Investigator	0	1 (0.3)	1 (0.2)
Other	1 (0.3)	1 (0.3)	2 (0.3)

Demographics and baseline characteristics

The treatment groups within each study were generally well matched with respect to gender, age, age group, ethnicity, race, BMI and type of cSSTI (see tables below). The majority of patients included were men. Approximately 10% of the subjects were >65 years of age. The majority of patients were recruited in North America. One out of six and one out of three patients were recruited in Europe in study TR701-112 and TR701-113, respectively. The most common type of infection was cellulitis/erysipelas. The proportion of patients enrolled with major cutaneous abscess did not exceed 30%, which was a pre-specified limit and in line with the current CHMP guidance. The number of patients with diabetes mellitus was 26 in each treatment group in study TR701-112 and 32 and 41 in the tedizolid phosphate and linezolid groups, respectively, in study TR701-113.

Table 7 Demographics and baseline characteristics in study TR701-112 (ITT analysis set)

Characteristic	Statistic	TR-701 FA (N=332)	Linezolid (N=335)	Total (N=667)	p-value
Sex					0.5797
Female	n (%)	128 (38.6)	137 (40.9)	265 (39.7)	
Male	n (%)	204 (61.4)	198 (59.1)	402 (60.3)	
Age (years)	**n**	**332**	**335**	**667**	0.6890
	Mean	43.6	43.1	43.3	
	Std	14.96	15.06	15.00	
	Median	43.0	42.0	43.0	
	Min, Max	18, 86	18, 100	18, 100	
Age group					
<65 years	n (%)	303 (91.3)	309 (92.2)	612 (91.8)	
≥65 to ≤75 years	n (%)	19 (5.7)	19 (5.7)	38 (5.7)	
>75 years	n (%)	10 (3.0)	7 (2.1)	17 (2.5)	
Ethnicity					0.5129
Hispanic or Latino	n (%)	115 (34.6)	108 (32.2)	223 (33.4)	
Not Hispanic or Latino	n (%)	217 (65.4)	227 (67.8)	444 (66.6)	
Race					0.4681
White	n (%)	280 (84.3)	275 (82.1)	555 (83.2)	
Asian	n (%)	2 (0.6)	7 (2.1)	9 (1.3)	
Black or African American	n (%)	39 (11.7)	38 (11.3)	77 (11.5)	
Native Hawaiian or Other Pacific Islander	n (%)	0	2 (0.6)	2 (0.3)	
American Indian or Alaskan Native	n (%)	4 (1.2)	5 (1.5)	9 (1.3)	
Other	n (%)	7 (2.1)	8 (2.4)	15 (2.2)	
BMI (kg/m^2)	**n**	**332**	**335**	**667**	0.7116
	Mean	27.9	28.0	28.0	
	Std	5.33	5.34	5.33	
	Median	27.5	27.3	27.4	
	Min, Max	15.99, 39.97	16.76, 39.99	15.99, 39.99	

Table 8 Demographics and baseline characteristics in study TR701-113 (ITT analysis set)

Characteristic	Statistic	TR-701 FA (N=332)	Linezolid (N=334)	Total (N=666)	p-value
Sex					0.3273
Female	n (%)	107 (32.2)	120 (35.9)	227 (34.1)	
Male	n (%)	225 (67.8)	214 (64.1)	439 (65.9)	
Age (years)	n	332	334	666	0.9563
	Mean	45.6	45.6	45.6	
	Std	15.79	15.57	15.67	
	Median	46.0	46.0	46.0	
	Min, Max	17, 86	15, 89	15, 89	
Age group					
<65 years	n (%)	289 (87.0)	301 (90.1)	590 (88.6)	
≥65 to ≤75 years	n (%)	32 (9.6)	19 (5.7)	51 (7.7)	
>75 years	n (%)	11 (3.3)	14 (4.2)	25 (3.8)	
Ethnicity					0.6964
Hispanic or Latino	n (%)	67 (20.2)	63 (18.9)	130 (19.5)	
Not Hispanic or Latino	n (%)	265 (79.8)	271 (81.1)	536 (80.5)	
Race					0.5822
White	n (%)	285 (85.8)	282 (84.4)	567 (85.1)	
Asian	n (%)	4 (1.2)	7 (2.1)	11 (1.7)	
Black or African American	n (%)	38 (11.4)	37 (11.1)	75 (11.3)	
Native Hawaiian or Other Pacific Islander	n (%)	2 (0.6)	1 (0.3)	3 (0.5)	
American Indian or Alaskan Native	n (%)	3 (0.9)	4 (1.2)	7 (1.1)	
Other	n (%)	0	3 (0.9)	3 (0.5)	
BMI (kg/m^2)	n	332	334	666	0.3442
	Mean	28.6	28.7	28.6	
	Std	7.89	6.90	7.41	
	Median	27.0	27.4	27.1	
	Min, Max	14.23, 69.88	14.75, 56.24	14.23, 69.88	

The cSSTI medical history in the two controlled studies was generally similar, although the current or recent IV drug use was more common in TR701-112 (approximately 35%-39%) than TR701-113 (approximately 20%-22%). Additionally, higher proportions of patients had recent trauma that resulted in primary infection and fever in study TR701-113 than TR701-112 (recent trauma that resulted in primary infection: approximately 45% in TR701-113 and 33% in TR701-112; fever: approximately 47% in TR701-113 and approximately 19% in TR701-112). In study TR701-113, fever was more common in patients who were maintained on IV treatment (82.2% TR701/FA and 89.7% for linezolid) than for those who switched from IV to oral (40.4% and 36.8%, respectively). A medical history of recent trauma that resulted in the primary infection was also more common in patients who were maintained on IV treatment (62.5% TR701/FA and 63.8% for linezolid) than for those who switched from IV to oral (40.1% and 41.6%, respectively).

In the Phase 3 Controlled Studies Group in the TR701/FA and linezolid groups, 45.3% versus 45.9% of patients had cellulitis/erysipelas, 25.3% versus 24.8% had major cutaneous abscess, and 29.4% versus 29.3% had wound infection, respectively. Lymphadenopathy was reported in 73.0% of patients in the Phase 2 Uncontrolled Studies Group, and in 78.9% and 78.3% of patients in the TR701/FA and linezolid groups, respectively, in the Phase 3 Controlled Studies Group.

Fever (temperature ≥38°C) was reported in only 4.1% of patients in the Phase 2 Uncontrolled Studies Group, whereas in the Phase 3 Controlled Studies Group, 23.3% of patients who received TR701/FA and 23.5% of patients who received linezolid had fever at baseline. Also, whereas the baseline characteristics of local disease indicated that approximately half of the patients had moderate or severe erythema and/or induration, higher proportions of patients maintained on IV treatment had severe signs and symptoms (erythema, swelling, warmth, tenderness on palpitation and purulent discharge) compared with those who were switched from IV to oral. Cellulitis/erysipelas was reported in approximately 45% of patients, infected wound was reported in approximately 30% of patients, and major cutaneous abscess was reported in approximately 25% of patients.

The median cSSTI surface area was larger and the number of patients with an increase or decrease of WBC count, having immature neutrophils or presenting with fever was higher in the IV to oral study, reflecting that infections were more severe in this study. The proportion of subjects meeting SIRS criteria was also higher in the IV to oral study. The proportion of patients meeting SIRS criteria in study TR701-112 was 19.0% vs. 12.8% and in study TR701-113 30.1% vs. 25.4% for tedizolid phosphate and linezolid groups, respectively.

Table 9 Baseline regional and systemic signs and symptoms of infection in study TR701-112 (ITT Analysis Set)

Regional/Systemic Sign of Infection	TR-701 FA (N=332) n (%)	Linezolid (N=335) n (%)	p-value
Lymphadenopathy	**289 (87.0)**	**289 (86.3)**	0.8202
Lymph node tenderness	283 (85.2)	286 (85.4)	
Lymph node increase in volume or palpable	287 (86.4)	281 (83.9)	
WBC ≥10,000 cells/mm^3 or <4000 cells/mm^3	**140 (42.2)**	**133 (39.7)**	0.5295
Immature neutrophils >10%	**12 (4.1)**	**8 (2.6)**	0.3697
Temperature ≥38°C (fever)	**56 (16.9)**	**63 (18.8)**	0.5447

Table 10 Baseline regional and systemic signs and symptoms of infection in study TR701-113 (ITT Analysis Set)

Regional/Systemic Sign of Infection	TR-701 FA (N=332) n (%)	Linezolid (N=334) n (%)	p-value
Lymphadenopathy, N1	**332**	**334**	**0.9323**
Lymphadenopathy	235 (70.8)	235 (70.4)	
Lymph node tenderness	230 (69.3)	229 (68.6)	
Lymph node increase in volume or palpable	231 (69.6)	229 (68.6)	
WBC ≥10,000 cells/mm^3 or <4000 cells/mm^3, N1	**332**	**334**	**0.0526**
	176 (53.0)	151 (45.2)	
Immature neutrophils >10%, N1	**328**	**327**	**0.1790**
	53 (16.2)	40 (12.2)	
Temperature ≥38°C (fever), N1	**332**	**334**	**0.6123**
	103 (31.0)	97 (29.0)	

In patients with a positive culture at baseline (MITT set), S aureus was identified in 81.0% of patients who received TR701/FA (374 baseline isolates across the two main studies) and 83.0% of patients who received linezolid (342 baseline isolates), with MRSA accounting for 34.7% and 35.4% of infections in the TR701/FA and linezolid groups, respectively, and MSSA accounting for 46.3% and 48.1% of infections, respectively. However, the baseline distribution of staphylococcal genotypes was different, as almost all MRSA strains were observed in the US. This is not unexpected, considering the usually described EU epidemiology in this regard.

The distribution of pathogens isolated from the primary site of infection is summarized in the below tables:

Table 11 Pathogenic organisms from baseline primary cSSTI site or blood culture by genus and species in study TR701-112 (MITT analysis set)

Pathogenic Organism	TR-701 FA (N=209) n (%)	Linezolid (N=209) n (%)
Gram-positive organisms (aerobes)	**207 (99.0)**	**205 (98.1)**
Staphylococcus aureus	171 (81.8)	175 (83.7)
MRSA	88 (42.1)	90 (43.1)
MSSA	83 (39.7)	87 (41.6)
PVL *Staphylococcus aureus*	97 (46.4)	102 (48.8)
Streptococcus pyogenes	8 (3.8)	4 (1.9)
Streptococcus anginosus-milleri group	15 (7.2)	15 (7.2)
Streptococcus anginosus	4 (1.9)	3 (1.4)
Streptococcus intermedius	3 (1.4)	4 (1.9)
Streptococcus constellatus	8 (3.8)	8 (3.8)
Enterococcus faecalis	5 (2.4)	0
Enterococcus faecium	1 (0.5)	2 (1.0)
Enterococcus gallinarum	1 (0.5)	0
Mycobacterium fortuitum	1 (0.5)	0
Staphylococcus haemolyticus	4 (1.9)	3 (1.4)
Staphylococcus lugdunensis	3 (1.4)	2 (1.0)
Streptococcus Group C	1 (0.5)	0
Streptococcus agalactiae	9 (4.3)	5 (2.4)
Streptococcus dysgalactiae	1 (0.5)	0
Streptococcus mitis	0	5 (2.4)
Streptococcus mutans	1 (0.5)	1 (0.5)
Streptococcus oralis	1 (0.5)	0
Streptococcus salivarius	2 (1.0)	2 (1.0)
Streptococcus sanguis	3 (1.4)	2 (1.0)
Streptococcus viridans group	3 (1.4)	3 (1.4)
Gram-positive organisms (anaerobes)	**3 (1.4)**	**8 (3.8)**
Actinomyces israelii	0	1 (0.5)
Actinomyces odontolyticus	0	1 (0.5)
Clostridium perfringens	1 (0.5)	1 (0.5)
Clostridium septicum	0	1 (0.5)
Finegoldia magna	1 (0.5)	2 (1.0)
Gemella morbillorum	0	1 (0.5)

Pathogenic Organism	TR-701 FA (N=209) n (%)	Linezolid (N=209) n (%)
Peptostreptococcus anaerobius	1 (0.5)	0
Peptostreptococcus asaccharolyticus	0	1 (0.5)
Peptostreptococcus micros	0	1 (0.5)
Peptostreptococcus prevotii	0	1 (0.5)
Gram-negative organisms (aerobes)	**6 (2.9)**	**6 (2.9)**
Acinetobacter baumannii	1 (0.5)	0
Eikenella corrodens	2 (1.0)	1 (0.5)
Enterobacter amnigenus	0	1 (0.5)
Enterobacter cloacae	1 (0.5)	0
Escherichia coli	1 (0.5)	1 (0.5)
Klebsiella oxytoca	1 (0.5)	2 (1.0)
Klebsiella pneumoniae	1 (0.5)	1 (0.5)
Proteus mirabilis	1 (0.5)	0
Pseudomonas aeruginosa	0	1 (0.5)
Gram-negative organisms (anaerobes)	**0**	**1 (0.5)**
Prevotella denticola	0	1 (0.5)
Prevotella intermedia	0	1 (0.5)

Table 12 Pathogenic organisms from baseline primary cSSTI site or blood culture by genus and species in study TR701-113 (MITT analysis set)

Pathogenic Organism	TR-701 FA (N=197) n (%)	Linezolid (N=202) n (%)
Gram-positive organisms (aerobes)	**192 (97.5)**	**199 (98.5)**
Staphylococcus aureus	158 (80.2)	167 (82.7)
MRSA	53 (26.9)	56 (27.7)
MSSA	105 (53.3)	111 (55.0)
PVL Staphylococcus aureus	93 (47.2)	78 (38.6)
Streptococcus pyogenes	25 (12.7)	16 (7.9)
Streptococcus anginosus-milleri group	15 (7.6)	12 (5.9)
Streptococcus intermedius	7 (3.6)	10 (5.0)
Streptococcus constellatus	7 (3.6)	2 (1.0)
Streptococcus milleri	1 (0.5)	0
Enterococcus faecalis	5 (2.5)	4 (2.0)
Staphylococcus capitis	0	1 (0.5)
Staphylococcus haemolyticus	1 (0.5)	5 (2.5)
Staphylococcus hominis	1 (0.5)	3 (1.5)
Staphylococcus lugdunensis	1 (0.5)	5 (2.5)
Streptococcus Group C	2 (1.0)	1 (0.5)
Streptococcus Group G	2 (1.0)	0
Streptococcus agalactiae	0	5 (2.5)
Streptococcus mitis	2 (1.0)	2 (1.0)
Streptococcus sanguinis	1 (0.5)	0
Streptococcus viridans group	0	4 (2.0)
Gram-positive organisms (anaerobes)	**7 (3.6)**	**5 (2.5)**
Actinomyces odontolyticus	1 (0.5)	1 (0.5)
Clostridium innocuum	1 (0.5)	0
Clostridium perfringens	3 (1.5)	1 (0.5)
Clostridium species	0	1 (0.5)
Gamella morbillorum	1 (0.5)	0

Pathogenic Organism	TR-701 FA (N=197) n (%)	Linezolid (N=202) n (%)
Peptostreptococcus anaerobius	0	1 (0.5)
Peptostreptococcus micros	1 (0.5)	0
Peptostreptococcus prevotii	1 (0.5)	1 (0.5)
Peptostreptococcus species	1 (0.5)	0
Gram-negative organisms (aerobes)	**3 (1.5)**	**1 (0.5)**
Enterobacter cloacae	1 (0.5)	0
Escherichia coli	0	1 (0.5)
Klebsiella pneumoniae	1 (0.5)	0
Proteus mirabilis	1 (0.5)	0
Pseudomonas aeruginosa	1 (0.5)	0
Serratia marcescens	1 (0.5)	0
Gram-negative organisms (anaerobes)	**0**	**1 (0.5)**
Prevotella melaninogenica	0	1 (0.5)

Numbers analysed

The analysis sets in the pivotal trials are presented in the below table:

Table 13 Populations for analysis in each pivotal study

Analysis Set	Study TR701-112		Study TR701-113	
	TR-701/FA (N=332) n (%)	Linezolid (N=335) n (%)	TR-701/FA (N=332) n (%)	Linezolid (N=334) n (%)
ITT	**332 (100.0)**	**335 (100.0)**	**332 (100.0)**	**334 (100.0)**
Safety	**331 (99.7)**	**335 (100.0)**	**331 (99.7)**	**327 (97.9)**
MITT	**209 (63.0)**	**209 (62.4)**	**197 (59.3)**	**202 (60.5)**
CE-EOT	**287 (86.4)**	**292 (87.2)**	**296 (89.2)**	**293 (87.7)**
CE-EOTSUS	**273 (82.2)**	**286 (85.4)**	**304 (91.6)**	**299 (89.5)**
CE-PTE	**279 (84.0)**	**280 (83.6)**	**290 (87.3)**	**280 (83.8)**
ME	**171 (48.5)**	**171 (49.0)**	**171 (51.5)**	**168 (50.3)**

MITT=microbiological ITT; CE-EOTSUS=clinically evaluable at EOT for sustained response;

ME=microbiologically evaluable (subjects in CE-PTE analysis set also in MITT analysis set)

The reasons for exclusion from the analysis sets were generally well balanced between treatment groups. In study TR701-113 there were 7 subjects that were randomized to receive linezolid but did not receive study drug.

