17 October 2019
EMA/CHMP/471386/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Quofenix

International non-proprietary name: delafloxacin

Procedure No. EMEA/H/C/004860/0000

Note

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

Table of contents

List of abbreviations

ABSSSI	Acute bacterial skin and skin structure infection
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AECB	Acute exacerbation of chronic bronchitis
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AUC	Area under the concentration-time curve
AUC_{0-12}	Area under the mean concentration-time curve from time 0 to 12 hours
AUC_{0-24}	Area under the mean concentration-time curve from time 0 to 24 hours
$AUC_{0-\infty}$	Area under the mean concentration-time curve from time 0 to infinity
AUC_{0-t}	Area under the mean concentration-time curve to the last observable concentration at time t
BA	Bioavailability
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BP	British Pharmacopoeia
BID	twice daily
BMI	Body mass index
CAP	Community-acquired pneumonia
CE	Clinically evaluable
CFU	Colony forming units
CI	Confidence interval
CL_{cr}	Creatinine clearance
CL_d	Dialysate clearance
CL_{nr}	Non-renal clearance
CL_r	Renal clearance
CL_u/F	Apparent urinary clearance
C_{max}	Maximum (peak) mean plasma drug concentration
C_{min}	Minimum (trough) mean plasma drug concentration
C_{trough}	Trough plasma concentration
CNS	Central nervous system
CQA	Critical Quality Attribute
CSR	Clinical Study Report
cSSTI	Complicated skin and soft tissue infections
cSSSI	Complicated skin and skin-structure infections
CV	Coefficient of variation
DDI	Drug-drug interaction
ECDC	European Centre for Disease Prevention and Control
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	End of treatment
ESRD	End-stage renal disease
EUCAST	European Committee on Antimicrobial Susceptibility Testing
$fAUC_{24}/MIC$	Ratio of free delafloxacin area under the mean concentration-time curve from

	time 0-24 hours to pathogen minimum inhibitory concentration
Frem%	Mean fraction of administered delafloxacin dose recovered in the dialysate
FT-IR	Fourrier Transform Infrared Spectroscopy
FU	Follow-up visit
GC	Gas Chromatography
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
h	hour/hours
HAI	Healthcare-acquired infections
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
IC	Ion chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
IIV	Inter-individual variability
IR	Infrared
ITT	Intent-to-treat
IV	Intravenous
LDPE	Low density polyethylene
LFU	Late follow-up
LS	Least squares
MAA	Marketing authorisation application
MCS	Monte Carlo simulation
ME	Microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
MITT	Microbiological ITT
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
MTD	Maximum tolerated dose
NOAEL	No observed adverse effect level
NMR	Nuclear Magnetic Resonance
NMT	Not more than
PAE	Post-antibiotic effect
PA-SME	Post-antibiotic sub MIC effect
PD	Pharmacodynamics
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PO	Per os, oral use
PopPK	Population PK
PTA	Probability of target attainment
PTE	Post-treatment Evaluation according to CSR EMA SAP
PTE7-14	Post-treatment Evaluation within a window of 7-14 days after End of Treatment
PTE6-15	Post-treatment Evaluation within a window of 6-15 days after End of Treatment
Q12h	Every 12 hours

Q24h	Every 24 hours
QC	Quality control
QD	Once daily
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia's correction
SAE	Serious adverse event
SAP	Statistical analysis plan
SBECD	Sulfobutyl ether-ß-cyclodextrin
SCE	Summary of Clinical Efficacy
SD	Standard deviation
SME	Sub MIC Effect
SmPC	Summary of Product Characteristics
SOC	System organ class
$t_{1/2}$	Elimination half-life
TEAE	Treatment-emergent adverse event
TK	Toxicokinetics
T_{max}	Time at which C_{max} was apparent
TOC	Test of cure
TPGS	tocopheryl polyethylene glycol 1000 succinate
UGT	Uridine diphosphate glucuronosyltransferase
ULN	Upper limit of normal
UV	Ultraviolet
VIS	Visible
V_{ss}	Volume of distribution at steady state
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant A. Menarini Industrie Farmaceutiche Riunite s.r.l. submitted on 6 March 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Quofenix, 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 22 June 2017.

The applicant applied for the following indication:

Quofenix is indicated for the treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI) in adults (see section 5.1).

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

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

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 P/0148/2018 on the granting of a (product-specific) waiver.

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.

Applicant's request for consideration

New active Substance status

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

Scientific advice

The applicant received Scientific Advice from the CHMP on 24 May 2012

(EMA/CHMP/SAWP/288884/2012). The scientific advice pertained to the following quality, non-clinical and clinical aspects:

- Starting materials, excipients, in process controls, stability and specifications.
- The adequacy of the vitro studies to assess the potential for clinically meaningful drug-drug interactions with delafloxacin.
- The preclinical program to investigate local toxicity, phototoxicity and potential for arthropathy.
- The phase 3 study, more specifically the:
    - Definition of cSSTI (inclusion criteria)
    - Choice of vancomycin as comparative agent
    - Not utilising an independent monitoring committee
    - The primary endpoint
    - The non-inferiority margin and the superiority testing provided non-inferiority is demonstrated
    - The co-administration of aztreonam (AZ) to cover Gram-negative infections
    - The submission on a single pivotal trial if superiority is demonstrated
- The proposal to conduct a second phase 3 study, to support MAA, if the single pivotal meets the non-inferiority criteria but does not show superiority
- The use of linezolid, IV +/- oral as comparator in the second Phase III study
- The development of an oral delafloxacin formulation and its use in the IV to oral switch phase III study

1.2. Steps taken for the assessment of the product

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

Rapporteur: Janet Koenig   Co-Rapporteur: Alar Irs

The application was received by the EMA on	6 March 2018
The procedure started on	24 May 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	13 August 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	21 August 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	28 August 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	20 September 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	28 March 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	06 May 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 May 2019
The CHMP agreed on a list of outstanding issues in writing to be sent to	29 May 2019

the applicant on	
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 August 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	05 September 2019
The CHMP agreed on a list of 2nd outstanding issues in writing to be sent to the applicant on	19 September 2019
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 Quofenix on	17 October 2019

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Acute Bacterial Skin and Skin Structure Infections (ABSSSI) are among the most common human bacterial infections and include cellulitis, erysipelas, wound infections (traumatic or post-surgical) and major abscesses. Cellulitis and abscesses are commonly encountered in the community setting and frequently result in hospitalisation. ABSSSI such as surgical site infections and burn infections are also seen in the hospital setting. Both erysipelas and cellulitis are characterised by rapidly spreading areas of oedema, redness, and heat, sometimes accompanied by lymphangitis and enlargement of the regional lymph nodes. ABSSSI are a common indication for antibiotic use in Europe and are associated with considerable morbidity. Data from the European Centre for Disease Prevention and Control (ECDC) estimated that 4% of all healthcare-acquired infections (HAI) reported between 2011 and 2012 were ABSSSI, with surgical-site infections being the second most frequently reported HAI (19.6%) (ECDC, Surveillance report 2011–2012).

Management of ABSSSI is dependent on the clinical presentation and the severity of the infection. Initial treatment of ABSSSI is usually empirical because culture results are not immediately available, and patients with ABSSSI benefit from rapid initiation of appropriate therapy (Clinical guideline (CG74), NICE 2014). Most streptococci remain susceptible to penicillin and β-lactam antibiotics, providing many treatment options for adults when culture results are known. Infections due to MRSA are more complex in terms of management in hospital because of the additional steps that must be implemented for their treatment (e.g. decolonisation, protective clothing for nurses, isolation units, more expensive antibiotics, frequent laboratory tests, or blood cultures).