Study drug exposure and concomitant procedures

In both studies fewer subjects received a full course of linezolid than tedizolid phosphate. Subjects were to receive a minimum of at least 5 doses of tedizolid phosphate or 10 doses of linezolid to be included as an "evaluable success" in the CE analysis sets resulting in a possible comparison of 5-6 days vs. 5-10 days and not 6 vs. 10 days of tedizolid phosphate vs. linezolid, respectively.

In the IV to oral study (TR701-113), the majority of patients received only 1 IV dose of tedizolid phosphate and 2 IV doses of linezolid. The pharmacokinetics of IV and oral tedizolid phosphate in healthy subjects indicates however that extrapolation of efficacy data of oral to IV tedizolid phosphate is possible.

There were no meaningful differences in site procedures and care between study groups

Outcomes and estimation

The following values were described for each main study and for the combined analysis for the primary clinical endpoint for EMA, the Investigator Assessment of Clinical Success at PTE, at both ITT and CE-PTE populations:

Table 14 Investigator Assessment of Clinical Success at PTE, in the ITT and CE-PTE populations

Efficacy Outcome Measure	**Investigator Assessment of Clinical Success at PTE**			**Investigator Assessment of Clinical Success at PTE**		
Analysis set	ITT			CE-PTE		
Study(ies)	TR112	TR113	Both	TR112	TR113	Both
TR-701 FA n (%)	284 (85.5)	292 (88.0)	576 (86.7)	264 (94.6)	268 (92.4)	532 (93.5)
Linezolid n (%)	288 (86.0)	293 (87.7)	581 (86.8)	267 (95.4)	269 (96.1)	536 (95.7)
Difference	-0.5	0.3	-0.1	-0.8	-3.7	-2.2
95% CI for difference	(-5.8, 4.9)	(-4.8, 5.1)	-3.8, 3.6	(-4.4, 3.2)	(-8.0, 0.0)	-5.0, 0.5

The results are quite similar for both studies within the pre-specified limit for non-inferiority for linezolid. Also, they are reasonably within the expectable values for the efficacy outcomes of linezolid in other studies in SSTI which used a similar mode of administration and duration of treatment.

The main reasons for clinical failure (rates of 4.5% for ITT, as 9.9% of patients had an indeterminate response, and 5.4% for CE-PTE, for study TR112; and 6.6%, with 5.4% IR at ITT and 7.6% for CE-PTE analysis, for study TR113) for the primary endpoint, were due to additional antibiotic therapy for primary lesion. However, the use of antibiotic within the previous 7 days had neither a significant impact on the efficacy rates for the primary endpoint when assessed in the ITT population, nor on the response rate for the primary endpoint was also not affected by such variables as lesion size, presence of fever or bacteraemic status for any of the two studies.

The results of the Investigator assessment of clinical success at the PTE Visit in the MITT and ME Analysis Set have shown success for 86.2% in the TR-701/FA group and 87.4% in the linezolid group for the MITT Analysis Set, and 94.4% and 97.9%, respectively, for the ME Analysis Set in the Phase 3 Controlled Studies Group. For both analysis sets, the lower limit of the 95% CI was greater than -10%.

In studies TR112 and TR113, the results for the main efficacy endpoint were subject to a sensitivity analysis, unadjusted for the stratification factors of presence/absence of fever at baseline and clinical syndrome. This sensitivity analysis has confirmed the results of the primary analysis.

The secondary efficacy analyses included the more relevant microbiology analyses for this procedure. The per-patient microbiologic analysis at PTE (MITT and ME) is shown below:

Table 15 Per-patient microbial response at PTE in the MITT and ME populations

Efficacy Outcome Measure	Per-patient microbial response at PTE			Per-patient microbial response at PTE		
Analysis set	MITT			ME		
	TR112	**TR113**	**Both**	**TR112**	**TR113**	**Both**
TR-701 FA n (%)	179/209 (85.6%)	173/197 (87.8)	352/406 (86.7)	164/171 (95.9%)	159/171 (93.0%)	323/342 (94.4)
Linezolid n (%)	181/209 (86.6%)	179/202 (88.6)	360/411 (87.6)	169/171 (98.8)	163/168 (97.0%)	332/339 (97.9)
Difference	-1.0	-0.8	-0.9	-2.9	-4.0	-3.5
95% CI for difference	-7.6, 6.0	-7.4, 5.5	-5.6, 3.7	-6.7, 1.3	-9.7, 0.4	-6.7, 0.7

The results for the secondary (US primary) endpoint of Investigator Assessment of Clinical Response at EOT (ITT and EOTUS populations, see above for definitions) are shown below for the consolidated analysis and are consistent with the results at PTE:

Table 16 Programmatic Assessment of Clinical Response at the EOT Visit in Controlled Studies (ITT Analysis Set)

Response	**Controlled Studies (112/113)**	
	TR-701/FA 200 mg n (%)	**Linezolid 1200 mg n (%)**
ITT Analysis Set, N	664	669
Clinical success	578 (87.0)	588 (87.9)
Clinical failure or indeterminate	86 (13.0)	81 (12.1)
Clinical failure	52 (7.8)	44 (6.6)
Indeterminate	34 (5.1)	37 (5.5)
Treatment Difference[a]	-0.8	
95% Confidence Interval	-4.4 , 2.7	

Table 17 Programmatic Assessment of Clinical Response at the EOT Visit in Controlled Studies (CE-EOTUS Analysis Set)

Response	Controlled Studies (112/113)	
	TR-701/FA 200 mg n (%)	Linezolid 1200 mg n (%)
ITT Analysis Set, N	597	598
Clinical success	547 (91.6)	562 (94.0)
Clinical failure	50 (8.4)	35 (5.9)
Indeterminate	0 (0.0)	1 (0.2)
Treatment Difference[a]	-2.4	
95% Confidence Interval	-5.4 , 0.6	

As shown above, the efficacy rates for the programmatic endpoint are quite similar to the ones observed for PTE, for each of the considered populations (ITT and CE-)

Table 18 Early Clinical Response at the 48-72 Hour Visit (ITT Analysis Set)

Response	Controlled Studies (112/113)		ABSSSI Studies (126/112/113)
	TR-701/FA 200 mg (N=664) n (%)	Linezolid 1200 mg (N=669) n (%)	TR-701/FA 200 mg (N=864) n (%)
Responder	542 (81.6)	531 (79.4)	701 (81.1)
Non-responder or indeterminate	122 (18.4)	138 (20.6)	163 (18.9)
Non-responder	94 (14.2)	100 (14.9)	123 (14.2)
Indeterminate	28 (4.2)	38 (5.7)	40 (4.6)
Treatment Difference [a]		1.8	
95% Confidence Interval		-2.2 , 5.8	
Treatment Difference [b]	2.2		
95% Confidence Interval	-2.0 , 6.5		

With regard to the clinical evolution, the results of the assessment of the intensity of pain, as measured by the Visual Analog Scale (VAS) and the Face Rating Scale (FRS) scales at different time-points after the treatment had been started, were plotted against lesion area, as a % of baseline area, and a good linear correlation was observed, thus supporting the consistency of the clinical assessments.

With regard to the clinical evolution of the response at the PTE, resolution of all signs and symptoms was seen in 72.9% of TR-701/FA patients and 71.4% of linezolid patients, compared to resolution rates of 43.5% and

47.1%, respectively, at the EOT Visit. The sample size of patients in the Phase 3 Controlled Studies Group with fever at baseline was small, and for the majority, the fever had resolved by Day 2.

Regarding the microbiologic results of the studies, the overall response rate was considered good for the isolated key pathogens, although a better response was observed for MSSA than for MRSA with regard to either tedizolid or linezolid, as shown below. Very few isolates were *Enterococcus faecalis*, while no *E. faecium* was isolated in either group at baseline. The response of *E. faecalis* to tedizolid was slightly lower than for linezolid, while the involved numbers are low:

Table 19 Investigator Assessment of Clinical Success by Key Target Pathogen from the Primary Infection Site or Blood Cultures at PTE Visit (MITT Analysis Set)

Visit / Key Target Pathogen	Studies TR701-104, TR701-112, TR701-113			
	TR-701/FA 200 mg (N=455)		Linezolid 1200 mg (N=412)	
	N1	Clinical Success n (%)	N1	Clinical Success n (%)
Staphylococcus aureus	374	331 (88.5)	342	303 (88.6)
MRSA	178	151 (84.8)	146	119 (81.5)
MSSA	196	180 (91.8)	198	186 (93.9)
Streptococcus pyogenes	33	30 (90.9)	20	19 (95.0)
Streptococcus anginosus-milleri group	30	21 (70.0)	28	25 (89.3)
Streptococcus anginosus	5	3 (60.0)	3	3 (100.0)
Streptococcus constellatus	15	10 (66.7)	10	8 (80.0)
Streptococcus intermedius	10	8 (80.0)	15	14 (93.3)
Peptostreptococcus spp.	6	4 (66.7)	6	3 (50.0)
Finegoldia magna	2	1 (50.0)	2	0
Peptostreptococcus anaerobius	2	2 (100.0)	1	0
Peptostreptococcus asaccharolyticus	0	0	1	1 (100.0)
Peptostreptococcus micros	1	0	1	1 (100.0)
Peptostreptococcus prevotii	2	2 (100.0)	2	2 (100.0)
Enterococcus faecalis	10	7 (70.0)	4	4 (100.0)
Staphylococcus haemolyticus	5	5 (100.0)	8	7 (87.5)
Staphylococcus lugdunensis	6	6 (100.0)	7	6 (85.7)
Streptococcus agalactiae	10	9 (90.0)	10	8 (80.0)
Streptococcus dysgalactiae	1	1 (100.0)	0	0

For the ME analysis set, the investigator assessment of clinical success by key target pathogen from the primary infection site or blood cultures showed a similar clinical success rate for all key pathogens in both treatment groups in Studies TR701-104, TR701-112 and TR701-113, and most patients in both groups were considered a clinical success at the PTE Visit. Greater than 95% of patients in both groups were considered a clinical success for the most common pathogen reported at baseline, *Staphylococcus aureus*. Similar rates of clinical success were seen with linezolid treatment and TR-701/FA treatment for the *Streptococcus anginosus-milleri* group (95.0% versus 95.8%, respectively).

Table 20 Investigator Assessment of Clinical Success by Key Target Pathogen from the Primary Infection Site or Blood Cultures at PTE Visit (ME Analysis Set)

Visit Key Target Pathogen	Studies TR701-104, TR701-112, TR701-113			
	TR-701/FA 200 mg (N=385)		Linezolid 1200 mg (N=340)	
	N1	Clinical Success n (%)	N1	Clinical Success n (%)
Staphylococcus aureus	324	310 (95.7)	284	279 (98.2)
MRSA	154	144 (93.5)	116	113 (97.4)
MSSA	170	166 (97.6)	170	168 (98.8)
Streptococcus pyogenes	30	28 (93.3)	18	18 (100.0)
Streptococcus anginosus-milleri group	20	19 (95.0)	24	23 (95.8)
Streptococcus anginosus	3	3 (100.0)	3	3 (100.0)
Streptococcus constellatus	9	9 (100.0)	7	6 (85.7)
Streptococcus intermedius	8	7 (87.5)	14	14 (100.0)
Peptostreptococcus spp.	4	4 (100.0)	3	2 (66.7)
Finegoldia magna	1	1 (100.0)	0	0
Peptostreptococcus anaerobius	2	2 (100.0)	1	0
Peptostreptococcus asaccharolyticus	0	0	1	1 (100.0)
Peptostreptococcus prevotii	2	2 (100.0)	1	1 (100.0)
Enterococcus faecalis	9	7 (77.8)	4	4 (100.0)
Staphylococcus haemolyticus	5	5 (100.0)	6	6 (100.0)
Staphylococcus lugdunensis	6	6 (100.0)	6	6 (100.0)
Streptococcus agalactiae	9	8 (88.9)	8	8 (100.0)
Streptococcus dysgalactiae	1	1 (100.0)	0	0

The Investigator assessment of clinical success by mono- and poly-microbial infections from the primary infection site or blood culture showed a similar clinical success rate in both treatment groups in Studies TR701-104, TR701-112, and TR701-113 at the PTE Visit in the MITT and ME Analysis Sets.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 21 Summary of efficacy for trial TR701-112

Title: A Phase 3 Randomized, Double-Blind, Multicentre Study Comparing The Efficacy And Safety Of 6-Day Oral TR-701 Free Acid And 10-Day Oral Linezolid For The Treatment Of Acute Bacterial Skin And Skin Structure Infections			
Study identifier	TR701-112		
Design	Randomized, double-blind, double-dummy, multicenter Phase 3 study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	First patient enrolled 23 August 2010 Last patient last visit 30 September 2011 not applicable not applicable	
Hypothesis	Non-inferiority		
Treatments groups	Oral tedizolid phosphate	Oral tedizolid phosphate 200 mg once daily for 6 days, number randomized 332 (ITT)	
	Oral linezolid	Oral linezolid 600 mg every 12 hours for 10 days, number randomized 335 (ITT)	
Endpoints and definitions	Co-Primary endpoints		Clinical success at the PTE visit in the ITT and CE-PTE analysis sets

	Secondary endpoints		To compare the per-patient favorable microbiological response rate at the PTE Visit in the microbiological ITT (MITT) and microbiologically evaluable (ME) Analysis Sets To compare the Investigator's assessment of clinical response at the 48-72 Hour, Day 7, and EOT Visits in the ITT and Clinically Evaluable at EOT (CE-EOT) Analysis Sets (for the EOT Visit only) (data not shown) To compare the per-pathogen favorable microbiological response rates at the PTE Visit in the MITT and ME Analysis Sets (data not shown) To compare the per-patient and per-pathogen favorable microbiological response rates at the EOT Visit in the MITT Analysis Set (data not shown)
Database lock	September 2011		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (n=667) and Per protocol (CE-PTE) (n=559) populations at PTE (post-therapy evaluation)		
Descriptive statistics and estimate variability	Treatment group	Tedizolid phosphate	Linezolid
	Number of subjects (ITT)	332	335
	Primary endpoint: Clinical success (ITT) at PTE (%)	284/332 (85.5)	288/335 (86.0)
	% treatment difference; (95% CI)	-0.5 (-5.8, 4.9)	

	Co-primary endpoint: Clinical success (CE) at PTE (%)	264/279 (94.6)	267/280 (95.4)
	% treatment difference; (95% CI)	-0.8 (-4.4, 3.2)	
	Secondary endpoint: Microbiol. response (MITT) at PTE (%)	179/209 (85.6)	181/209 (86.6)
	% treatment difference; (95% CI)	-1.0 (-7.6, 6.0)	
	Secondary endpoint: Microbiol. response (ME) at PTE (%)	164/171 (95.9)	169/171 (98.8)
	% treatment difference; (95% CI)	-2.9 (-6.7, 1.3)	

Table 22 Summary of efficacy for trial TR701-113

Title: A Phase 3 Randomized, Double-Blind, Multicentre Study Comparing The Efficacy And Safety Of Intravenous To Oral 6-Day Tr-701 Free Acid And Intravenous To Oral 10-Day Linezolid For The Treatment Of Acute Bacterial Skin And Skin Structure Infections		
Study identifier	TR701-113	
Design	Randomized, double-blind, double-dummy, multicenter Phase 3 study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Date of First Enrollment: 28 September 2011 Date of Last Completed: 10 January 2013 not applicable not applicable
Hypothesis	Non-inferiority	

Treatments groups	IV/oral tedizolid phosphate		IV to oral 6-day tedizolid phosphate 200 mg once daily, number randomized 332 (ITT)
	IV/oral linezolid		IV to oral linezolid 600 mg every 12 hours for 10 days, number randomized 334 (ITT)
Endpoints and definitions	Co-Primary endpoints		Clinical success at the PTE visit in the ITT and CE-PTE analysis sets
	Secondary endpoints		To compare the per-patient favorable microbiological response rate at the PTE Visit in the Microbiological ITT (MITT) and Microbiologically Evaluable (ME) Analysis Sets To compare the Investigator's assessment of clinical response at the 48-72 Hour, Day 7, and EOT Visits in the ITT and Clinically Evaluable at EOT (CE-EOT) Analysis Sets (for the EOT Visit only) (data not shown) To compare the per-pathogen favorable microbiological response rates at the PTE Visit in the MITT and ME Analysis Sets (data not shown) To compare the per-patient and per-pathogen favorable microbiological response rates at the EOT Visit in the MITT Analysis Set (data not shown)
Database lock	January 2013		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (n=666) and Per protocol (CE-PTE) (n=570) populations at PTE (post-therapy evaluation)		
Descriptive statistics and estimate variability	Treatment group	Tedizolid phosphate	Linezolid
	Number of subject (ITT)	332	334

	Primary endpoint: Clinical success (ITT) at PTE (%)	292/332 (88.0)	293/334 (87.7)
	% treatment difference; (95% CI)	0.3 (-4.8, 5.1)	
	Co-primary endpoint: Clinical success (CE) at PTE (%)	268/290 (92.4)	269/280 (96.1)
	% treatment difference; (95% CI)	-3.7 (-8.0, 0.0)	
	Secondary endpoint: Microbiol. response (MITT) at PTE (%)	173/197 (87.8)	179/202 (88.6)
	% treatment difference; (95% CI)	-0.8 (-7.4, 5.5)	
	Secondary endpoint: Microbiol. response (ME) at PTE (%)	159/171 (93.0)	163/168 (97.0)
	% treatment difference; (95% CI)	-4.0 (-9.7, 0.4)	

Analysis performed across trials (pooled analyses and meta-analysis)

Subgroup analyses showed that, overall, the rates of clinical response across subgroups (age, sex, race, BMI group, geographic region, clinical syndrome, in IV drug users, in patients with diabetes, NSAID/oral steroid use, bacteraemia, baseline lesion area group, anatomical location of infection, lesion area and infection type) were high (generally >80%) in patients who received TR-701/FA, and no significant differences in response rate were observed for age, sex or race. Subjects with a BMI of <30 kg/m^2 had higher percentage of clinical success with any treatment than those with BMIs of >30 kg/m^2 or >35 kg/m^2 (clinical success from All Studies: 95.0%, 91.1% and 84.7%, respectively). Only 27 subjects across the two main studies had bacteraemia, and a

favourable result is reported for 24 of these subjects. For diabetic patients, a lower response rate was observed for TR701, while the number of included subjects is small and inconclusive.

Supportive studies

The phase 2 study TR107-104 was a multicentre, randomized, double-blind, dose-ranging, non-comparative study evaluating the clinical and microbiological response, safety, and population PK of the disodium salt of tedizolid phosphate for 5 to 7 days in adult patients with cSSTI. A total of 188 cSSTI patients received tedizolid phosphate orally at doses of 200, 300, or 400 mg per day. Clinical cure rates were uniformly high across all 3 tedizolid dose groups (200, 300, and 400 mg per day) at 7 to 14 days post treatment (98.2%, 94.4%, and 94.4% in the CE population; 88.9%, 88.9%, and 85.5% in the cMITT population, respectively). Microbiological response rates were uniformly high across all 3 tedizolid phosphate dose groups. Thus, all tested doses showed similar efficacy and these results were supportive for the 6 days duration of therapy and for the selection of the 200 mg dose in the phase 3 pivotal studies.

Study TR701-126 was a phase 2, open-label, multicentre trial primarily designed to assess the safety of oral tedizolid phosphate 200 mg once daily for 6 days for the treatment of 100 patients each suffering from major cutaneous abscess or cellulitis/erysipelas. The cure rate was similar across subgroups defined by infection type (85.0% vs. 91.0% at the EOT visit and 83.0 vs. 90.0% at the PTE visit in patients with cellulitis/erysipelas and major cutaneous abscess, respectively).

2.5.3. Discussion on clinical efficacy

Compliance of study designs with European regulatory guidance

The overall design of the studies is considered acceptable, as the included types of infections were cellulitis/erysipelas and wound infections and that major abscesses did not represent more than 30 % of the cases. A minimum affected area was well defined and the estimated size of abscesses was pre-defined. A set of signs and symptoms associated with the ongoing acute infection was defined in the protocol, while not all enrolled patients complied with this requirement. Exclusions included patients with burns, infected diabetic foot ulcers and local complications such as osteo-articular or necrotizing infections.

The established non-inferiority margin (-10%) and the primary endpoint (clinical outcome measured at the TOC visit) were both in accordance with the EU guidance recommendations.

The choice of the comparator, linezolid at the recommended dose of 600 mg BID for 10 days, with the possibility of IV to oral switch in study TR113, was not thoroughly discussed, since while linezolid is an accepted antibacterial for the treatment of cSSTI, the current wording of the linezolid approved indication states that the treatment of complicated skin and soft tissue infections should be made only when microbiologic testing has established that the infection is caused by susceptible Gram-positive bacteria. This is justified by the antibacterial spectrum of linezolid, which is largely shared by tedizolid. CHMP included a warning on the antibacterial spectrum of tedizolid in section 4.4. of the SmPC.

Efforts were made to adequately characterize the severity of the infections, both by establishing a minimum area of involved skin structures by erythema, induration and fluctuation and by creating a set of clinical criteria that would indicate the presence of acute infection and inflammation (local or regional lymphadenitis, fever, leucocytosis). Overall, the predefined criteria for disease severity were met in a significant proportion of the included subjects, so that the relevance of antibiotic treatment, either orally or IV, could be considered acceptable at the proposed experimental conditions for both main studies. Adjuvant treatment, either non-programmed drainage of abscesses and antibiotic use were to be considered as failures.

The populations defined for the major efficacy analyses are well described and allow for the evaluation of the predefined endpoints. The visit for the evaluation of the EU primary endpoint (TOC visit, alias post-treatment evaluation, PTE) was scheduled at 7-14 days after the final dose had been administered, in accordance with the EU guidance. The studies were also powered for an early efficacy endpoint, as per the US guidance requirements (either clinical response, in TR112, or early assessment of at least a 20% reduction in lesion area, in TR113) and this allowed for an additional perspective on the clinical outcome. The two pivotal studies are in line with EU guidance with regard to the geographic distribution of the included patients and include a significant proportion of European patients.

Design and conduct of clinical studies

The efficacy of tedizolid phosphate was evaluated in two randomized, double blind, double dummy, non-inferiority studies in patients with ABSSSI. Oral and IV to oral tedizolid phosphate 200 mg once daily for 6 days was compared with linezolid 600 mg twice daily for 10 days. Even though a beta-lactam regimen would be considered first-line treatment in many cases of cSSTI/ABSSSI, the use of linezolid as comparator is considered adequate by the CHMP, considered the high number of MRSA included. A shorter course of tedizolid phosphate than linezolid was chosen, based on the efficacy results of tedizolid phosphate generated in the phase 2 studies. As the recommended duration of treatment of cSSTI with linezolid is 10 to 14 days, the use of 10 days of linezolid in the clinical trials is considered acceptable.

Adults and adolescents (the latter included in the IV to oral study), with suspected or documented gram-positive ABSSSI(cellulitis/erysipelas, major cutaneous abscess (not more than 30%) or wound infection) with a minimum surface area of 75cm^2 and at least one regional or systemic sign of infection were included. Thus patients without systemic signs of infection could be included. There were no specific severity criteria indicating the necessity of IV antibiotic therapy in the IV to oral study. The co-primary endpoints were the investigator´s assessment of clinical response at PTE in the ITT and CE-PTE analysis sets, which are in line with CHMP guidance.

Non-inferiority of tedizolid phosphate to linezolid was to be shown if the lower limit of the 95% CI for the difference in the ITT and CE-PTE analysis sets exceeded -10%, which is also in line with the CHMP guidance for cSSTI studies.

Approximately 90% of the patients completed the studies. In study TR701-113 seven patients were randomized but did not receive linezolid, disfavouring this group. The information provided by the applicant on the reasons for this imbalance was considered acceptable by the CHMP.

The treatment groups within each study were well matched with respect to gender, age, age group, ethnicity, race, BMI and type of cSSTI. The majority of patients included were men. Approximately 10% of the subjects were >65 years of age. The majority of patients were recruited in North America. One out of six and one out of three patients were recruited in Europe in study TR701-112 and TR701-113, respectively. The most common type of infection was cellulitis/erysipelas. The proportion of patients enrolled with major cutaneous abscess did not exceed 30% which was the pre-specified limit and in line with current CHMP guidance.

The treatment groups were well balanced with respect to criteria for disease severity (local, regional and systemic signs and symptoms of infection). The most commonly isolated pathogen was *S. aureus*, of which approximately 40% consisted of MRSA, followed by *S. pyogenes* and species in the *S. anginosus-milleri* group. The numbers of *S. pyogenes* was unexpectedly low.

In both studies fewer subjects received a full course of linezolid than tedizolid phosphate. Subjects were to receive a minimum of at least 5 doses of tedizolid phosphate or 10 doses of linezolid to be included as an

"evaluable success" in the CE analysis sets resulting in a comparison of 5-6 days vs. 5-10 days and not 6 vs. 10 days of tedizolid phosphate vs. linezolid, respectively. In the IV to oral study, the majority of patients received only 1 IV dose of tedizolid phosphate and 2 doses of linezolid. The efficacy results from study TR701-113 is therefore almost exclusively based on oral tedizolid phosphate.

Efficacy data and additional analyses

Non-inferiority of tedizolid phosphate compared to linezolid was demonstrated for the co-primary endpoints in both pivotal studies. The lower limits of the 95% CIs were within -10%. Results for the sensitivity analyses (unadjusted) of the primary efficacy outcome supported the results seen for the primary analyses.

It should be noted that at all time points from EOT to late follow-up the point estimates for success were generally lower for tedizolid phosphate and 7/8 failure or relapses at late follow-up were noted.

2.5.4. Conclusions on the clinical efficacy

The comparative clinical efficacy of tedizolid administered either at 200 mg orally or with initial IV administration at the same dose, and subsequent switch to oral, for 6 days, with linezolid, at 600 mg BID, either orally or with initial IV administration and subsequent switch to oral, for 10 days, was evaluated for the treatment of ABSSSI in two well designed and well conducted studies. These studies included an adequate number of adult patients with skin infections caused by key bacterial pathogens, mainly *Staphylococcus aureus*, either MSSA or MRSA, but also by streptococci.

The results of each of the studies –which used an accepted EMA/CHMP endpoint- were consistent with the predefined criteria for showing that the treatment with 200 mg tedizolid daily for 6 days was non-inferior to the treatment with linezolid at 600 mg BID for 10 days. The results were within the expected efficacy rate for linezolid in these situations. A slightly lower response rate was overall detected for tedizolid when MRSA was the baseline isolated pathogen. The efficacy results for the subgroup of patients initially treated with IV tedizolid, in whom the signs of systemic inflammation were generally more frequent, were similar to the overall result with PO administration. Infections caused by enterococci were rare across the two main studies.

Administration of tedizolid in the absence of a proven or strongly suspected Gram-positive bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria.

TR-701 FA is not active against Gram-negative bacteria. To date, there is no known cross resistance between TR-701 FA and other classes of antibiotics. The most commonly observed mutations in staphylococci and enterococci that result in drug resistance in the clinic with the oxazolidinone, linezolid, are in one or more copies of the 23S rRNA genes (G2576U and G2500A). The 4- to 16-fold increased potency of tedizolid versus linezolid is maintained against strains harbouring these mutations.

CHMP agreed that the available clinical data are sufficient to conclude that oral and IV formulation of tedizolid phosphate exerts a similar clinical efficacy as that of linezolid in patients with cSSTI caused by Gram-positive bacteria. Despite the fact that for tedizolid powder for concentrate for solution for infusion the applicant initially proposed pack sizes of 1 and 10 vials, the CHMP supported the revised pack sizes of 1 and 6 vials as they are more consistent with the posology of the product.

2.6. Clinical safety

Patient exposure

In total, the safety of tedizolid phosphate has been evaluated in 1488 subjects (1050 patients in the phase 2 and phase 3 studies and 438 subjects in the phase 1 studies) including both oral and IV administration routes. Of the 1488 subjects, 1050 were patients and 438 were healthy subjects.

A total number of 969 patients completed the phase 2 and 3 studies and received ≥200 mg, and of these 623 patients were exposed to ≥ 5 doses of 200 mg which roughly corresponds to the recommended dosage (200 mg once daily for 6 days).