When MRSA is identified as a single pathogen, a number of treatment options are available in Europe, including vancomycin, daptomycin, linezolid, tigecycline, tedizolid, oritavancin, dalbavancin, and ceftaroline. Agents like vancomycin, linezolid, and daptomycin have been available for some time. However, these older agents, along with many of the drugs more recently approved for ABSSSI, provide only Gram-positive coverage. In particular, linezolid is one of the most used agents for an empirical starting of the treatment due to its activity against aerobic and anaerobic Gram-positive organisms.

Ceftaroline and tigecycline are active against Gram-negative organisms but are only available in an IV formulation. Cephalosporins, carbapenems (meropenem, imipenem), and ureido-penicillins (such as piperacillin), aminoglycosides, or quinolone antibacterials can be used to provide Gram-negative coverage in these situations, as well. In cases where MRSA and Gram-negative organisms are isolated, these agents can be added to MRSA active agents. Among the fluoroquinolone class, levofloxacin, ofloxacin and moxifloxacin may be indicated for complicated Skin and Soft Structure Infections (cSSSI) with some limitations, on the basis of the high rate of MRSA resistant to both levofloxacin and ofloxacin and the known safety profile of fluoroquinolones. It should be considered that in the EU moxifloxacin and levofloxacin are currently only approved as last line indication cSSTI due to safety concerns. Furthermore, the originator of ofloxacin adapted the PI regarding the indication cSSTI (last line) to be in line with the approved indications of levofloxacin.

Delafloxacin possesses both Gram-positive / MRSA and Gram-negative activity and a potential improved safety profile in respect to the other fluoroquinolones. It offers the flexibility of both IV and oral treatment of ABSSSI, with a considerable reduction of hospitalisation costs and related risks and does not require therapeutic drug monitoring. These factors support the addition of delafloxacin to the ABSSSI armamentarium.

The most common bacteria identified in ABSSSI are Gram-positive pathogens, including streptococci and staphylococci. In Europe, the most frequently isolated Gram-positive ABSSSI pathogen is S. aureus (including methicillin-resistant S. aureus (MRSA) and methicillin-susceptible S. aureus (MSSA)), followed by β-haemolytic streptococci. The prevalence of MRSA has increased worldwide in both healthcare- and community-based settings. In Europe, the prevalence of MRSA varies greatly across countries, with much higher frequencies seen in southern and south-eastern countries. Based on the European Antimicrobial Resistance Surveillance Network (EARS-Net), the European population-weighted mean percentage for MRSA was 13.7% in 2016, ranging from 1.2% in the Netherlands to 50.5% in Romania (ECDC, Surveillance of antimicrobial resistance in Europe, 2016).

In particular, in patients with comorbidities and those previously treated with antibiotics, ABSSSI can often be polymicrobial, with Gram-negative and obligate anaerobic pathogens found together with Gram-positive organisms. Gram-negative aetiology is common in surgical-site infections setting as reported in the SENTRY programme (1998 – 2004), with *P. aeruginosa* being the second most important pathogen after MRSA, followed by *E. coli*.

Drug-resistant bacteria are playing an increasing role as causative pathogens in ABSSSI.

P. aeruginosa, *Acinetobacter* species and vancomycin-resistant *Enterococcus* spp. can play an important role in polymicrobial long-standing infections such as diabetic foot infection and decubiti, but are also increasingly recognised in monomicrobial ABSSSI. The presence of MRSA in surgical site infections is independently associated with mortality compared with patients with MSSA.

2.1.2. About the product

Delafloxacin N-methylglucamine salt (delafloxacin meglumine) hereafter referred to as delafloxacin is an anionic fluoroquinolone with broad-spectrum activity including Gram-positive and Gram-negative bacteria. It binds to both DNA gyrase and topoisomerase IV thereby preventing bacterial DNA replication and transcription. Unlike other fluoroquinolones it is anionic at physiological pH and uncharged at acidic pH ($\leq$ 5.5). As the non-ionised form of a drug better penetrates through biological membranes, delafloxacin accumulates particularly in bacteria in acidic environments such as infection sites thereby improving its potency.

2.2. Quality aspects

2.2.1. Introduction: Powder for concentrate for solution for infusion

The finished product is presented as powder for concentrate for solution for infusion containing delafloxacin meglumine equivalent to 300 mg of delafloxacin.

Other ingredients are: meglumine, sulfobutylbetadex sodium, disodium edetate, sodium hydroxide (for pH-adjustment) and hydrochloric acid (for pH-adjustment).

The product is available in 20 ml clear type I glass vials outfitted with 20 mm type I rubber stoppers and 20 mm flip-off caps.

2.2.2. Introduction: Tablets

The finished product is presented as tablets containing delafloxacin meglumine equivalent to 450 mg delafloxacin.

Other ingredients are: microcrystalline cellulose, povidone; crospovidone; sodium hydrogen carbonate; sodium dihydrogen phosphate monohydrate; citric acid and magnesium stearate.

The product is available in laminated aluminium / aluminium foil blisters perforated unit dose blister packs.

2.2.3. Active substance

General information

The chemical name of delafloxacin meglumine is (D-glucitol, 1-deoxy-1-(methylamino)-, 1-(6-amino-3,5-difluoro-2-pyridinyl)-8-chloro-6-fluoro-1,4-dihydro-7-(3-hydroxy-1-azetidinyl)-4-oxo-3 quinolinecarboxylate) corresponding to the molecular formula $C_{18}H_{12}ClF_3N_4O_4.C_7H_{17}NO_5$. It has a relative molecular mass of 635.97 Da g/mol and the following structure:
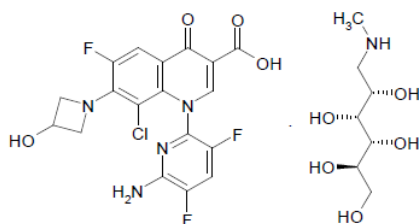
Figure 1: active substance structure

The chemical structure of delafloxacin meglumine was elucidated by a combination of IR, UV-VIS, ^{1}H-NMR, ^{13}C-NMR and ^{19}F-NMR spectroscopy and mass spectrometry. Information on molar absorptivity has also been provided.

The delafloxacin meglumine is a crystalline white to tan powder, it belongs to BCS Class 4, has pH dependent solubility in aqueous media and is hygroscopic in nature. The aqueous solubility of delafloxacin meglumine increases with pH (from < 0.10 mg/mL to 32 mg/mL at pH values ≤ 6 and pH 9, respectively). The solubility of delafloxacin meglumine in most organic solvents is low (< 3 mg/mL in acetone,

acetonitrile, 1-butanol, dichloromethane, isopropyl alcohol, ethyl acetate). Higher solubility was measured for the compound in methanol (6 mg/mL).

The acid component (delafloxacin) has no chiral centres. The base component (*N*-methylglucamine = meglumine) exhibits stereoisomerism due to the presence of four chiral centres.

Polymorphism has been observed for delafloxacin meglumine. A stable form 1A, a metastable form 1B and a trihydrate have been observed. Form 1A is a variable hemihydrate, which is kinetically stable over a wide relative humidity range and only converting to the trihydrate at very high relative humidity (> 90%).