The majority of the patients were treated orally. IV dosing of tedizolid phosphate was included in one phase 3 study, i.e. TR701-113, in which 331 patients were treated with ≥ 1 IV dose.

At the request of CHMP, the applicant has presented separate tabulations to enable a comparison of the safety profile after "oral", "IV-to-oral" and "IV-only" dosing, respectively, in line with the recommendation in the guidance document "Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections" (CPMP/EWP/558/95 rev 2).

In the TR701-113 study the predominant treatment regimen was a single IV dose followed by 5 oral doses and the majority of the subjects are included in the "IV-to-oral" subgroup (N=267). In the "IV-to-oral" subgroup, 120 subjects received ≥ 2 IV doses and 64 subjects received ≥ 3 IV doses. In addition, there were 64 subjects who only received IV doses ("IV-only" group) ≥1 IV doses and among these subjects 54 received ≥ 6 IV doses. Overall, the number of patients exposed to tedizolid phosphate at the recommended dosage was considered sufficient by CHMP.

The majority of the subjects in the clinical development program were white men between 18-65 years. Only 81 patients were aged 65 years or more, and only one subject was aged below 18 years. There was no major difference in the demographic characteristics between the tedizolid phosphate and the comparator (linezolid) group. A number of medications were prohibited by protocol; among these were selective serotonin re-uptake inhibitors [SSRI], serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, MAOI, triptans, and other medications with potential adrenergic or serotonergic activity.

Approximately 90% of the subjects completed the studies. In the phase 3 studies, approximately 7 to 9 % of subjects discontinued during the blinded treatment phase, across tedizolid phosphate and comparator treatment groups. There was no major difference between tedizolid phosphate and the comparator.

Adverse events

Overall, the incidence and severity of AEs reported for tedizolid was not high, indicating that the safety profile of tedizolid with the chosen short term treatment course (6 days) at the dose of 200 mg OD may be considered favourable.

In the phase 3 controlled studies group, the incidence of AEs, TEAEs, severe TEAEs, and serious TEAEs were similar for the TR701 FA and the linezolid treatment groups, with 42.7% and 43.2% of patients, respectively, experiencing at least 1 TEAE. Treatment-related TEAEs were less frequent in the TR701 FA group than in the linezolid group (22.4% versus 27.9%, respectively). Early discontinuation of study drug for a TEAE was infrequent in either group, with 2 patients (0.3%) in the TR701 FA group and 5 (0.8%) in the linezolid group. Two patients in the TR701 FA group and 1 patient in the linezolid group had TEAEs resulting in death (see below for the assessment of relatedness).

Adverse events most commonly involved the SOCs of gastrointestinal (GI), infections and infestations, and nervous system disorders. The incidence in the GI disorders SOC was lower in the TR701 FA group (16.0%) compared with the linezolid group (23.0%).

The most common TEAEs by preferred term (reported by at least 2% of patients) in the TR701 FA group were nausea, headache, abscess, diarrhoea, vomiting, and cellulitis. The profile and incidence of TEAEs was similar in the linezolid group although it was noted that nausea and vomiting were reported at lower incidences in the TR701 FA group than in the linezolid group (nausea: 8.2% versus 12.2%, and vomiting: 2.9% versus 5.6%); additionally dizziness was reported by 1.8% in the TR701 FA group and 2.1% in the linezolid group.

Out of the patients experiencing a TEAE, the majority experienced events with a maximum severity of mild (195/283 [68.9%] TR701 FA group and 193/286 [67.5%] linezolid group); the incidences of patients with moderate or severe events were also similar across the groups (moderate: 75/283 [26.5%] TR701 FA group, 80/286 [28.0%] linezolid group; and severe: 13/283 [4.6%], 13/286 [4.5%], respectively).

In the phase 2 uncontrolled studies group, the incidence of TEAEs was greater (57.0%) than for the TR701 FA treatment group in the Phase 3 controlled studies group (42.7%) as was the incidence of related TEAEs (36.9% versus 22.4%); this is considered due to the higher incidence of TEAEs obtained with the higher doses (300 mg and 400 mg) used in the TR701-104 study.

The incidence of severe TEAEs and serious TEAEs were similar for the TR701 FA treatment group and for the comparator group in the phase 3 controlled studies group. Early discontinuation of study drug for a TEAE was infrequent with 2 patients (0.5%) affected. There were no TEAEs resulting in death in the phase 2 studies.

Table 23 Overview of Treatment-Emergent Adverse Events: of Phase 3 Integrated Analysis Set

Phase III: Category	TR701 FA (200 mg) (N=662) n (%)	Linezolid (1200 mg) (N=662) n (%)
Treatment-Emergent Adverse Events	283 (42.7)	286 (43.2)
Related Treatment-Emergent Adverse Events	148 (22.4)	185 (27.9)
Severe Treatment-Emergent Adverse Events	13 (2.0)	13 (2.0)
Serious Adverse Events	12 (1.8)	13 (2.0)
Serious Treatment-Emergent Adverse Events	12 (1.8)	13 (2.0)
TEAE Leading to Study Drug Discontinuation	3 (0.5)	6 (0.9)
TEAE with Outcome of Death	2 (0.3)	1 (0.2)

Abbreviations: N=Number of subjects in the Safety Analysis set; n=Number of subjects in the specified category; TEAE=treatment-emergent adverse event.

Table 24 Overview of Treatment-Emergent Adverse Events: of Phase 2 Integrated Analysis Set

Phase II studies: Category	TR701 FA (≥ 200 mg) (N=388) n (%)
Treatment-Emergent Adverse Events	221 (57.0)
Related Treatment-Emergent Adverse Events	143 (36.9)
Severe Treatment-Emergent Adverse Events	9 (2.3)
Serious Adverse Events	7 (1.8)
Serious Treatment-Emergent Adverse Events	7 (1.8)
TEAE Leading to Study Drug Discontinuation	2 (0.5)
TEAE with Outcome of Death	0

Abbreviations: N=Number of subjects in the Safety Analysis set; n=Number of subjects in the specified category; TEAE=treatment-emergent adverse event.

For the phase 1 studies group, the incidence of TEAEs, severe TEAEs, and serious TEAEs were similar for the TR701 FA and placebo treatment groups, with 47.3% and 47.4% of subjects, respectively, experiencing at least 1 TEAE. Treatment-related TEAEs were less frequent in the TR701 FA group than in the placebo group (33.3% versus 36.8%, respectively). Early discontinuation of study drug for a TEAE was similar in both groups (3.4% in the TR701 FA group and 2.3% in the placebo group). No patients had TEAEs resulting in death in the phase 1 studies group.

Table 25 Overview of Treatment-Emergent Adverse Events: of Phase 1 Integrated Analysis Set

Phase I: Category	TR701 FA (≥200 mg) (N=438) n (%)	Placebo (N=133) n (%)
Treatment-Emergent Adverse Events	207 (47.3)	63 (47.4)
Related Treatment-Emergent Adverse Events	146 (33.3)	49 (36.8)
Severe Treatment-Emergent Adverse Events	4 (0.9)	0
Serious Adverse Events	2 (0.5)	0
Serious Treatment-Emergent Adverse Events	2 (0.5)	0
TEAE Leading to Study Drug Discontinuation	15 (3.4)	3 (2.3)
TEAE Leading to Study Discontinuation	14 (3.2)	2 (1.5)
TEAE with Outcome of Death	0	0

Abbreviations: N=Number of subjects in the Safety Analysis set; n=Number of subjects in the specified category; TEAE=treatment-emergent adverse event.

Table 26 Treatment-Emergent Adverse Events with Incidence ≥2% in any Study, by Study and by Dose: Phase 2 and Phase 3 Studies

	Study TR701-112		Study TR701-113		Study TR701-104	Study TR701-126
System Organ Class / Preferred Term	TR701 FA 200 mg (N=331) n (%)	Linezolid 1200 mg (N=335) n (%)	TR701 FA 200 mg (N=331) n (%)	Linezolid 1200 mg (N=327) n (%)	TR701 200 mg (N=63) n (%)	TR701 FA 200 mg (N=200) n (%)
Gastrointestinal Disorders	55 (16.6)	87 (26.0)	53 (16.0)	67 (20.5)	19 (30.2)	44 (22.0)
Nausea	29 (8.8)	48 (14.3)	27 (8.2)	36 (11.0)	10 (15.9)	22 (11.0)
Diarrhoea	15 (4.5)	18 (5.4)	11 (3.3)	17 (5.2)	7 (11.1)	13 (6.5)
Vomiting	10 (3.0)	21 (6.3)	11 (3.3)	17 (5.2)	7 (11.1)	9 (4.5)
Toothache	0	0	3 (0.9)	2 (0.6)	2 (3.2)	1 (0.5)
Abdominal Pain	4 (1.2)	3 (0.9)	1 (0.3)	1 (0.3)	1 (1.6)	2 (1.0)
Constipation	5 (1.5)	5 (1.5)	4 (1.2)	1 (0.3)	0	4 (2.0)
Dry Mouth	1 (0.3)	3 (0.9)	1 (0.3)	2 (0.6)	0	1 (0.5)
Dyspepsia	2 (0.6)	6 (1.8)	2 (0.6)	2 (0.6)	0	0
Infections And Infestations	51 (15.4)	37 (11.0)	40 (12.1)	41 (12.5)	14 (22.2)	27 (13.5)
Abscess	21 (6.3)	15 (4.5)	14 (4.2)	11 (3.4)	6 (9.5)	8 (4.0)

System Organ Class / Preferred Term	Study TR701-112		Study TR701-113		Study TR701-104	Study TR701-126
	TR701 FA 200 mg (N=331) n (%)	Linezolid 1200 mg (N=335) n (%)	TR701 FA 200 mg (N=331) n (%)	Linezolid 1200 mg (N=327) n (%)	TR701 200 mg (N=63) n (%)	TR701 FA 200 mg (N=200) n (%)
Skin Infection	0	2 (0.6)	0	0	4 (6.3)	0
Nasopharyngitis	0	1 (0.3)	1 (0.3)	3 (0.9)	2 (3.2)	0
Cellulitis	8 (2.4)	8 (2.4)	9 (2.7)	6 (1.8)	2 (3.2)	9 (4.5)
Vulvovaginal Mycotic Infection	0	2 (0.6)	2 (0.6)	7 (2.1)	1 (1.6)	1 (0.5)
Folliculitis	3 (0.9)	0	0	1 (0.3)	0	2 (1.0)
Fungal Infection	1 (0.3)	2 (0.6)	0	2 (0.6)	0	0
Nervous System Disorders	36 (10.9)	33 (9.9)	30 (9.1)	36 (11.0)	11 (17.5)	19 (9.5)
Headache	21 (6.3)	19 (5.7)	20 (6.0)	22 (6.7)	5 (7.9)	7 (3.5)
Dizziness	8 (2.4)	7 (2.1)	5 (1.5)	7 (2.1)	4 (6.3)	7 (3.5)
Dysgeusia	0	3 (0.9)	1 (0.3)	2 (0.6)	2 (3.2)	1 (0.5)
Somnolence	4 (1.2)	1 (0.3)	2 (0.6)	4 (1.2)	1 (1.6)	5 (2.5)
Skin And Subcutaneous Tissue Disorders	27 (8.2)	20 (6.0)	24 (7.3)	22 (6.7)	7 (11.1)	12 (6.0)
Skin Lesion	1 (0.3)	1 (0.3)	1 (0.3)	0	3 (4.8)	2 (1.0)
Pruritus	4 (1.2)	9 (2.7)	0	1 (0.3)	1 (1.6)	1 (0.5)
Pruritus Generalised	5 (1.5)	3 (0.9)	7 (2.1)	5 (1.5)	1 (1.6)	1 (0.5)
Rash	1 (0.3)	1 (0.3)	2 (0.6)	1 (0.3)	0	0
General Disorders And Administration Site Conditions	13 (3.9)	15 (4.5)	24 (7.3)	25 (7.6)	6 (9.5)	14 (7.0)
Fatigue	1 (0.3)	5 (1.5)	8 (2.4)	7 (2.1)	3 (4.8)	3 (1.5)
Chills	1 (0.3)	2 (0.6)	1 (0.3)	2 (0.6)	2 (3.2)	4 (2.0)
Pain	0	0	0	3 (0.9)	2 (3.2)	1 (0.5)
Pyrexia	2 (0.6)	0	2 (0.6)	3 (0.9)	0	2 (1.0)
Psychiatric Disorders	9 (2.7)	4 (1.2)	10 (3.0)	4 (1.2)	3 (4.8)	3 (1.5)
Insomnia	6 (1.8)	2 (0.6)	4 (1.2)	3 (0.9)	1 (1.6)	3 (1.5)
Sleep Disorder	0	0	1 (0.3)	0	0	0
Respiratory, Thoracic And Mediastinal Disorders	12 (3.6)	4 (1.2)	6 (1.8)	14 (4.3)	3 (4.8)	6 (3.0)
Oropharyngeal Pain	1 (0.3)	2 (0.6)	0	3 (0.9)	1 (1.6)	1 (0.5)
Rhinorrhoea	1 (0.3)	0	0	3 (0.9)	1 (1.6)	0
Cough	3 (0.9)	0	3 (0.9)	4 (1.2)	0	0
Blood And Lymphatic System Disorders	1 (0.3)	0	5 (1.5)	1 (0.3)	2 (3.2)	1 (0.5)
Lymphadenopathy	1 (0.3)	0	0	0	2 (3.2)	0
Cardiac Disorders	6 (1.8)	6 (1.8)	3 (0.9)	2 (0.6)	2 (3.2)	1 (0.5)
Tachycardia	2 (0.6)	4 (1.2)	0	0	2 (3.2)	0
Investigations	6 (1.8)	6 (1.8)	2 (0.6)	5 (1.5)	1 (1.6)	0

System Organ Class / Preferred Term	Study TR701-112		Study TR701-113		Study TR701-104	Study TR701-126
	TR701 FA 200 mg (N=331) n (%)	Linezolid 1200 mg (N=335) n (%)	TR701 FA 200 mg (N=331) n (%)	Linezolid 1200 mg (N=327) n (%)	TR701 200 mg (N=63) n (%)	TR701 FA 200 mg (N=200) n (%)
Blood Pressure Increased	1 (0.3)	1 (0.3)	2 (0.6)	2 (0.6)	1 (1.6)	0
Metabolism And Nutrition Disorders	7 (2.1)	7 (2.1)	9 (2.7)	7 (2.1)	1 (1.6)	2 (1.0)
Decreased Appetite	0	1 (0.3)	0	0	1 (1.6)	1 (0.5)

The most frequently reported TEAEs considered to be related to the study compound, all with < 10% frequency, were nausea, headache, dizziness and abscess. Nausea, the most frequently individually reported TEAE, was less frequently reported for tedizolid than for linezolid in both phase 3 studies. Abscesses were reported similarly for the study compound and the comparator in phase 3 studies, whereas slightly less frequently for linezolid. Dizziness, fatigue and pruritus generalized were reported by between 1-2% of patients in the TR701 FA and linezolid groups.

SAEs were reported, overall, for approximately 2% of the patients across treatment groups in the phase 2 and 3 studies.