Manufacture, characterisation and process controls

Delafloxacin meglumine is synthesized in five main steps using well-defined starting materials with acceptable specifications.

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

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 have been adequately discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in in double low density polyethylene (LDPE) bags sealed and placed inside a high density polyethylene (HDPE) drum and secured with a HDPE pail cover. The LDPE bags are manufactured from granules complying with Ph. Eur. 3.1.4 and the food contact EC directive (EU 10/2011).

Specification

The active substance specification shown in Table 1 includes tests for appearance, identity (FT-IR), identification of delafloxacin (HPLC), identification of *N*-methylglucamine (ion chromatography, IC), assay (HPLC), *N*-methylglucamine content (IC), impurities (HPLC), water content (Ph. Eur.), residual solvents (GC), residue on ignition (Ph. Eur), particle size (light scattering), microbial purity (Ph. Eur.), and bacterial endotoxin (Ph. Eur.).

The limits set two specified identified impurities have been tightened in line with batch and stability data. The applicant is recommended to re-evaluate the limit of one impurity as soon as additional batch data will become available. The omission of the test for polymorphic form 1A from the specifications is justified based on the presence of the IPC during the manufacturing process and the provision of stability data.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. However, the applicant is recommended to develop and validate an improved method for assessing the microbiological purity of the active substance and the powder for concentrate for solution for infusion Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on 14 batches of active substance, of which 4 were manufactured at commercial scale, were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three pilot-scale and three commercial-scale batches of active substance manufactured by the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 36 months (pilot batches) and 24 months (commercial batches) under long term conditions (25 ºC / 60% RH) and for up to six months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The parameters tested were appearance, water content, assay, related substances, particle size, polymorphic form and microbial testing. The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications. Only minimal degradation was observed under accelerated conditions.

Photostability testing following the ICH guideline Q1B was performed on one batch. Minor photolytic degradation was observed with light exposure in an open container. No photolytic degradation was observed when the active substance was packaged in the representative container. Results under stressed conditions (heat, heat with humidity and exposure to oxygen) were also provided on one batch and confirm that delafloxacin meglumine in the solid state is stable under stressed conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable when packaged in a light protective container. The stability results justify the proposed retest period of 36 months with the recommendation for storage "Store in the original package, in order to protect from light".

2.2.4. Finished medicinal product: Powder for concentrate for solution for infusion

Description of the product and Pharmaceutical development

Delafloxacin 300 mg powder for concentrate for solution for infusion is a light yellow to tan cake, which may exhibit cracking and shrinkage and slight variation in texture and colour.

Table 1: composition of powder for concentrate for solution for infusion

Component and Quality Standard	Function	Quality
Delafloxacin meglumine (amount as free acid)	Active	In house
Meglumine	Basifying agent	Ph.Eur. (Current) / USP
Betadex Sulfobutyl Ether Sodium	Solubilizer	USP
Disodium edetate	Chelator	Ph.Eur. (Current) / USP
Sodium hydroxide (as 1 N solution in WFI)[a]	pH adjustment	Ph.Eur. (Current) / NF
Hydrochloric acid, concentrated (as 1 N solution in WFI)[b]	pH adjustment	Ph.Eur. (Current) / NF
Nitrogen[c]	Inert gas	Ph.Eur. (Current) / NF

[a] 1N sodium hydroxide solution and / or 1N hydrochloric acid solution may be used if necessary to adjust the final solution pH to 9.0 ± 0.1.
[b] Nitrogen is used as inert gas during filtration, filling and at the end of the lyophilization process.
Abbreviations: USP = United Stated Pharmacopeia NF = National Formulary Ph. Eur. = European Pharmacopeia

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. During the procedure, it has been confirmed that sulfobutylbetadex sodium is compliant with the recently implemented monograph published in version 9.6 of the Ph. Eur., which came into force in July 2019. Throughout the report sulfobutylbetadex sodium is also referred to as sulfobutylether-β-cyclodextrin (SBECD), betadex sulfobutyl ether sodium or Captisol; these names are used interchangeably. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. Compatibility of the active substance with the excipients was confirmed via means of binary studies and stability data.

Prior to administration, the powder is reconstituted with sterile 5% dextrose solution or 0.9% saline solution for a final volume of 12.4 mL, equivalent to the target fill volume in the vial prior to lyophilisation. The target fill volume has been adjusted to allow withdrawal of the labelled amount of active substance. Each 12.0 mL of the reconstituted solution provides a 300 mg dose. The reconstituted solution is further diluted with 5% dextrose solution or 0.9% Saline solution in a 250 mL infusion bag for administration. The variability in appearance has no impact on reconstitution of the powder under the proposed conditions.

There are no accompanying reconstitution diluents with the finished product. The description of reconstitution and dilution process and use of acceptable diluents have been evaluated during the development and are further described and discussed under the finished product stability section.

The formulation used during phase III clinical studies is the same as that intended for marketing. The formulation development has been described in sufficient details.

The development of Delafloxacin 300 mg powder for concentrate for solution for infusion is considered a traditional development program from a Quality by Design perspective. However principles, as described in ICH Q8, were utilised to guide the formulation and manufacturing process development.

The quality target product profile (QTPP) was defined as:

- A dosage form for IV administration as a concentrate for dilution (preferred) or as a lyophilized powder for reconstitution and dilution;
- A shelf life of at least 18 months at room temperature (preferred) or refrigerated conditions;
- Well tolerated formulation;
- Product to be manufactured using a standard and scalable manufacturing process;
- Use of compendially precedented excipients.

The critical quality attributes (CQAs) identified were: appearance of the product before and after reconstitution, appearance of the vial and closure, identification, assay, impurities, uniformity of dosage units, pH of the reconstituted solution, sterility, bacterial endotoxin, particulate matter, water content, reconstitution time and container closure integrity. Adequate argumentation has been provided in support of the fact that osmolarity of the reconstituted solution, extractable volume/container content and polymorphic form are not considered CQAs.

The formulation development has been evaluated through the use of risk assessment to identify the critical material attributes. The risk identification was based on experience from formulation and process development. The critical process parameters have been adequately identified.

The primary packaging is 20 ml clear type I glass vials outfitted with 20 mm type I rubber stoppers and 20 mm flip-off caps. The materials 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, shown in Figure 3 along with the IPCs, consists of five main steps: preparation of bulk solution, sterile filtration, filling and pre-stoppering of vials, lyophilisation, stoppering,

and capping/crimping of vials. The process is considered to be a non-standard manufacturing process (sterile filtration). In response to a major objection raised during the procedure, the applicant has adequately justified the choice of the sterilisation method according to the Ph. Eur. 5.1.1 and the "Decision Trees for the Selection of sterilization Methods" (CPMP/QWP/054/98): both the dry heat and the gamma irradiation terminal sterilisation methods would lead to an unacceptable increase in impurity content and decrease in assay.

The critical manufacturing steps have been identified (pH adjustment prior to active substance addition, complete dissolution of the active substance, bioburden test before second filtration and vial filling). The process is sufficiently controlled by IPCs (test on bulk solution, filter integrity test, and fill weight) and are adequate for a product manufactured by sterile filtration. The suitability of the manufacturing process has been sufficiently demonstrated by process validation data on three consecutive commercial scale batches. The suitability of the aseptic processing has been demonstrated by media fill studies.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The powder for concentrate for solution for infusion release specifications shown in Table 3 include appropriate tests for this kind of dosage form: appearance of the product before and after reconstitution, appearance of the vial and closure, identification (HPLC and UV), assay (HPLC), impurities (HPLC), uniformity of dosage units (Ph. Eur.), pH of the reconstituted solution (Ph. Eur.), bacterial endotoxins, (Ph. Eur.) sterility (Ph. Eur.), particulate matter (Ph. Eur.), water content (Ph. Eur.), and reconstitution time and container closure integrity (in-house method, visual).