IV and oral dosing

At the CHMP request, the applicant has presented separate tabulations to enable a comparison of the safety profile after "oral", "IV-to-oral" and "IV-only" dosing, respectively, in line with the recommendation in the guidance document "Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections" (CPMP/EWP/558/95 rev 2).

Table 27 Treatment-emergent Adverse Events With Incidence ≥1% in Any Group by Route of Administration of TR-701/FA 200 mg (Safety Analysis Set)

System Organ Class Preferred Term	ORAL Phase 2 N=263	ORAL TR701-112 N=331	IV-to-ORAL TR701-113 N=267	IV ONLY TR701-113 N=64
Blood and lymphatic system disorders	3 (1.1)	1 (0.3)	3 (1.1)	2 (3.1)
Anaemia	1 (0.4)	0	3 (1.1)	2 (3.1)
Cardiac disorders	3 (1.1)	6 (1.8)	2 (0.7)	1 (1.6)
Palpitations	1 (0.4)	0	0	1 (1.6)
Eye disorders	3 (1.1)	5 (1.5)	2 (0.7)	2 (3.1)
Vision blurred	1 (0.4)	0	1 (0.4)	1 (1.6)
Visual impairment	0	0	0	1 (1.6)
Gastrointestinal disorders	63 (24.0)	54 (16.3)	49 (18.4)	3 (4.7)
Abdominal discomfort	2 (0.8)	3 (0.9)	2 (0.7)	1 (1.6)
Abdominal pain	3 (1.1)	4 (1.2)	1 (0.4)	0

System Organ Class Preferred Term	ORAL Phase 2 N=263	ORAL TR701-112 N=331	IV-to-ORAL TR701-113 N=267	IV ONLY TR701-113 N=64
Constipation	4 (1.5)	5 (1.5)	4 (1.5)	0
Diarrhoea	20 (7.6)	15 (4.5)	11 (4.1)	0
Nausea	32 (12.2)	28 (8.5)	24 (9.0)	2 (3.1)
Toothache	3 (1.1)	0	3 (1.1)	0
Vomiting	16 (6.1)	9 (2.7)	10 (3.7)	0
General disorders and administration site conditions	20 (7.6)	13 (3.9)	15 (5.6)	8 (12.5)
Chills	6 (2.3)	1 (0.3)	1 (0.4)	0
Fatigue	6 (2.3)	1 (0.3)	2 (0.7)	6 (9.4)
Localised oedema	0	0	0	1 (1.6)
Oedema peripheral	1 (0.4)	0	3 (1.1)	0
Pain	3 (1.1)	0	0	0
Pyrexia	2 (0.8)	2 (0.6)	1 (0.4)	1 (1.6)
Infections and infestations	41 (15.6)	51 (15.4)	39 (14.6)	1 (1.6)
Abscess	14 (5.3)	21 (6.3)	14 (5.2)	0
Cellulitis	11 (4.2)	8 (2.4)	8 (3.0)	1 (1.6)
Skin infection	4 (1.5)	0	0	0
Upper respiratory tract infection	1 (0.4)	4 (1.2)	0	0
Wound infection	1 (0.4)	2 (0.6)	4 (1.5)	0
Metabolism and nutrition disorders	3 (1.1)	7 (2.1)	5 (1.9)	3 (4.7)
Dehydration	0	3 (0.9)	0	2 (3.1)
Fluid overload	0	0	0	1 (1.6)
Musculoskeletal and connective tissue disorders	10 (3.8)	10 (3.0)	7 (2.6)	2 (3.1)
Arthralgia	1 (0.4)	1 (0.3)	3 (1.1)	0
Groin pain	0	0	0	1 (1.6)
Joint swelling	1 (0.4)	0	0	1 (1.6)
Pain in extremity	3 (1.1)	2 (0.6)	0	0
Nervous system disorders	29 (11.0)	36 (10.9)	25 (9.4)	4 (6.3)
Dizziness	11 (4.2)	8 (2.4)	3 (1.1)	1 (1.6)
Dysgeusia	3 (1.1)	0	1 (0.4)	0
Headache	12 (4.6)	21 (6.3)	18 (6.7)	2 (3.1)
Paraesthesia	0	1 (0.3)	1 (0.4)	1 (1.6)
Somnolence	5 (1.9)	4 (1.2)	2 (0.7)	0
Psychiatric disorders	6 (2.3)	8 (2.4)	5 (1.9)	4 (6.3)
Insomnia	4 (1.5)	6 (1.8)	1 (0.4)	3 (4.7)
Nervousness	0	0	0	1 (1.6)
Respiratory, thoracic and mediastinal disorders	9 (3.4)	12 (3.6)	6 (2.2)	0
Cough	0	3 (0.9)	3 (1.1)	0
Skin and subcutaneous tissue disorders	19 (7.2)	24 (7.3)	21 (7.9)	2 (3.1)

System Organ Class Preferred Term	ORAL Phase 2 N=263	ORAL TR701-112 N=331	IV-to-ORAL TR701-113 N=267	IV ONLY TR701-113 N=64
Dermatitis	0	4 (1.2)	0	0
Pruritus generalised	2 (0.8)	4 (1.2)	6 (2.2)	1 (1.6)
Skin lesion	5 (1.9)	1 (0.3)	1 (0.4)	0
Urticaria	1 (0.4)	1 (0.3)	1 (0.4)	1 (1.6)
Vascular disorders	3 (1.1)	8 (2.4)	4 (1.5)	2 (3.1)
Essential hypertension	0	0	0	1 (1.6)
Flushing	0	4 (1.2)	0	0
Hypertension	1 (0.4)	2 (0.6)	2 (0.7)	1 (1.6)

Note: TR-701/FA refers to both TR-701 and TR-701 FA.
N=Number of patients in the Safety Analysis Set. n= Number of patients in the specified category.
Note: A patient with an event coding to the same System Organ Class (SOC) or Preferred Term (PT) on more than one occasion is only counted one time for that SOC and PT using the event with the maximum severity.

In general there are no major differences between in incidences of TEAEs between the oral, IV-to-oral and IV-only administration routes. Although the incidence of fatigue was increased (9.4%) in the IV-only group in comparison to the other groups, oral and IV-to oral groups.

Taken together the data at hand do not indicate different safety profiles after oral and IV administration of tedizolid phosphate.

To conclude the overall number of patients exposed to tedizolid phosphate at the recommended dosage is considered sufficient. The safety profile after oral and IV dosing seems comparable. “Prolonged use >7 days” is included in the RMP as missing information, which is considered sufficient.

Serious adverse event/deaths/other significant events

In the pool of all phase 2/3 studies, a total of 2 (0.2%) deaths were reported in the tedizolid phosphate group compared with 1 (0.2%) deaths in the all comparator groups. The two deaths occurring in tedizolid phosphate group were due to myocardial infarction and septic shock, respectively. The third death, in the linezolid group, was due to TB (tuberculosis) meningitis. The three deaths seemed therefore unrelated to the study treatment.

In the phase 3 controlled studies group, the overall incidence of SAEs was similar between groups (12 patients, 1.8% in the TR701 FA group and 13, 2.0% in the linezolid group). SAEs most commonly affected the Infections and Infestations SOC (0.9% in TR701 FA and 0.6% in linezolid). The majority of SAEs were singular events; however, in the TR701 FA group 2 patients experienced pneumonia and 2 experienced septic shock.

Table 28 Serious Adverse Events: Phase 3 Controlled Studies Group

System Organ Class Preferred Term	TR701 FA (200 mg) (N=662)	Linezolid (1200 mg) (N=662)
Number (%) of Patients with at least 1 SAE:	**12 (1.8)**	**13 (2.0)**
Infections and infestations	**6 (0.9)**	**4 (0.6)**
Abscess	1 (0.2)	0
Pneumonia	2 (0.3)	0
Septic Shock	2 (0.3)	0
Staphylococcal Infection	1 (0.2)	0
Cellulitis	0	2 (0.3)
Endophthalmitis	1 (0.2)	0
Urinary Tract Infection	1 (0.2)	1 (0.2)
Meningitis Tuberculous	0	1 (0.2)
Cardiac disorders	**2 (0.3)**	**2 (0.3)**
Cardiac Arrest	1 (0.2)	0
Myocardial Infarction	1 (0.2)	0
Acute Coronary Syndrome	0	1 (0.2)
Acute Myocardial Infarction	0	1 (0.2)
Gastrointestinal disorders	**2 (0.3)**	**0**
Upper Gastrointestinal Haemorrhage	1 (0.2)	0
Vomiting	1 (0.2)	0
Metabolism & nutrition disorders	**2 (0.3)**	**1 (0.2)**
Dehydration	1 (0.2)	0
Diabetes Mellitus	1 (0.2)	0
Diabetic Ketoacidosis	0	1 (0.2)
Investigations	**1 (0.2)**	**1 (0.2)**
Weight Decreased	1 (0.2)	0
Blood Glucose Increased	0	1 (0.2)
Nervous system disorders	**1 (0.2)**	**0**
VIIth Nerve Paralysis	1 (0.2)	0
Psychiatric disorders	**0**	**2 (0.3)**
Suicidal Ideation	0	1 (0.2)
Alcoholic Psychosis	0	1 (0.2)
Major Depression	0	1 (0.2)
Renal and urinary disorders	**1 (0.2)**	**0**
Nephrolithiasis	1 (0.2)	0
Vascular disorders	**1 (0.2)**	**1 (0.2)**
Hypertension	1 (0.2)	0
Thrombophlebitis Superficial	0	1 (0.2)
Immune system disorders	**0**	**1 (0.2)**
Anaphylactic Reaction	0	1 (0.2)
Pregnancy, puerperium & perinatal conditions	**0**	**1 (0.2)**
Abortion Spontaneous	0	1 (0.2)

Abbreviations: N=number of patients in the Safety Analysis Set; SAE=serious adverse event.

Note**:** A subject with an event coding to the same System Organ Class (SOC) or Preferred Term (PT) on more than 1 occasion is only counted 1 time for that SOC and PT.

In the phase 2 uncontrolled studies group, 7 (1.8%) of patients experienced 1 or more SAEs; these included 2 patients with abscess. The only SAEs in common between patients treated with TR701/FA in phase 2 and phase 3 studies were abscess and staphylococcal infection.

Events of special interest

Myelosuppression

The mean values of haematology parameters evaluated for both tedizolid phosphate and the comparator linezolid remained generally stable over the course of the studies (change from baseline to worst value) with the exception of leukocytes which decreased over time as expected with response to treatment of an infection, in both treatment groups. The substantially abnormal decrease in values observed for leucocytes was approximately 0.4% for both tedizolid phosphate as well as for the comparator linezolid.

Table 29 Modified Division of Microbiology and Infectious Diseases Adult (November 2007)

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hematology					
Hemoglobin (g/dL)	>10.5	9.5-10.5	8.0-9.4	6.5-7.9	<6.5
Absolute Neutrophil Count (cells/mm^3)	>1500	1000-1500	750-999	500-749	<500
Platelets (cells /mm^3)	≥100,000	75,000-99,999	50,000-74,999	20,000-49,999	<20,000
WBC (cells /mm^3)	1000-10,999	11,000-12,999	13,000-14,999	15,000-30,000	>30,000 or <1000
% Polymorphonuclear Leucocytes + Band Cells	≤80%	>80%-90%	>90%-95%	>95%	N/A

Table 30 Criteria for Substantially Abnormal Laboratory Test Results

	Criteria
Hematology	
Hemoglobin, Platelets	*<75% of LLN for values normal at baseline; or* *<75% of the LLN and <75% of baseline for values abnormal at baseline*
Absolute Neutrophil Count	*<50% of LLN for values normal at baseline; or* *<50% of the LLN and <50% of baseline for values abnormal at baseline*

Increases of ⩾2 toxicity grades from baseline to the worst post baseline result are presented below for the TR-701 FA and linezolid treatment groups.

Table 31 Toxicity Grade Shifts ⩾2 from Baseline to Worst Postbaseline Value in Haematology Parameters: Phase 3 Controlled Studies Group

	TR-701 FA (200 mg)		*Linezolid (1200 mg)*	
Parameter	***N***	***n (%)***	***N***	***n (%)***
Haemoglobin	*602*	*6 (1.0%)*	*597*	*4 (0.7%)*
Leukocytes	*583*	*15 (2.6%)*	*581*	*10 (1.7%)*
Neutrophils	*567*	*3 (0.5%)*	*554*	*7 (1.3%)*
Platelets	*579*	*8 (1.4%)*	*577*	*4 (0.7%)*

Abbreviations: N=number of patients with non-missing data at both baseline and post-baseline visits; n=number of patients for each toxicity grade at baseline.

The applicant states regarding the haematology results that in the phase 3 controlled studies group, decreases of ⩾2 toxicity grades from baseline were noted in 65/583 (11.1%) of tedizolid phosphate patients and in 45/581 (7.7%) of linezolid patients.

The incidence of substantially abnormal absolute neutrophil count (ANC), haemoglobin values, and platelet counts in the phase 3 controlled studies group are roughly similar between the tedizolid phosphate and linezolid treatment groups.

Table 32 Incidence ofSubstantially Abnormal Absolute Neutrophil Count, Haemoglobin Values, and Platelet Counts: Phase 3 Controlled Studies Group

Parameter	Time Point		TR-701 FA (200 mg) (N=662) n (%)	Linezolid (1200 mg) (N=662) n (%)
ANC	Study Day 7-9	N1	536	527
		<50%X LLN	2 (0.4)	1 (0.2)
	Study Day 11-13	N1	537	516
		<50%X LLN	1 (0.2)	2 (0.4)
	Last Dose of Active Drug	N1	526	499
		<50%X LLN	3 (0.6)	2 (0.4)
	Any Post-Baseline through Last Dose of Active Drug	N1	618	617
		<50%X LLN	3 (0.5)	4 (0.6)
Hemoglobin value	Study Day 7-9	N1	574	562
		<75%X LLN	11 (1.9)	11 (2.0)
	Study Day 11-13	N1	560	553
		<75%X LLN	10 (1.8)	10 (1.8)
	Last Dose of Active Drug	N1	564	538
		<75%X LLN	12 (2.1)	12 (2.2)
	Any Post-Baseline through Last Dose of Active Drug	N1	632	633
		<75%X LLN	18 (2.8)	22 (3.5)
Platelet Count	Study Day 7-9	N1	554	551
		<75%X LLN	8 (1.4)	12 (2.2)
	Study Day 11-13	N1	552	537
		<75%X LLN	7 (1.3)	20 (3.7)
	Last Dose of Active Drug	N1	546	520
		<75%X LLN	9 (1.6)	17 (3.3)
	Any Post-Baseline through Last Dose of Active Drug	N1	627	626
		<75%X LLN	13 (2.1)	28 (4.5)

Abbreviations: ANC=absolute neutrophil count; LLN=lower limit of normal; N=number of patients in the Safety Analysis Set; N1=number of patients with non-missing data at the summarized visit; n=number of patients in the specified category.

Note: All patients in the safety analysis set with non-missing data at the summarized visit (N1) are used as the denominator to calculate percentages.

Although, a slight trend for a higher incidence of substantially abnormal platelet counts is seen in the linezolid group (4.5% vs 2.1% for tedizolid phosphate). The use of the comparator regimen linezolid is associated with anemia, leukopenia, neutropenia and thrombocytopenia.

Laboratory events were rare and unremarkable. Laboratory events of interest are those related to the haematology count. A small number of shifts from baseline to worst post-baseline in haemoglobin values (1.0%), leukocytes (2.6%) and platelets (1.4%), were reported in phase III studies, whereas the interpretation of these shifts is difficult as they might have reflected improvement in inflammatory response.

In a phase 1 study in healthy subjects (TR701-101), subjects received oral 200, 300, or 400 mg once-daily TR701 or 600 mg twice-daily linezolid or placebo for 21 days (N=8 per group). A trend toward decline over time was noted for platelet, red blood cell (RBC), and ANC counts at the highest dose of TR701 (400 mg) and in the linezolid group. Overall, hematologic effects over the 21-day administration period were unremarkable for subjects receiving 200 mg TR701 once daily but were more pronounced as the dose increased.

Overall, the haematology results seem quite similar for tedizolid phosphate (200 mg/day) and linezolid (1200 mg/day). Therefore, evidence that exposure to tedizolid may be associated with bone marrow supression was observed. The clinical relevance of these findings, which are also expected for linezolid, may be mitigated by the short term treatment course that is proposed. Thus, a warning was included in section 4.4 regarding myelosuppression (see SmPC). An adequate warning regarding the possibility to exceed the 6 days treatment course is included in the SmPC.

Lactic acidosis

Tedizolid phosphate inhibits mitochondrial protein synthesis. Lactic acid levels were not affected over the 21-day period of drug administration in a phase 1 study in healthy volunteers (Study TR701-101). Lactic acidosis has not been reported in patients treated with tedizolid phosphate at the recommended treatment duration of 6 days. The applicant was requested by CHMP and has subsequently included a warning on lactic acidosis in SmPC section 4.4.

Peripheral neuropathy and optic nerve disorders

From the published clinical and post-marketing experience, AEs associated with linezolid, particularly for prolonged treatment exposures >28 days, include optic and peripheral neuropathy. Two phase 1 studies, TR-701-101 (part B) and TR-701-110, included ophthalmologic (including optic neuropathy) and neurologic (including peripheral neuropathy) examinations. In study TR-701-101 (part B, N=8/group, tedizolid phosphate and linezolid dosed up to 21 days), no difference was observed between tedizolid phosphate and linezolid treated subjects in the small group of subjects studied. In the tedizolid exposed group ocular hyperaemia and blurred vision was reported as TEAEs. In study TR-701-110 (200 mg tedizolid phosphate dosed up to 10 days), only dry eyes and blurred vision was reported.

There was no difference between tedizolid phosphate and linezolid with regard to the standardized MedDRA queries (SMQ) results for peripheral neuropathy and optic nerve disorders in the phase 3 study group.

Table 33 Peripheral Neuropathy Standard Medical Queries and Cranial Nerve Disorders: Phase 3 Controlled Studies Group

System Organ Class Preferred Term	TR701 FA (200 mg) (N=662) n (%)	Linezolid (1200 mg) (N=662) n (%)
Number (%) of Patients with at least 1 TEAE:	8 (1.2)	5 (0.8)
Nervous System Disorders	8 (1.2)	4 (0.6)
Hypoaesthesia	4 (0.6)	1 (0.2)
Paraesthesia	3 (0.5)	3 (0.5)
VIIth Nerve Paralysis	1 (0.2)	0
Sensory Loss	0	1 (0.2)
Ear And Labyrinth Disorders	0	1 (0.2)
Tinnitus	0	1 (0.2)

The applicant has provided the requested review of all the cases of peripheral neuropathy and optic nerve disorders (identified by standardized MedDRA queries (SMQ) for peripheral neuropathy and optic nerve disorders) in the complete safety database (1, 2 and 3 studies). Twenty-two subjects who received at least 1 dose of tedizolid phosphate in the complete safety database experienced TEAEs within the peripheral neuropathy SMQ, compared to 11 subjects in the control groups (placebo 6, linezolid 5 subjects). Overall, there was no difference between tedizolid phosphate, placebo, and linezolid with regard to the standardized MedDRA queries (SMQ) results for peripheral neuropathy disorders.

Optic Nerve Disorders

In the phase 3 controlled studies group, 2 (0.3%) patients in the TR701 FA group and 1 (0.2%) patient in the linezolid group experienced at least 1 TEAE identified by the optic nerve disorder SMQ (see below table) The incidence of events was low and the small numbers preclude comparison by TEAE. Most events were mild, generally transient, with spontaneous resolution.

Table 34 Optic Nerve Disorder Standard Medical Query Results: Phase 3 Controlled Studies Group

System Organ Class Preferred Term	TR701/FA (200 mg) (N=662) n (%)	Linezolid (1200 mg) (N=662) n (%)
Number (%) of Patients with at least 1 treatment-emergent adverse event:	2 (0.3)	1 (0.2)
Eye Disorders	2 (0.3)	1 (0.2)
Visual Acuity Reduced	1 (0.2)	1 (0.2)
Visual Impairment	1 (0.2)	0

In the phase 1 studies group, the incidence of optic and peripheral neurologic TEAEs was low and similar between the TR701/FA group and the placebo group, suggesting that events seen were unlikely to be related to TR701/FA (neurologic TEAEs: 2.3% in the TR701/FA group versus 4.5% in the placebo group and optic/eye disorders: 0.2% and 0.8%, respectively.

Overall, there was no difference of TEAEs between tedizolid phosphate and linezolid in the performed clinical program with a maximum duration of treatment of 6 days for tedizolid phosphate and 10 days for linezolid. Optic and peripheral neuropathy has mainly been observed in patients treated with linezolid for a longer duration time than the approved duration of 28 days. Peripheral and optic nerve toxicity has been included as an important potential risk in the RMP for tedizolid phosphate which is endorsed. Thus, a relevant precautionary statement in SmPC section 4.4 was requested by the CHMP and was included by the applicant.

Hypersensitivity reactions

In the phase 2 and 3 study pool the related TEAEs indicating potential allergic reactions seem roughly similar between the tedizolid phosphate and linezolid groups. In the phase 2 and 3 study pool there was one serious adverse event, anaphylactic reaction in the linezolid group. Two cases lead to permanent discontinuation, i.e., drug hypersensitivity (tedizolid phosphate arm) and anaphylactic reaction (linezolid arm). In line with request for clarification of the safety profile the applicant provided a specific MedDRA query for potential allergic reactions. The available data did not indicate different safety profiles after oral and IV administration of tedizolid phosphate.

Cardiac and Vascular Disorders

Blood pressure increased was reported as a TEAE for 2 patients (0.3%) each in TR-701 FA and linezolid groups in the Phase 3 Controlled Studies Group. Hypertension was reported as a TEAE for 5 patients (0.8%) in the TR-701 FA group and 2 patients (0.3%) in the linezolid group; 1 patient (0.2%) in the TR-701 FA group had a TEAE of essential hypertension. Incidence of hypotension was lower; 1 patient in each treatment group experienced hypotension. Potentially clinically significant high or low SBP abnormalities occurred in ≤0.6% of patients in either treatment group when SBP was measured at the 48-72 hours or EOT Visits. Potentially clinically significant high abnormal values in SBP at any time postbaseline were observed in 1.2% of patients in the TR701 FA group and 0.6% of the linezolid group, and low value abnormalities in 0.2% and 1.2%, respectively. Similarly, PCS high or low DBP readings were observed for ≤0.8% of patients in either treatment group at the 48-72 hour or EOT Visits. At any time after beginning study drug, abnormally high DBP values were recorded in 2.4% of patients in the TR701 FA group and 1.7% of the linezolid group, and low value abnormalities

in 1.1% and 1.4%, respectively. In the phase 2 and 3 study pool, mean changes of systolic and diastolic blood pressure was minimally affected (< 1 mm Hg). In the Phase 3 study pool, mean reduction from baseline to end of treatment of heart rate was 4.9 beats/min and 2.1 beats/min for tedizolid phosphate and linezolid, respectively. In the Phase 3 Controlled Studies Group, mean values for systolic blood pressure (SBP) and diastolic blood pressure (DBP) were similar at the 48-72 hour and EOT Visits for the TR701 FA and linezolid treatment groups. Mean greatest increases in SBP were +11.0 mmHg with TR701 FA and +9.5 mmHg with linezolid, and mean largest decreases were −9.5 mmHg and −10.9 mmHg, respectively. For DBP, mean greatest increases were +8.2 mmHg (TR701 FA) and +7.6 mmHg (linezolid); corresponding mean largest decreases from baseline were −7.6 mmHg and −7.7 mmHg, respectively.

In Phase 3 studies, TEAEs of tachycardia were reported for 2 patients in the TR-701 FA group and 4 patients in the linezolid group. Only 1 TEAE of bradycardia was reported; this occurred in a patient receiving TR-701 FA. Similarly, mean heart rate were similar between the 2 treatment groups at 48-72 hour and EOT visits. The mean greatest increase in heart rate from baseline to any postbaseline was 7.0 bpm for TR701 FA and 7.6 bpm for linezolid and corresponding mean largest decreases were −12.1 bpm and −10.4 bpm, respectively. Potentially clinically significant heart rate abnormalities were infrequent in both treatment groups at the 48-72 hour and EOT Visits (<1%). At any postbaseline measurement, 1.4% of patients in the TR701 FA group and 1.2% in the linezolid group had high heart rates and 1.1% and 0.5%, respectively, had low heart rates considered to be of potential clinical significance.

Overall in the complete clinical safety pool, 9 unique patients in the TR-701 FA group and 15 unique patients in the linezolid group had 1 or more postbaseline QTcB or QTcF value >500 msec or >60 msec increase from baseline, although 1 and 4 patients, respectively, had QTcB >500 msec at baseline also. In the Phase 3 Controlled Studies Group, 6 patients (0.9%) in the TR701 FA group and 10 subjects (1.6%) in the linezolid group had QTcB >500 msec for at least 1 evaluation after the first dose of study drug, or double the number at baseline in both groups. Increases in QTcB >60 msec from baseline to the worst post-baseline result were infrequent; 6 patients (0.9%) in the TR701 FA group and 4 patients (0.6%) in the linezolid group had such increases in QTcB. Increases of 30 to 60 msec were more frequent in the linezolid group (15.2%) than the TR701 FA group (8.9%). Potentially clinically significant abnormal QTcF post-baseline high values were less frequent; 1 patient (0.2%) in the TR701 FA group and 1 patient (0.2%) in the linezolid group had QTcF >500 msec, compared with 1 and 2 patients, respectively, at baseline. No patients in either treatment group had QTcF values <350 msec after beginning treatment, but 1 patient in the TR701 FA group had a PCS low value at baseline. Increases >60 msec in QTcF from baseline to any post-baseline evaluation were also infrequent, occurring in 2 (0.3%) and 4 (0.6%) patients in TR701 FA and linezolid groups, respectively; increases of 30 to 60 msec were also balanced (13.1% and 13.6%). The overall blood pressure and heart rate and ECG results for the comparative phase 3 studies appear similar for tedizolid phosphate (200 mg/day) and linezolid (1200 mg/day).

Therefore, individual values > 500 msec or changes from baseline of > 60 msec, for QTc, generally considered of high risk for torsade des pointes, although infrequent, were observed throughout the two main studies in patients exposed to tedizolid, while eventually less frequently with linezolid. Nevertheless, based on the additional information provided by the applicant (narratives for the relevant cases) during the assessment, CHMP was reassured that clinically relevant QTc interval prolongation was unlikely with tedizolid treatment.

The cardiac safety and thorough QTc study TR701-115 evaluated tedizolid phosphate for the potential for QT interval prolongation in healthy subjects using a Holter monitor for continuous ECG recording. TR-701 FA administered in single doses of 200 mg or 1200 mg did not prolong the QT interval relative to placebo when

evaluated by time-matched or time-averaged QTcF values; the positive control, moxifloxacin, confirmed assay sensitivity.

Additional Cardiovascular Safety Studies

The potential of tedizolid to induce an increased sensitivity to tyramine was considered lower than for linezolid in direct comparison, but these findings not only do not exclude but also indicate that this potential may have clinical impact. The applicant was asked to discuss this potential impact with special regard to the IV administration and consider the need for further warnings regarding this issue in the SmPC. In its provided responses, the applicant provided a justification that it was expected that the proposed short term-use of tedizolid will not have a significant impact on individual tyramine sensitivity. This was considered sufficient by the CHMP.

Venous tolerability

The venous tolerability of tedizolid was explored in a crossover study in adult healthy volunteers and was unremarkable. In Phase III study TR113, infusion-site events of dermatitis, erythema, extravasation, induration, oedema, pain, phlebitis, urticaria, hematoma, and vessel puncture site pain were reported as TEAEs. The incidence of any specific TEAE was <1% in each group.

Laboratory findings

Overall, the use of tedizolid phosphate is associated with a low incidence of elevated hepatic enzymes ALT, AST and alkaline phosphatase which is similar to what is observed for the comparator linezolid. The potential for inducing severe liver injury seems to be low although one case of Hy's law occurred in a linezolid treated patient in the clinical program.

Safety in special populations

Within patient subgroups defined by intrinsic factors the incidence of any 1 or more TEAEs was similar between TR701 FA and linezolid treatment groups. The safety results from the Phase I PK studies in special populations, including in voluntary subjects with renal disease, hepatic disease and aged > 65 years, did not show an increase in the frequency or pattern of events in comparison with a reference safety population. In patients ≥65 years of age, the incidence of severe TEAEs or SAEs increased with age in the TR701 FA treatment group; SAEs were reported for 1.0% of patients <65 years, 8.3% of patients ≥65 years, and 16.7% of patients ≥75 years. Two SAEs resulted in death; both were patients ≥75 years in the TR701 FA group. Both deaths were already discussed and are considered to be unrelated to the exposure to the compound. A slightly greater proportion of females experienced TEAEs than males. Similarly, the incidence of SAEs was higher among female patients than male patients whether receiving TR701 FA or linezolid. The incidence of TEAEs was similar for obese (43.5%) and normal/overweight (43.1%; BMI of 25 to <30 kg/m^2) subgroups of the TR701 FA treatment group, but was greater among obese patients than normal/overweight patients in the linezolid group (48.5% and 40.1%, respectively). The most common TEAEs for both subgroups in each treatment group were in the SOCs of GI Disorders, Infections and Infestations, and Nervous Disorders. The most common TEAEs for both subgroups in each treatment group were in the SOCs of GI Disorders, Infections and Infestations, and Nervous Disorders. A population PK analysis of patients in the Phase 3 Controlled Studies Group found no exposure differences between obese (≥30 kg/m^2) and all other patients. Only a few patients with renal impairment were exposed in clinical trials. Nearly 30% of patients in the Phase 3 Controlled Studies Group had hepatic disease, defined by positive hepatitis C results or baseline ALT or AST >2× ULN. Hepatic impairment characterized by a Child-Pugh classification of B or C was much less common (approximately 2% of the population). No notable differences in terms of the pattern or incidence of AEs were observed in patients with hepatic disease. Approximately 10% of

patients in the Phase 3 Controlled Studies Group had diabetes. Apart from a slight overall increase in TEAEs no notable change in pattern was observed.