The potential presence of elemental impurities in the finished product has been assessed using a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The analysis of the contribution of the finished product components to the elemental impurity levels confirms that all elements of concern that are potentially present in the finished product would be present at levels significantly below the PDE stated in ICHQ3D. Based on the risk assessment, it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for four commercial scale batches and three pilot scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from four pilot scale batches (validation batches) of finished product stored for up to 48 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. ICH stability studies for one commercials-scale batch over 24 months at long-term conditions and 6 months at accelerated conditions have been provided. The batches of Quofenix powder for concentrate for solution for infusion are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested according to the stability specification which includes all the release specification tests. The analytical procedures used are stability indicating. The results meet the specifications and no significant changes or trends in any of the tested parameters were observed. The proposed limits are considered acceptable; however, the applicant is recommended to evaluate tightening the assay limit in the shelf-life specification as soon as additional stability data for commercial scale batches are available

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant trend is also observed in the photostability study.

Based on available stability data, the proposed shelf-life of 48 months and without any particular storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

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

2.2.5. Finished medicinal product: Tablets

Description of the product and Pharmaceutical development

Delafloxacin tablet, 450 mg, is an immediate release, capsule-shaped tablet, of beige to mottled beige colour with RX3341 debossed on one side. The tablets are packaged into unit dose laminated aluminium / aluminium foil blisters.

Table 2: composition of tablets

Component	Function	Reference to Quality Standard
Drug Granulation		
Delafloxacin Meglumine	Drug substance	In-House Standard
Cellulose, Microcrystalline	Filler / manufacturing aid	Ph. Eur. (Current) / NF
Povidone K-30, LP	Binder	Ph. Eur. (Current) / USP
Crospovidone	Disintegrant	Ph. Eur. (Current) / NF
Total Drug Granules		
Extra-Granular / Buffering Blend		
Sodium Hydrogen Carbonate	Base	Ph. Eur.
Sodium Phosphate Monobasic Monohydrate	Buffering agent	BP
Citric Acid anhydrous	Counteragent for base	Ph. Eur. (Current) / USP
Crospovidone	Disintegrant	Ph. Eur. (Current) / NF
Cellulose, Microcrystalline	Filler / manufacturing aid	Ph. Eur. (Current) / NF
Magnesium Stearate	Lubricant	Ph. Eur. (Current) / NF
Nitrogen [1]	Inert gas	Ph. Eur. (Current) / NF
Final Tablet		

(1) Nitrogen is used as inert gas during blistering phase.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards except for sodium phosphate monobasic monohydrate which complies with BP. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.2 of this report. During the review the applicant was requested to update the specification of microcrystalline cellulose and crospovidone with the defined functional characteristics. The specification of microcrystalline cellulose has been integrated with particle size distribution and bulk density. The specification of crospovidone was updated with loss on drying only. The applicant is recommended to evaluate the functional characteristics of crospovidone and update the excipient specification as applicable

The aim of the oral formulation development was to achieve *in vivo* exposure equivalent to that of the 300 mg IV formulation to allow for switching between the two formulations.

Delafloxacin formulations were initially developed by two different companies. For Phase I and Phase II clinical studies, two capsule formulations were developed: 1. Formulation A consisting of active substance only and 2. Formulation B consisting of formulated capsules (wet granulation of delafloxacin meglumide with povidone, pre-gelatinised starch, microcrystalline cellulose, and silicon dioxide). In addition, two prototype tablet formulations (Formulations C and D) were developed for use in a comparative bioavailability study; each tablet contains delafloxacin meglumide, povidone (in formulation C only), crospovidone, microcrystalline cellulose and magnesium stearate. Several other oral formulations (formulations E through J), were developed to be used in the clinical trials together with IV formulation.

The formulation development has been described in sufficient details.

The development of the dissolution method has been described. The dissolution test used for Phase 3 was modified so that the solubility is less than sink conditions with the proposed acceptance criteria. A study has demonstrated that the dissolution rates and discriminatory ability of the two methods are comparable over the entire range of formulation and manufacturing variables explored; hence, methods are comparable at all time points tested. Data generated on tablet alterations that would potentially produce slower dissolution profiles (i.e. reducing the amount of disintegrant in both the intra-granular and extra-granular portions of the tablet blend, increasing the amount of magnesium stearate and the wet-massing time of the granulation, and compressing the tablets to different hardness values), confirmed that the discriminatory power of the dissolution method has been demonstrated.

The primary packaging is unit dose laminated aluminium/aluminium foil blisters. The materials comply with EC requirements. The blisters are purged with ultra-high purity nitrogen just prior to heat sealing to reduce oxidation of the tablets. Both aluminium-aluminium foil blistering materials provide suitable protection in terms of providing a barrier to light and in preventing oxygen and moisture vapour ingress. Absence of pinholes is assured by the pinhole detector of the blistering machine.

Manufacture of the product and process controls

The manufacturing process consists of six main steps: high-shear granulation, fluid bed drying, screening and milling of dried granules, blending and lubrication, compression, and packaging. The process is considered to be a standard manufacturing process.

The IPCs and associated acceptance criteria are provided. The critical steps of the manufacturing process are the fluid bed drying of the wet granules and compression of the final blend and both are considered to be adequately controlled. Three consecutive commercial scale batches have been manufactured using the commercial manufacturing process, demonstrating that the process consistently produces delafloxacin tablets, 450 mg that meet the predetermined specifications and quality attributes.

Product specification

The tablet release and shelf life specifications shown in Table 7: Tablet release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance, identification (HPLC and UV), assay (HPLC), impurities (HPLC), dissolution (Ph. Eur.), uniformity of Dosage Units (HPLC), water (Ph. Eur.) and microbial testing (Ph. Eur.). The shelf-life specification is identical to the release specification. The limits proposed have been adequately justified.

The potential presence of elemental impurities in the finished product has been assessed using a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk

assessment it was concluded that the risk of contamination with elemental impurities is low so it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results were provided for three commercial batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three pilot scale batches of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. During the review, data from three commercial scale batches stored for up to 12 months under long term conditions (25 ºC / 60% RH), were provided to address a major objection. The batches of medicinal product are representative of those proposed for marketing and packed in the primary packaging representative of the primary container closure proposed for marketing.

Samples were tested for the same tests listed in the release specification. The analytical procedures used are stability indicating. The results meet the specifications and no significant trend in any of the parameters tested was observed.

In addition, three batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. During the study, a change in the colour of the tablets was observed. The recommendation for storage (light sensitivity) is therefore required and included in the SmPC and PIL.

Based on available stability data, the proposed shelf-life of 36 months stored in the original package in order to protect from light as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

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

2.2.6. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented and updated 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 two finished products should have a satisfactory and uniform performance in clinical use. The major objections on the justification of the choice of the sterilisation method for the concentrate for solution for infusion and on the substantiation of the proposed shelf life of the tablet have been satisfactorily addressed during the procedure. Clear instructions for preparation and handling of the reconstituted solutions for infusion have been included in the SmPC.