An integrated population PK analysis of phase 1, phase 2, and phase 3 studies was performed (CLN-13-0701-072). In the population PK analysis, ideal body weight was found to be the most important covariate for explaining observed variability, but predicted changes were relatively modest at the extremes of body size (<40% change from 5^{th} to 95^{th} percentile of ideal body weight). No other demographic or clinical covariates that were assessed which included sex, race, ethnicity, age, weight, BMI, creatinine clearance, ALT, AST, and bilirubin were associated with meaningful changes in PK.

Extrinsic factors studied were geographic region and IV drug use. The Phase 3 Studies were conducted in the US, Canada, Europe, South America, Australia, New Zealand, and South Africa. The occurrence of cSSTIs is relatively common among IV drug users and this subgroup was of sufficient size (29% of patients in the Phase 3 Safety Analysis Set) to compare safety in users to nonusers.

Use in pregnancy, which occurred in only a trace proportion of exposed patients, and during lactation are the object of adequate warnings in the SmPC and PL.

The paediatric program is ongoing, while the use in this population is adequately managed in the SmPC.

Safety related to drug-drug interactions and other interactions

The PK interactions are discussed in the pharmacokinetic section. There are some raised OC regarding PK interactions and clinically relevant drug interactions by tedizolid phosphate at intestinal CYP3A4 cannot be excluded at the moment.

Tedizolid phosphate is a weak nonselective reversible MAO inhibitor when assayed in vitro with endogenous or expressed human MAO-A or MAO-B.

The use of certain medications (selective serotonin re-uptake inhibitors [SSRI], serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, MAOI, triptans, and other medications with potential adrenergic or serotonergic activity) was prohibited in the protocol. A few patients in the Safety Analysis Set from Phase 2/3 studies, although, received these medications. However, no conclusion can be drawn from the safety data since data is scarce. The potential for peripheral inhibition of MAOA was evaluated using tyramine in study TR701-105, and pseudoephedrine in study TR701-114. No meaningful changes in blood pressure, heart rate with pseudoephedrine were observed in the healthy volunteers, and no clinically relevant increase in tyramine sensitivity were observed. However,. a potential peripheral inhibition of MAOA cannot be excluded based on the limited clinical experience to date..

Discontinuation due to adverse events

The overall discontinuation rate in the tedizolid phosphate group in phase 3 studies is very low, 0.5%, and mostly concerned the GI SOC which is not unexpected considering that class of the substance and further that the majority of the subjects were treated orally.

The discontinuation rate was slightly higher in the phase 1 studies pool, 3.2 % vs 2.3% in the placebo group. In particular events leading to discontinuation were mostly in the General Disorders and Administrative Site Conditions SOC, and was related the infusion site TEAEs, i.e., infusion site pain (4 subjects), infusion site swelling (4 subjects), and infusion site erythema (2 subjects), infusion site anaesthesia (1 subject), infusion site discomfort (1 subject), infusion site warmth (1 subject) and vessel puncture site swelling (1 subject). At the request of CHMP, the applicant has adequately clarified the incidence of discontinuation in the phase 1 study pool for the group of subjects who received IV dosing of tedizolid phosphate. Most of the subjects who

discontinued due to TEAEs that were related to IV site pain, tenderness, or swelling had received a higher dose (300 mg daily, 2 days up to 6 days) of tedizolid phosphate.

2.6.1. Discussion on clinical safety

Overall, 1488 subjects have been exposed to tedizolid phosphate ≥ 200 mg for at least one dose, out of which 612 have been exposed to 200 mg tedizolid phosphate once daily for ≥ 5 doses which roughly corresponds to the recommended dosage (200 mg once daily for 6 days).

The majority of these patients were, however, only treated orally. With respect to IV dosing, there were 331 patients treated with ≥ 1 IV dose (study TR-701-113). Although, the proposed posology recommendation for the powder for infusion formulation includes a daily IV dose of 200 mg for 6 days the actual number of patients exposed of 5-6 IV doses is limited to only 67 in Phase 3 studies safety pool. To conclude, the overall number of patients exposed to tedizolid phosphate at the recommended dosage is considered sufficient by the CHMP. It is acknowledged that the pharmacokinetic profile of tedizolid is relatively similar between the oral and the IV administration with the exposure (AUC) and Cmax of tedizolid being increased approximately 20% and 30% respectively after IV administration as compared to oral administration.

The most common adverse events associated with tedizolid phosphate in controlled phase 3 studies are nausea (8.2%), headache (6.2%), secondary abscess (5.3%), diarrhoea (3.9%), vomiting (2.9%) and cellulitis (2.6%). The incidence of abscess (5.3% vs. 3.9%) was higher in the tedizolid phosphate group than in the comparator group. Among these adverse events, the related TEAEs in the phase 3 group are nausea, headache, diarrhoea and vomiting. A dose dependent relationship was seen between tedizolid phosphate and nausea incidence. The adverse events occurring in the phase 1 studies with a frequency of ≥ 1% for the tedizolid phosphate group and >1.5 times the incidence in placebo were diarrhoea (6.2%), vessel puncture site reaction (2.5%), oropharyngeal pain (1.8%), pain in extremity (1.6%), and dry mouth (1.4%) and nasal congestion (1.4%).

In the pool of all phase 2/3 studies, a total of 2 (0.2%) deaths were reported in the tedizolid phosphate group compared with 1 (0.2%) deaths in the all comparator groups. All 3 deaths were considered not related to study treatment. The overall incidence of SAEs was low (approx. 2%) and similar between the tedizolid phosphate and linezolid exposed groups. Although, it is noted that a few more cases of infection were seen in the tedizolid phosphate group compared to the linezolid group. A discussion regarding these cases with regard to the underlying disease and why they were classified as serious adverse events was presented together with the narratives for these patients and was considered reassuring by CHMP.

The focus of the summary of safety according to the applicant has been to compare safety of tedizolid phosphate to the marketed oxazolidinone, linezolid, in the intended patient population, patients with cSSTI. Oxazolidinones inhibit bacterial and human mitochondrial protein synthesis. As a result, the use of these, and other antibiotic agents, that inhibit protein synthesis can be associated with adverse effects linked to mitochondrial protein synthesis inhibition such as myelosuppression, peripheral and optic neuropathies, and lactic acidosis.

The overall haematology and serum chemistry results are quite similar for tedizolid phosphate (200 mg/day) and linezolid (1200 mg/day).The incidence of substantially abnormal absolute neutrophil count (ANC), haemoglobin values, and platelet counts in the phase 3 controlled studies group are roughly similar between the tedizolid phosphate and linezolid treatment groups. Although, a slight trend for decreased platelet counts is seen in the linezolid group (4.5% vs 2.1% for tedizolid phosphate). Thus, a warning was included in section 4.4 regarding myelosuppression (see SmPC). The use of tedizolid phosphate is associated with a low incidence of elevated hepatic enzymes ALT, AST and alkaline phosphatase which is similar to what is observed for the comparator linezolid.

A case of related TEAE of *Clostridium difficile* colitis was reported in the tedizolid phosphate group. An adequate warning is included in SmPC section 4.4.

Two studies, TR701-101 and TR701-110, carried out ophthalmic and neurologic examinations to evaluate potential optic and peripheral neuropathy which has been observed for the linezolid after exposure of 21 days. Overall, there was no difference of TEAEs between tedizolid phosphate and linezolid in the performed clinical program with a maximum duration of treatment of 6 days for tedizolid phosphate and 10 days for linezolid. Optic and peripheral neuropathy has mainly been observed in patients treated with linezolid for a longer duration time than the approved duration of 28 days. Peripheral and optic nerve toxicity has been included as an important potential risk in the RMP for tedizolid phosphate which is endorsed. Thus, a relevant precautionary statement in SmPC section 4.4 was included.

Regarding the potential cardiovascular effects, the overall blood pressure and heart rate and ECG results seem quite similar for tedizolid phosphate (200 mg/day) and linezolid (1200 mg/day). The cardiac safety and thorough QTc study TR701-115 evaluated tedizolid phosphate for the potential for QT interval prolongation in healthy subjects indicated no concern.

There are very limited data from drug interaction studies and on the safety of tedizolid when administered to patients with underlying conditions and/or on concomitant medications which might put them at risk from MAO inhibition.

The overall incidence of TEAEs in subpopulations, i.e., age, sex, race, and BMI, and underlying disease characteristics relating to renal function, hepatic function, and diabetes, were analysed. Overall, with respect to TEAEs there were roughly no large differences regarding age groups, between men and women, or between obese and normal/overweight patients and between non-diabetic and diabetic patents. Based on analysis of PK data no dose adjustments or warnings for patients with hepatic impairment or patients with renal impairment or on dialysis are warranted.

2.6.2. Conclusions on the clinical safety

In conclusion, the safety profile of tedizolid administered either at a daily dose of 200 mg for 6 days, by the oral route or IV, daily, is considered acceptable by the CHMP.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 0.3 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 0.4 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Myelosuppression (eg, decreased platelets, decreased haemoglobin, decreased neutrophils) *C. difficile* associated diarrhoea (CDAD)
Important potential risks	Serotonin syndrome Peripheral and optic nerve toxicity Lactic acidosis Emergence of drug-resistance (cross-resistance to linezolid and tedizolid mediated by L3 or L4 ribosomal protein mutations)
Missing information	Experience in pregnant or lactating women Safety profile for prolonged use (>7 days) Treatment of ABSSSI in severely immunocompromised patients (eg, patients with neutropenia, transplant recipients, HIV/AIDS) Treatment of elderly patients, diabetic patients, and patients with acute polymicrobial infections such as major abscesses or traumatic wounds Potential for drug-drug interactions mediated by induction of Cytochrome P450 isoenzyme 3A4 (CYP3A4) or inhibition of Breast Cancer Resistance Protein (BCRP) or organic anion transporting polypeptide (OATP-1B1) Cardiac safety (ie, QT prolongation) in patients with pre-existing cardiovascular risk factors

Pharmacovigilance plan

Study / activity Type, title and category	Objectives	Safety concerns addressed	Status	Date for submission of interim and final reports
Long term treatment (Category 3)	To evaluate the safety of tedizolid phosphate administered as long-term treatment of Gram-positive infections	Long term safety and potential for myelosuppression, neuropathy, or optic nerve toxicity.	Planned	Planned for 2018
In vitro surveillance study (Category 3)	To evaluate the potential for emergence of drug resistance in clinical Gram-positive isolates	Monitor cross-resistance to linezolid and tedizolid mediated by L3 or L4 ribosomal protein mutations or *cfr* gene	Planned	Annually for 5 years (2016-2020)
Drug-drug interaction study (Category 3)	Drug-drug interaction study in healthy volunteers administered midazolam with oral tedizolid at steady state	Potential for drug-drug interaction mediated by induction of CYP3A4	Planned	Final report planned 1Q 2016

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Myelosuppression (eg, decreased platelets, decreased haemoglobin, decreased neutrophils)	Section 4.2 (Posology): The recommended dosage is 200 mg once daily for 6 days. The safety and efficacy of tedizolid phosphate when administered for periods longer than 6 days have not been established. Section 4.4 of the SmPC states: Decreased platelets, decreased haemoglobin and decreased neutrophils have been observed in a few subjects during treatment with tedizolid phosphate. In cases where tedizolid was discontinued, the affected haematological parameters have returned back to pre-treatment levels.	None

	Myelosuppression (including anaemia, leucopenia, pancytopenia and thrombocytopenia) has been reported in patients treated with another member of the oxazolidinone class and the risk of these effects appeared to be related to the duration of treatment.	
C. difficile associated diarrhoea	Section 4.4 of the SmPC and patient information leaflet will include warnings regarding the risk of CDAD during and following antibiotic therapy. Section 4.8 of the SmPC includes diarrhoea as an undesirable effect.	None
Serotonin syndrome	As there is no in vivo evidence of serotonin syndrome or other forms of interaction with MAO from completed studies with tedizolid phosphate it is proposed that the following warnings be included in Section 4.4 of the SmPC. <u>Serotonin syndrome</u> Spontaneous reports of serotonin syndrome associated with the co-administration of another member of the oxazolidinone class together with serotonergic agents have been reported. There is no Phase 3 clinical experience in patients with co-administration of Sivextro with serotonergic agents such as selective serotonin re-uptake inhibitors [SSRI], serotonin norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants, MAO inhibitors, triptans, and other medications with potential adrenergic or serotonergic activity. Section 4.5 of the SmPC includes the statement below. Tedizolid is a reversible inhibitor of monoamine oxidase (MAO) *in vitro;* however, no interaction is anticipated when comparing the IC_{50} for MAO-A inhibition and the anticipated plasma exposures in man. Drug interaction studies to determine effects of 200 mg oral Sivextro at steady state on pseudoephedrine and tyramine pressor effects were conducted. No meaningful changes in blood pressure, heart rate with pseudoephedrine, and no clinically relevant increase in tyramine sensitivity were observed. The potential for serotonergic interactions has not been studied in either patients or healthy volunteers. Section 5.2 of the SmPC includes the statement below. Serotonergic effects at doses of tedizolid phosphate up to 30-fold above the human equivalent dose did not differ from vehicle control in a mouse model that predicts brain serotonergic activity. There are limited data in patients on the interaction between serotonergic agents and tedizolid phosphate. In Phase 3 studies, subjects taking serotonergic agents including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and serotonin 5 hydroxytryptamine (5-HT1) receptor agonists (triptans), meperidine, or buspirone were excluded.	None
Lactic acidosis Peripheral and optic neuropathy Prolonged treatment >7 days	The SmPC (Section 4.2) outlines that the recommended dose is 200 mg once daily for 6 days. The safety and efficacy of tedizolid phosphate when administered for periods longer than 6 days have not been established. Section 4.4 of the SmPC warnings include: Mitochondrial dysfunction Tedizolid inhibits mitochondrial protein synthesis. Adverse reactions such as lactic acidosis, anaemia and neuropathy (optic and peripheral) may occur as a result of this inhibition. These events have been observed with another member of the oxazolidinone class when administered over a duration exceeding that recommended for Sivextro. Peripheral neuropathy and optic nerve disorders Peripheral neuropathy, as well as optic neuropathy sometimes progressing to loss of vision, have been reported in patients treated with another member of the oxazolidinone class with treatment durations exceeding that recommended for Sivextro. Neuropathy (optic and peripheral) has not been reported in patients treated with tedizolid phosphate at the recommended treatment duration of 6 days. All patients should be advised to report symptoms of visual impairment, such as changes in visual acuity, changes in colour vision, blurred vision, or visual field defect. In such cases, prompt evaluation is recommended with referral to an ophthalmologist as necessary. Lactic acidosis Lactic acidosis has been reported with the use of another member of the oxazolidinone class. Lactic acidosis has not been reported in patients treated with tedizolid phosphate at the recommended treatment duration of 6 days.	None
Emergence of drug-resistance (cross-resistance to linezolid)	Section 4.4 of the SmPC includes the statement below. Non-susceptible microorganisms Prescribing tedizolid phosphate in the absence of a proven or strongly suspected bacterial infection increases the risk of the development of drug-resistant bacteria. Tedizolid phosphate is generally not active against Gram-negative bacteria (see section 5.1).	None