2.2.7. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of the two products 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.

2.2.8. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP the CHMP recommends several points for investigation as described above.

2.3. Non-clinical aspects

2.3.1. Pharmacology

Delafloxacin meglumine is a novel anionic fluoroquinolone with binding affinity to both DNA gyrase and topoisomerase IV. The delafloxacin molecule exhibits different chemical features compared to other fluoroquinolones, i.e. delafloxacin shifts from an anion at physiological pH to a non-ionised (zwitterion) structure at acidic pH (≤ 5.5).

Primary pharmacodynamic studies

Refer to the clinical assessment.

Secondary pharmacodynamic studies

The secondary pharmacodynamics program explored potential off-target activity of delafloxacin in screens including 75 radioligand binding assays. These assessments included *in vitro* evaluations of receptor subtypes for gamma-aminobutyric acid (GABA), benzodiazepine (BZD), N-methyl-D-aspartate (NMDA), adenosine, and muscarinic ligands, targets previously implicated in the neurological symptoms of marketed fluoroquinolones, as well as in tendinopathies. The results of these studies demonstrated no noteworthy or clinically relevant inhibition of radioligand binding to such receptors. For the metabolites M3 and M5 (ester glucuronides), major metabolites of delafloxacin seen in rats, dogs, and humans, no further pharmacological characterization or specific studies are required based on calculated exposure rates in performed toxicological studies and data, which clearly demonstrate that the unchanged delafloxacin is the predominant circulating compound in urine and plasma following oral and intravenous administration.

Safety pharmacology programme

An extensive core battery of central nervous system (CNS), cardiovascular, and respiratory evaluations were conducted with delafloxacin, including supplemental gastrointestinal (GI) evaluations. In several studies, the effects of delafloxacin were compared to those of other fluoroquinolones. These studies did not indicate a risk to human safety at delafloxacin plasma concentrations exceeding those observed in clinical studies.

These studies were originally conducted prior to full implementation of the ICHS7 guidance on Safety Pharmacology and thus were not conducted in accordance with GLP but were more extensive than those

outlined in the ICHS7 Core Battery. Furthermore, these studies were conducted under compliance with standard operating procedures ensuring data quality, integrity and reliability.

CNS: An extensive battery of CNS evaluations was conducted with delafloxacin after oral administration in mice and rats. Doses in mice up to 300 mg/kg (a dose associated with mean C_{max} values at least approximately 5-fold greater than that observed in humans following therapeutic IV dosing (9.29 µg/mL) had no consistent effects on general behaviour, motor coordination, body temperature, nociception, and barbital- or ethanol-induced sleep, although transient sedation was observed. At a high dose of 1000 mg/kg, transient signs of CNS stimulation (excitation with hypersensitivity to external stimuli) prior to sedation were observed. Delafloxacin also had no meaningful effects on the electro-shock threshold and latency to pentylenetetrazole (PTZ)-induced convulsions in mice up to the highest dose tested (300 mg/kg). In contrast, trovafloxacin, and norfloxacin decreased the time to PTZ-induced tonic convulsions and / or death at comparable doses. Delafloxacin did not cause convulsions when co-administered with fenbufen, a nonsteroidal anti- inflammatory drug (NSAID) reported to induce seizures in humans when co-administered with enoxacin, a second-generation fluoroquinolone; accordingly, a non-convulsant dose of enoxacin induced convulsions in mice when co-administered with fenbufen.

Taken together, these results suggest the absence of clear CNS activity for delafloxacin in mice and rats after p.o. administration up to 300 mg/kg.

Cardiovascular: There was no significant inhibition of the delayed rectifier potassium current in hERG-transfected HEK-293 cells up to 75 µg/mL and no significant prolongation of action potential duration in dog Purkinje fibres up to 50 µg/mL, both concentrations being the highest tested. The no-effect concentration of 50 µg/mL is 33-fold greater than the unbound human C_{max} plasma level at the therapeutic IV dose.

Also, QTc prolongation was not observed in instrumented dogs following IV administration of delafloxacin up to plasma concentrations of 121 µg/mL (13 x therapeutic C_{max} following repeat IV dosing). At these high plasma concentrations there was a transient increase in pulmonary arterial pressure and a transient decrease in mean arterial pressure and contractile function which quickly returned to baseline as peak plasma levels declined.

A thorough contemporary QT clinical study, which included the positive control moxifloxacin, demonstrated no QT prolongation risk following administration of delafloxacin to humans.

Respiratory System: delafloxacin produced no statistically significant effects on any respiratory parameter relative to the vehicle and thus does not affect respiratory function in rats at oral doses up to 600 mg/kg, a dose which corresponds to at least twice the mean plasma C_{max} observed in humans after IV administration.

Gastrointestinal System: delafloxacin had no significant effect on GI transit times in rats up to 100 mg/kg orally, indicating no physiologically significant effect on stomach emptying or small intestinal motility. However, the ferret model indicated a potential for emesis and diarrhoea.

In toxicology studies, GI effects have been observed in rats and dogs with delafloxacin administered either orally or IV and are characterized primary as abnormal stool, dilated caecum, and decreased food intake and / or body weight in rats, and emesis and abnormal stool / diarrhoea in dogs. As no microscopic signs of GI injury have been seen with delafloxacin in rats and dogs up to 3 months in duration, the GI effects observed in toxicology studies were not considered serious or adverse.

Pharmacodynamic drug interactions

No specific studies on pharmacodynamic drug interactions have been conducted but in safety pharmacology studies no meaningful pharmacodynamic drug interactions of delafloxacin with fenbufen, barbital, or ethanol in mice did occur.

2.3.2. Pharmacokinetics

The conducted pharmacokinetic (ADME) studies were conducted in mice, rats, dogs, and cynomolgus monkeys following oral and / or IV administration of delafloxacin and used analytical methods were sufficiently validated and are considered adequate for toxicokinetics of the toxicology studies.

Delafloxacin was rapidly absorbed from the GI tract following oral administration of solution formulations to mice, rats and dogs, with absolute bioavailability of > 50% in mice and dogs and approximately 28% in rats when tested at 5 mg/kg. PK of delafloxacin was linear, it did not change with repeat doses and it did not show potential for accumulation or gender-related differences. Food was shown to decrease the systemic exposure to orally administered delafloxacin by about 2-fold in rats and dogs independent of formulation used. Similar to delafloxacin, the meglumine salt of delafloxacin (the salt form used for clinical trials) was also rapidly absorbed from the GI tract when delivered as an oral suspension in 0.2% hydroxypropyl-methylcellulose (HPMC) to rats or as neat drug substance in gelatin capsules to dogs.

Delafloxacin exhibits a high protein binding, the rank order for mean protein binding across various species was mouse (97.0%) > rat (91.5%) > human (83.7%) > monkey (78.9%) > dog (75.1%). The majority of delafloxacin protein binding in human plasma has been identified as albumin.