	In addition, section 5.1 of the SmPC contains the following information: The most commonly observed mutations in staphylococci and enterococci that result in oxazolidinone resistance are in one or more copies of the 23S rRNA genes (G2576U and T2500A). Organisms resistant to oxazolidinones via mutations in chromosomal genes encoding 23S rRNA or ribosomal proteins (L3 and L4) are generally cross-resistant to tedizolid. A second resistance mechanism is encoded by a plasmid-borne and transposon associated chloramphenicol-florfenicol resistance (cfr) gene, conferring resistance in staphylococci and enterococci to oxazolidinones, phenicols, lincosamides, pleuromutilins, streptogramin A and 16-membered macrolides. Due to a hydroxymethyl group in the C5 position, tedizolid retains activity against strains of Staphylococcus aureus that express the cfr gene in the absence of chromosomal mutations The mechanism of action is different from that of non-oxazolidinone class antibacterial medicinal products; therefore, cross-resistance between tedizolid and other classes of antibacterial medicinal products is unlikely.	
Pregnant or lactating women	The SmPC includes the following advice in Section 4.6: There are no data from the use of tedizolid phosphate in pregnant women. Studies in mice and rats showed developmental effects. As a precautionary measure, it is preferable to avoid the use of Sivextro during pregnancy. A decision must be made as to whether to discontinue breast-feeding or to discontinue/abstain from Sivextro therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Additional information for the prescriber on the studies in mice and rats that showed developmental effects is also provided in section 5.3 of the SmPC.	None
Treatment of ABSSSI in severely immunocompromised patients (eg, patients with neutropenia, transplant recipients, HIV/AIDS)	Section 4.4 of the SmPC states: Patients with neutropenia The safety and efficacy of tedizolid phosphate in patients with neutropenia (neutrophil counts <1000 cells/mm3) have not been investigated. In an animal model of infection, the antibacterial activity of tedizolid phosphate was reduced in the absence of granulocytes. The clinical relevance of this finding is unknown. Alternative therapies should be considered when treating patients with neutropenia and ABSSSI (see section 5.1). Limitations of the Clinical Data: Controlled clinical trials did not include patients with neutropenia (neutrophil counts <1000 cells/mm3) or severely immunocompromised patients.	None
Treatment of ABSSSIs in patient populations/conditions that were under-represented in pivotal studies (eg, elderly patients, diabetic patients, patients with polymicrobial infections)	Section 4.2 of the SmPC includes the statement below. The clinical experience in patients ≥75 years is limited. Section 4.4 of the SmPC includes the statement below. Limitations of the Clinical Data: The safety and efficacy of tedizolid phosphate when administered for periods longer than 6 days have not been established. In ABSSSI, the types of infections treated were confined to cellulitis/erysipelas or major cutaneous abscesses, and wound infections only. Other types of skin infections have not been studied. There is limited experience with tedizolid phosphate in the treatment of patients with concomitant acute bacterial skin and skin structure infections and secondary bacteremia and no experience in the treatment of ABSSSI with severe sepsis or septic shock.c	None.
Drug-drug interactions mediated by induction of CYP3A4 or inhibition of BCRP or OATP-1B1	Section 4.5 of the SmPC for oral tedizolid phosphate includes the statement below. Based on in vitro results, there is a risk for enzyme induction by tedizolid phosphate. This may result in reduced efficacy of co-administered medicinal products that are narrow substrates of CYP3A4 (such as oral midazolam, triazolam, alfentanil, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus), CYP2B6 (efavirenz), CYP2C9 (warfarin), and P-gp (digoxin). The enzyme induction by tedizolid phosphate may also reduce the efficacy of oral hormonal contraceptives (see section 4.4). This is not a complete list; please consult the SmPC of the co-administered medicinal product. There is a potential for interaction between oral tedizolid phosphate and orally administered substrates of Breast Cancer Resistance Protein (BCRP). The BCRP inhibition could result in increased exposure of medicinal products such as imatinib, lapatinib, methotrexate, pitavastatin, rosuvastatin, sulfasalazine, and topotecan (see section 5.2). If possible, an intermission of the co-administered medicinal product should be considered during the six days of treatment with tedizolid phosphate.	None.

	There is a potential for tedizolid phosphate to inhibit organic anion transporter (OATP1B1) based on in vitro data. The in vivo relevance is unknown. The OATP1B1 inhibition could result in increased exposure of medicinal products such as statins (atorvastatin, fluvastatin, pitavastatin, and lovastatin), repaglinide, bosentan, valsartan, olmesartan, and glyburide. If possible, an intermission of the co-administered medicinal product should be considered during the six days of treatment with tedizolid phosphate. Section 5.2 of the SmPC includes the statements below. Drug metabolizing enzymes In vitro studies in human liver microsomes indicate that tedizolid phosphate and tedizolid do not significantly inhibit metabolism mediated by any of the following cytochrome P450 isoenzymes (CYP1A2, CYP2C19, CYP2A6, CYP2C8, CYP2C9, CYP2D6, and CYP3A4). Induction of CYP3A4 mRNA was observed in vitro in hepatocytes (see section 4.5). Membrane transporters The potential for tedizolid or tedizolid phosphate to inhibit transport of probe substrates of important drug uptake (OAT1, OAT3, OATP1B3, OCT1, and OCT2) and efflux transporters (P-gp and BCRP) was tested in vitro. No consistent inhibition of any transporter was observed with the exception of BCRP, which was inhibited by tedizolid. Tedizolid inhibited OATP-1B1 by ~30% at 30 µM.	
Cardiac safety (ie, QT prolongation) in patients with pre-existing cardiovascular risk factors	There is no evidence from in vitro, animal, or thorough QT human clinical studies to suggest a risk for QT prolongation with tedizolid phosphate. However, data are limited to assess the cardiac safety of tedizolid in patients with pre-existing cardiovascular conditions. This item has been added to the list of safety concerns as "missing information". Therefore, routine risk minimisation measures are not applicable.	None

Minor points to be addressed in the next RMP update:

- Sections V.3 and V.1.4 should be shortened by summarising the routine risk minimisation activities in the form of SmPC recommendations, as per the *Guideline on Good Pharmacovigilance Practices, Module V*.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Tedizolid is a novel antibiotic belonging to the oxazolidinone class. Oxazolidinones are protein synthesis inhibitors that interact with the bacterial ribosome and prevent translation. The *in vitro* activity of tedizolid was largely bacteriostatic against the evaluated Gram-positive pathogens. The spectrum of activity includes mainly Gram-positive species, in particular those that are common aetiological agents of ABSSSI and overlaps with that of linezolid, including with regard to important resistance phenotypes associated with the target pathogens, such as MRSA. Of note, there was no cross-resistance observed with linezolid-resistant *cfr* positive *S. aureus*.

The clinical efficacy of tedizolid phosphate in ABSSSI has been evaluated in two phase 3 randomised controlled studies (TR701-112 and TR701-113) and in two supportive phase 2 studies (TR701-104 and TR701-126) that

recruited a total of 1725 patients (1056 and 669 to receive tedizolid phosphate or linezolid, respectively). The populations for the two phase 3 studies were similar. Patients were required to have cellulitis/erysipelas, major cutaneous abscess or wound infection with a minimum total lesion surface area of 75 cm^2 and at least one regional or systemic sign of infection. Oral (study TR701-112) and IV to oral (study TR701-113) tedizolid phosphate 200 mg once daily for 6 days was compared with linezolid 600 mg twice daily for 10 days. Patients required IV antibiotic therapy for a minimum of one IV dose of tedizolid phosphate or two doses of linezolid before an oral switch could be made.

Non-inferiority of tedizolid phosphate compared to linezolid was shown for the co-primary endpoints, clinical success at PTE in the ITT and the CE-PTE populations (study TR701-112, ITT: 85.6% vs. 86.6% and CE-PTE: 95.9% vs. 98.8%; study TR701-113, ITT: 88.0% vs. 87.7% and 92.4% vs. 96.1%). The lower limits of the 95% CIs were within the pre-defined non-inferiority margin of -10%. Secondary outcomes at 48-72 h, day 7 visit and EOT visit were in line with the outcomes at PTE in both studies.

The most commonly isolated pathogen in the pivotal studies was *S. aureus*, of which approximately 40% consisted of MRSA, followed by *S. pyogenes* and species belonging to the *S. anginosus-milleri* group. The microbiological response by pathogen showed overall similar response rates for tedizolid phosphate and linezolid.

The clinical response rate in the non-comparative phase 2 studies was similar to that from the pivotal trials and thus in support of the shown beneficial effect.

The following additional features may be considered as potential benefits for the product:

- The shorter duration of treatment with tedizolid phosphate may decrease the risk for the occurrence of the well-known class-related adverse reactions, mainly of the bone marrow suppression.
- The availability of the IV and PO tedizolid is an additional favourable feature, considering the very similar systemic exposures obtained with either of the two routes of administration.

Uncertainty in the knowledge about the beneficial effects.

The majority of the infections included in the two pivotal studies did not tend to be severe, and the existence of signs and/or symptoms of systemic involvement was not required, provided signs of regional infection were present at screening. CHMP requested the applicant to further present and discuss the clinical response data with respect to all possible evaluable severity criteria (e.g. lesion size, number of systemic signs of infection, SIRS criteria etc.) to assure that the efficacy of tedizolid phosphate is sufficient in more severe infections. The applicant provided tabulated clinical response data with respect to a number of severity criteria except number of systemic signs of infection and different levels of CRP, which were not collected. Despite the mentioned limitations, CHMP considered that the provided data were adequate and were supporting the conclusion that tedizolid phosphate is also effective in more severe infections. The number of patients with concomitant bacteraemia was low and this is adequately reflected in the SmPC.

In response to the CHMP concerns regarding the number of doses administered to patients in the linezolid arm, the applicant provided supplementary data, which were reassuring of the fact that the majority of patients received all the planned doses of tedizolid phosphate and linezolid (one daily dose for 6 days and two daily doses for 10 days, respectively) and that the mean number of active doses received were close the planned number of doses.

The outcomes in the performed subgroup analyses of the pooled clinical data were generally comparable between tedizolid phosphate and linezolid. However, a numerically lower response in the tedizolid phosphate group compared to the linezolid one was seen in patients with higher BMI, in patients with diabetes, and in patients with major cutaneous abscess. This relative lack of data has been adequately addressed in the SmPC.

The AUC/MIC ratio to achieve stasis in neutropenic mice was at least 16 times that of immunocompetent animals. An extrapolation of animal model data to humans raises concerns that a 200 mg once daily dose of tedizolid phosphate would be too low to achieve the target attainment in a large number of neutropenic patients, provided that the PK was the same as in immunocompetent patients. CHMP therefore decided to request the applicant to include adequate information on the lack of data in neutropenic patients. This has been added by the applicant in section 4.4 of the SmPC.

Risks

Unfavourable effects

The most frequent unfavorable effects associated with tedizolid phosphate are nausea (6.9%), headache (3.5%), diarrhea (3.2%) and vomiting (2.3%), which occurred during the treatment time (between day 0 and day 6). The overall discontinuation rate in the tedizolid phosphate group in phase 3 studies was very low (0.5%), and mostly concerned the GI SOC. This is not unexpected, considering the fact that tedizolid is an oxazolidinone and that the majority of the subjects were treated orally.

The most important unfavorable effect associated with tedizolid phosphate is myelosuppression. Six patients receiving tedizolid phosphate (6/1050=0.6%) in phase 2 and phase 3 studies had at least one value that was over than or equal to two toxicity grades higher than baseline or a grade 4 value for hemoglobin, 8 for platelet counts (8/1050=0.8%) and 7 for absolute neutrophil count, ANC, (7/1050=0.7%). The applicant stated that in the phase 3 controlled studies group, decreases of more than or equal to 2 toxicity grades from baseline were noted in 65/583 (11.1%) of the TR-701 FA patients and in 45/581 (7.7%) of linezolid patients. A warning regarding myelosuppression was included in section 4.4 of the Sivextro SmPC. The use of tedizolid phosphate is associated with a low incidence of elevated hepatic enzymes ALT, AST and alkaline phosphatase. A case of related TEAE of *Clostridium difficile* colitis was reported in the tedizolid phosphate group. An adequate warning is included in SmPC section 4.4.

Uncertainty in the knowledge about the unfavourable effects

Oxazolidinones inhibit bacterial and human mitochondrial protein synthesis. As a result, the use of these and other antibiotic agents that inhibit protein synthesis can be associated with adverse effects linked to mitochondrial protein synthesis inhibition such as myelosuppression, peripheral and optic neuropathies, and

lactic acidosis. Two studies, TR701-101 and TR701-110, carried out ophthalmic and neurologic examinations to evaluate potential optic and peripheral neuropathy.

Overall, there was no difference of TEAEs between tedizolid phosphate and linezolid in the performed clinical program, with a maximum duration of treatment of 6 days for tedizolid phosphate and 10 days for linezolid. Optic and peripheral neuropathy has mainly been observed in patients treated with linezolid for a longer duration time than the approved duration of 28 days. Peripheral and optic nerve toxicity has been included as an important potential risk in the RMP for tedizolid phosphate which is endorsed. Thus, a relevant precautionary warning was required by the CHMP and was included by the applicant in section 4.4 of the SmPC.

Tedizolid phosphate is a weak nonselective reversible monoaminooxidase (MAO) inhibitor when assayed *in vitro* with endogenous or expressed human MAO-A or MAO-B. A potential peripheral inhibition of MAO-A cannot be excluded. The use of certain medications (selective serotonin re-uptake inhibitors [SSRI], serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, MAOI, triptans, and other medications with potential adrenergic or serotonergic activity) was prohibited in the protocols of the performed trials. Very limited data are therefore available from the performed drug interaction studies on the safety of tedizolid when administered to patients with underlying conditions and/or on concomitant medications which might put them at risk of a MAO inhibition. Corresponding statements in SmPC sections 4.4 and 4.5 were therefore requested by the CHMP and were included by the applicant.

Benefit-risk balance

Importance of favourable and unfavourable effects

A number of antimicrobial agents are available for the treatment of cSSTI/ABSSSI. Because of the worldwide increase of antimicrobial resistance in general and of the increase in the methicillin resistant strains of *S. aureus* in particular(relevant for ABSSSI), there is a need for new antibacterial agents, especially for those available as an oral formulation. Tedizolid phosphate represents an alternative treatment option against ABSSSI and is available in both oral and IV formulation, allowing an IV-to-oral switch treatment scheme possible without the need of a change in the antibiotic and/or dose. The spectrum of activity of tedizolid phosphate generally overlaps with that of linezolid, with the noteworthy potential advantage of maintained *in vitro* efficacy against linezolid-resistant *cfr*+ S. aureus. The observed safety profile of tedizolid phosphate was similar to that of the comparator linezolid.

Discussion on the benefit-risk balance

The CHMP agreed that the antimicrobial effect of tedizolid phosphate in the claimed indication has been adequately demonstrated. This is supported by preclinical data, PK/PD considerations, as well as the outcome of the pivotal studies.

Based on the applicant's responses during the procedure (e.g. the submission of tabulated clinical response data with respect to a number of severity criteria), CHMP agreed that the data provided by the applicant were sufficiently supportive of the fact that tedizolid phosphate is also effective in more severe ABSSSIs. CHMP noted nevertheless the low number of patients with concomitant bacteraemia in the pivotal trials and requested that this is adequately described in the SmPC.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Sivextro in the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults, is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that tedizolid phosphate is qualified as a new active substance.