Delafloxacin PK in animals is characterised by low plasma clearance (relative to hepatic blood flow) and a moderate to high volume of distribution (i.e. indicating good-to-excellent distribution into the tissues) followed by rapid elimination from non-pigmented as well as pigmented tissue. Unlike other fluoroquinolones, delafloxacin does not specifically bind to melanin as it is anionic at physiological pH. Little-to-no tissue uptake is seen in CNS tissues or cartilage, but trace levels of ^{14}C-delafloxacin were seen in bone up to 3 weeks following a single dose. In the whole-body autoradiography study the trace levels of ^{14}C-delafloxacin were seen in bone up to 3 weeks (504 h) following a single dose (RBX-01). A new tissue distribution study (MEL/01), completed in 2018, used a more sophisticated quantitative whole-body autoradiography technology that allows differentiation between labelling of mineral bone and labelling of the endosteum. In this study only Below the Limit of accurate Quantification (BLQ) levels in bone (true mineral bone) following similar oral and IV doses to pregnant Sprague Dawley (SD) rats were observed. The applicant has also clarified that the reversible delayed ossification in foetuses in study R&D/01/534, is a sign of growth retardation due to decreased food consumption in treated mothers and the direct effect of delafloxacin on foetal tissue is negligible.

Placental transfer of delafloxacin was shown after single dose application in pregnant rats with foetal levels approximately reaching 10% of maternal blood levels. A study comparing the tissue distribution of oral and the Captisol containing IV formulation showed that the distribution of delafloxacin in foetal tissues, maternal reproductive organs and maternal organs (blood, brain, liver, muscle) was not altered by the presence of Captisol.

Delafloxacin is minimally metabolised by CYP450 and undergoes direct glucuronidation. In rats, dogs and humans, unchanged delafloxacin was the major radioactive species in plasma.

Following both oral and IV dosing, unchanged delafloxacin is the major radioactive component in faeces from rats (70% to 80% of total dose), dogs (62% to 64% of total dose), and humans (oral ~ 48%, IV ~ 28% of total dose). The ester glucuronide of delafloxacin is also found in plasma of rats, dogs, and humans. Although plasma levels of the ester glucuronide in rats and dogs are low relative to

humans, high levels of these metabolites (M3, M5) are found in bile of rats and dogs indicating substantial hepatic exposure. Ester glucuronides are also found in urine of rats, dogs, and humans. All metabolites found *in vivo* in humans have been found in rats and dogs, except M6A, a minor ether glucuronide found in human urine at 1.5% of the total dose and also identified in human urine (1.5% of total dose).

After oral and IV dosing in rats and dogs, approximately 90% of delafloxacin-derived radioactivity is eliminated after dosing within 96 h (rats), 120 h (dogs), and 72 h (humans). Of the total radioactive dose, faecal elimination accounted for 70% to 80% in rats, 85% to 88% in dog, and 48% (oral) and 28% (IV) in humans, with the remaining eliminated via urine. Biliary excretion is a major route of elimination in rats and dogs. Although at a lesser extent than rats and dogs, biliary clearance and transintestinal elimination may also play a role in the excretion of delafloxacin in humans. In humans, 50% to 65% of the dose is eliminated via urine.

Radiolabelled delafloxacin was orally applied to nursing rats. Radiolabel was detected in the milk of nursing rats with milk to plasma ratios of 8.5 to 4.0 and in the stomach of nursed pups at approximately 10-fold maternal plasma levels.

The potential of delafloxacin to precipitate DDIs appears minimal, if any. The metabolism of the drug by cytochromes P450 is negligible, and the drug does not inhibit drug transporters such as MDR1 and BCRP at clinically relevant concentrations. Likewise, only a minor inhibitory effect of the drug on UDP-glucuronosyltransferases was detected at very high concentrations.

2.3.3. Toxicology

Single- and Repeat-dose toxicity

Acute toxicity of delafloxacin was studied in mice, rats and dogs. Following single oral doses mortality in mice and rats occurred at doses ≥ 1664 mg/kg, however, no deaths occurred in rats administered twice daily (BID) doses of 800 mg/kg / dose (1600 mg/kg). In dogs, single doses of up to 320 mg/kg were non-lethal, but dose-related emesis or diarrhoea occurred at ≥ 40 mg/kg or ≥ 80 mg/kg following oral as well as IV administration. Following single 60 minute IV infusion of 120 and 150 mg/kg, no delafloxacin-related deaths occurred in rats and dogs.

Repeat-dose toxicity studies were conducted in rats and dogs administered either oral doses of delafloxacin for up to 13 weeks in duration or by IV infusions (60 to 90 minute) for up to 4 weeks. Thus, treatment periods in animal studies are well beyond the recommended clinical use, which is limited to 5 to 14 days. The pivotal studies in rats and dogs included clinical and anatomic pathology examinations along with toxicokinetic (TK) evaluations.

Oral administration to rats for 3 months (with 4 week reversal period) resulted in caecal dilatation in both studies at all doses (BID 100, 300 or 600/800 mg/kg i.e. total daily exposure of 200, 600 and 1200/1600 mg/kg). At the highest dose at 1600 mg/kg, reversible decreased body weight, food consumption and abnormal stool in both sexes were noted. Parallel to the clinical signs, a reversible, dose-dependent decrease in serum globulin levels occurred at ≥ 600 mg/kg. Other clinical signs noted were noisy respiration and matted hair on muzzle; at the highest dose (1600 mg/kg) animals of both sexes exhibited statistically significant increases in adrenal gland weight, and decreases in the absolute prostate and thymus weights in males. As there were no histopathologic changes in the examined tissues, these organ effects are considered stress related. NOAEL in rats following oral administration for 3 months was established in both genders as 600 mg/kg.

Oral administration to dogs for 3 months (with 4-week recovery period) resulted in emesis, salivation, and abnormal stool / diarrhoea (0, 80, 160 and 320 mg/kg/day). The incidence and severity of these

findings were dose-dependent. At various time points during this study increased alanine aminotransferase (ALT), alkaline phosphatase (ALP), and / or gamma-glutamyltransferase (GGT) was noted (3M, 1F), but returned to near baseline at the end of the recovery period. No histopathologic changes were observed in the livers of these dogs and, electron microscopy of samples of liver from 2 of the males showed no ultrastructural changes. Thus, the NOAEL identified for dogs administered delafloxacin via gelatine capsule for 3 months was considered 160 mg/kg / day.

In rats IV infusions of delafloxacin was administered in two pivotal studies, i.e. daily for a duration of 60 minutes (0, 10, 60 and 180 mg/kg) or 90 minutes (0, 10, 75 and 150 mg/kg/day) for two or four weeks (with 1-week or 2-week recovery). Mortality occurred at doses ≥ 150 mg/kg/day. Decreases in mean body weights (males) and / or food consumption (males and females) occurred at doses of ≥ 120 mg/kg/day. In the 2-week study, reversible, statistically significant decreases in mean absolute / relative liver, spleen and or thymus weights occurred at ≥ 60 mg/kg / day. Similar to the effects after oral administration, the decreases in organ weights were without histopathologic correlates and thus, were considered associated to the changes of body weight, food intake and / or stress-related. Histopathologic changes in the rat IV toxicity studies secondary to the dosing procedure (i.e., inflammation at the injection sites, thrombosis of the vena cava) were seen at all doses (including control). Based on the mortality at 150 mg/kg/day, the NOAEL in both male and female rats following IV infusion for 4 consecutive weeks was established as 75 mg/kg/day.

In dogs two pivotal studies were performed following IV infusion for daily 60 minutes duration in both studies resulting into administered doses of 0, 10, 25 and 75 mg/kg for two or four weeks (with 1 or 2 week(s) recovery), respectively. For doses of up to 75 mg/kg/day no deaths occurred, however, as seen with oral dosing, gastrointestinal (GI)-related clinical observations (e.g., emesis, mucoid or discoloured stools, diarrhoea) occurred at ≥ 25 mg/kg/day. At the high-dose in the 4-week study (75 mg/kg/day), notable increases in ALT and ALP occurred in 1 male and, slight increases in ALT and / or ALP were noted in 2 males and 1 female; no histopathologic changes were noted in any of the tissues examined from these dogs. In addition, reversible decreases in total protein and globulin values were recorded at the end of the treatment period for the 75 mg/kg/day males and were most likely secondary to the antibiotic related changes in the intestinal environment and / or decreased nutritional status resulting from frequent emesis. Reversible increases in absolute / relative adrenal weights and kidney weights for the 75 mg/kg / day males, without histopathologic correlates, were most likely stress-related. Local histopathologic changes were observed at or near the injection sites in dogs at all doses (including controls) and were secondary to the dosing procedure (i.e., inflammation, haemorrhage, and muscle degeneration / regeneration at the injection sites). Delafloxacin-related changes observed during the study essentially reversed at the end of the recovery period. Based on post-dose observations and the elevations in serum enzymes during the treatment period, the NOAEL in dogs administered delafloxacin by IV infusion for 4 consecutive weeks was set at 25 mg/kg/day.

In the 4-week dog IV study the vehicle was a mixture of Captisol, meglumin, EDTA and sterile water, which is also used in the clinical IV formulation. Captisol (sulfobutyl ether of beta cyclodextrin) is a known excipient and functions as a solubilizer and stabilizer in infusion solutions. Reversible mild renal tubule vacuolation is known to be caused by Captisol in animal studies, but no cellular degeneration or loss of kidney function has been reported. More recently, the safe parenteral use for sulfobutyl ether of beta cyclodextrin doses up to 200 mg/kg/day and use for > 2 weeks was confirmed by the CHMP in the revised Q&A document on cyclodextrins (EMA/CHMP/495747/2013, published 09/10/2017). The intended clinical use of Quofenix 300 mg IV (contains 2.4 g SBECD per dose) twice a day results in an exposure below the reported safe dose of 10 g SBECD per day considering a body weight of 50 kg.

Based on TK parameters established at NOAELs of the pivotal (oral/IV) repeat dose toxicity studies in rats and dogs and reported human plasma level following therapeutic treatment corresponding animal:human exposure multiples ("safety margins") were calculated. In rats, safety margins are in the range of 1.3 to

4 for AUC and in the range of 1.9 to 7.3 for C_{max}, respectively. Comparably, the safety margins in dogs are lower, i.e. in the range of 0.5 to 0.8 for AUC and in the range of 1.6 to 2.3 for C_{max}. Taking into consideration the good toxicity profile of delafloxacin, the established exposure margins of both formulations (oral and IV) do support therapeutic doses and a treatment duration up to 2 weeks.

Genotoxicity and Carcinogenicity

Delafloxacin was tested *in vitro* and *in vivo* for genotoxicity in a standard battery of test. The test results did not provide evidence for any clinically relevant genotoxic potential.

Delafloxacin is not intended for long term treatment requiring carcinogenicity testing. Therefore, no carcinogenicity studies were performed.

Reproductive and developmental toxicity

Reproductive and developmental toxicity of delafloxacin was investigated in a study on fertility and early embryonic development and a pre-postnatal study with intravenous application of delafloxacin in the rat. Furthermore, embryo-foetal development studies were conducted in rats and rabbits with oral application of delafloxacin. Concomitantly with embryo-foetal development studies toxicokinetic parameters were evaluated.

No adverse effects on fertility and early embryonic development were noticed with IV administration of delafloxacin in rats up to 120 mg/kg/day. Parental toxicity was observed at 10 mg/kg/day.

In embryo-foetal development studies, oral application of delafloxacin to pregnant rats resulted in reduced foetal weights at 1600 mg/kg/day and maternal toxicity and reversible foetal ossification delays at all doses studied. No malformations were observed. The maternal and developmental NOAEL was less than 200 mg/kg/day. After oral application to pregnant rabbits no adverse effects on embryo-foetal development were observed up to the highest dose of 1.6 mg/kg/day. Since maternal toxicity was noticed the maternal NOAEL was established at 0.4 mg/kg/day. Altogether, rabbits are more susceptible towards some antibiotics and to disturbances of the gastrointestinal tract. Accordingly, doses and resulting plasma levels of delafloxacin were much lower in the embryo-foetal development studies in rabbits than in rats.

In a pre-postnatal development study with IV administration of delafloxacin, lower body weights and longer gestation length were noticed for high dose dams (120 mg/kg/day). Adverse effects were also observed on F1 pups at that dose and included increased mortality during lactation, lower body weights and small stature. However, sexual maturation, sensory function, learning and memory were not affected. Reproductive performance of the F1 generation was also not impacted by delafloxacin treatment as well as F2 neonatal and early postnatal development. The NOAEL was established at 120 mg/kg/day.

Exposure margin calculations were performed at the NOAEL of the reproductive toxicity studies towards human therapeutic exposure based on AUC. No effects were detected on male and female fertility in rats at 5-times human therapeutic exposures. Foetal effects occurred at an exposure level of about 2-fold in rats and below human therapeutic exposures in rabbits. Severe toxicity on neo-natal rats was observed in the pre-postnatal development study at exposures about 5-times higher than in humans with an exposure level of about two at the NOAEL.

Local tolerance

The haemolytic potential of delafloxacin and various delafloxacin placebo formulations was assessed in rat, rabbit, dog and human blood. The local, venous and peri-venous irritation of delafloxacin was

assessed in rats and rabbits. Delafloxacin was not haemolytic in rat, dog, or human plasma; but, produced local (subplantar), venous, and peri-venous irritation. However, these effects are not regarded as clinically relevant, but as a stress reaction to the dosing procedure. In the IV infusion studies in rat and dog on the general toxicology, various histopathological changes occurred at the injection sites, both in the treated animals and in the control animals. In Phase 3 clinical trials, such effects were not considered as a concern.

There were no specific toxicology data regarding the antigenicity and immunotoxicity presented. With regards to immunotoxicity, a 3-month oral repeat dose toxicity study in rats indicated decreased thymic weight (atrophy). This is considered likely to be a treatment-related stress reaction, as following repeated delafloxacin IV administration there was no significant thymic atrophy seen in rats.

Juvenile Toxicity

To elucidate whether delafloxacin shows chondrotoxicity like known for some quinolone antibiotics, a study was performed in juvenile Beagle dogs. Up to the highest dose of 320 mg/kg/day p.o. no adverse effects were observed. However, delafloxacin is not currently intended for paediatric use and the study was therefore not considered for the present application.

2.3.4. Ecotoxicity/environmental risk assessment

The applicant provided an Environmental Risk Assessment (ERA) in accordance with the respective EMA guidance (EMEA/CHMP/SWP/4447/00, corr. 2).

Summary of main study results

Substance (INN/Invented Name): delafloxacin meglumine			
CAS-number (if available): 189279-58-1 (free acid), 352458-37-8 (salt)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	2.4 at pH 5 1.04 at pH 7 -0.91 at pH 9	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2.4	not B
	BCF	not required	Not available
Persistence	DT50 or ready biodegradability	open	P/not P
Toxicity	NOEC or CMR	open	T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater , default or refined (e.g. prevalence, literature)	4.5 (default) 0.047 (refined)	µg/L	> 0.01 threshold (Y)

At present, only a phase I assessment is available. The available data do not allow to conclude definitively on the potential risk of delafloxacin to the environment. The applicant commits to complete Phase II of the Environmental Risk Assessment and provide the updated ERA including all study reports.

2.3.5. Discussion on non-clinical aspects

Delafloxacin meglumine is a novel anionic fluoroquinolone with binding affinity to both DNA gyrase and topoisomerase IV. The delafloxacin molecule exhibits different chemical features compared to other fluoroquinolones, i.e. delafloxacin shifts from an anion at physiological pH to a non-ionised (zwitterion) structure at acidic pH (≤ 5.5). Thus in acidic environments, characteristic of the milieu at infection sites, a better penetration through biological membranes may lead to higher accumulation in bacteria and enhanced antimicrobial effectiveness.

Results from a core battery of safety pharmacology studies including the CNS-, cardiovascular-, respiratory- and gastrointestinal system did not indicate any risk to human safety at delafloxacin plasma concentrations exceeding those observed in clinical studies. The no effect concentration for *in vitro* cardiovascular effects such as hERG current and action potential duration exceeds the unbound human C_{max} plasma level at the therapeutic IV dose by $\geq$ 33-fold, and also *in vivo* in anesthetized dogs no QTc prolongation was recorded up to plasma concentration of 121 µg/mL, which is 13-fold greater than C_{max} at therapeutic levels in humans following repeat IV dosing.

In several studies, the effects of delafloxacin were compared to those of other fluoroquinolones. Following co-administration with the NSAID fenbufen, enoxacin but not delafloxacin did induce convulsions in mice. A thorough contemporary QT clinical study, which included the positive control moxifloxacin, demonstrated no QT prolongation risk following administration of delafloxacin to humans.

A complete set of pharmacokinetic studies addressing relevant ADME aspects of delafloxacin has been conducted in rodents and dogs. Delafloxacin PK in animals is characterized by low plasma clearance and a moderate to high volume of distribution followed by rapid elimination from non-pigmented as well as pigmented tissue. The lack of binding to melanin differs from other fluoroquinolones and is probably related to the fact that only delafloxacin is anionic at physiological pH. Little-to-no tissue uptake is seen in CNS tissues or cartilage. The distribution profile of delafloxacin in rats and dogs indicate that the new fluoroquinolone may offer some safety advantages with respect to uptake in CNS tissues or cartilage.

Placental transfer of delafloxacin and excretion into milk was shown in rats. In the absence of human data and findings in non-clinical studies at human therapeutic exposures, delafloxacin is contraindicated during pregnancy and lactation.

One additional tissue distribution study was performed to compare distribution of IV and oral ^{14}C-delafloxacin in pregnant rats during the period of organogenesis in order to determine whether Captisol might provoke differences in distribution of delafloxacin to foetal and maternal tissues. No differences in tissue distribution were detected.

In rats, dogs and humans, unchanged delafloxacin was the major radioactive species in plasma. Delafloxacin is minimally metabolised by CYP450 and undergoes direct glucuronidation. All metabolites found in vivo in humans have been found in rats and dogs, except M6A, a minor ether glucuronide found in human urine at 1.5% of the total dose. Thus, the chosen animal species and the proposed routes of administration are adequate for the performed toxicity studies.

Faecal elimination (with biliary excretion) predominates in rats and dogs compared to lower rates in humans (48% oral, 28% IV), where 50% to 65% of the dose is eliminated via urine.

Based on *in vitro* drug transporter studies (MDR1 and BCRP) and UDP-glucuronosyltransferases data generated at clinically relevant doses, there is only a low potential for DDIs following delafloxacin administration.

The conducted toxicology programme is considered appropriate for the proposed clinical use of the new fluoroquinolone antibiotic delafloxacin, i.e. the chosen animal species (rat and dog) are appropriate based on performed PK studies, toxicity in animals following both clinically relevant routes of administration (oral/IV) has been examined, and treatment periods in animal studies are well beyond the recommended clinical use.

Repeat-dose toxicity studies in rats and dogs following both routes of drug administration (oral/IV) revealed mainly dose-dependent gastrointestinal related clinical symptoms, such as caecal dilatation and abnormal stool (rat) or emesis, salvation, discoloured stools and diarrhoea (dog) beside decreased body weight. The repeated IV administration (up to two weeks/rats and up to four weeks/dogs) resulted in both species into local inflammatory reactions and secondary local histopathological changes at the injection site, which are not relevant for the intended short-term clinical use. In rats, stress related effects on adrenal gland weight (both sexes) and decreases in prostate and thymus (males) occurred and NOAEL was established as 600 mg/kg (oral) or 75 mg/kg/day (IV). In dogs, elevations in liver enzymes (ALT, ALP and/or GGT) occurred, but no corresponding histopathologic changes were noted in any of the tissues examined, thus NOAEL was considered 160 mg/kg/day (oral for 3 months) or was set 25 mg/kg/day (IV for 4 weeks). Based on TK parameters established at NOAELs of the pivotal (oral/IV) repeat dose toxicity studies and reported human exposure following therapeutic treatment exposure multiples were calculated. In rats, safety margins are in the range of 1.3 to 4 for AUC and in the range of 1.9 to 7.3 for C_{max}, respectively. Comparably, the safety margins in dogs are lower, i.e. in the range of 0.5 to 0.8 for AUC and in the range of 1.6 to 2.3 for C_{max}. Taking into consideration the good toxicity profile of delafloxacin, the established exposure margins of both formulations (oral and IV) do support therapeutic doses and a treatment duration up to 2 weeks. In the 4-week dog IV study the vehicle was a mixture of Captisol, meglumin, EDTA and sterile water, which is also used in the clinical IV formulation. More recently, the safe parenteral use for sulfobutyl ether of beta cyclodextrin doses up to 200 mg/kg/day and use for > 2 weeks was confirmed by the CHMP in the revised Q&A document on cyclodextrins, thus there is no safety concern with respect to the intended clinical use of Quofenix 300 mg IV.

Delafloxacin was tested *in vitro* and in vivo for genotoxicity in a standard battery of test. The test results did not provide evidence for any clinically relevant genotoxic potential. No carcinogenicity studies were performed, which is acceptable as delafloxacin is not intended for long term treatment.

No effects on fertility or early embryonic development were observed in a study with IV administration of up to 120 mg/kg/day delafloxacin to rats.

No malformations were noticed in embryo-foetal development studies performed with oral application of delafloxacin to rats or rabbits. Reversible ossification delays and maternal toxicity were the main findings in rats starting at the lowest dose of 200 mg/kg/day. In rabbits, no adverse effects on embryo-foetal development were observed up to 1.6 mg/kg/day. However, rabbits were extremely sensitive towards treatment with delafloxacin. It is known that antibiotics may lead to disturbances of the gastrointestinal tract. Therefore, doses and resulting plasma levels in the embryo-foetal development studies with delafloxacin in rabbits are much lower than in rats.

In a pre-postnatal development study with i.v. administration to rats maternal toxicity and impaired neonatal development of F1 pups was observed along with the excretion of delafloxacin in maternal milk with a respective NOAEL of 60 mg/kg/day. Therefore, the contraindication of delafloxacin during breast-feeding is recommended.

Delafloxacin was not haemolytic in rat, dog, or human plasma, but produced local (subplantar), venous, and peri-venous irritation. However, these effects are not regarded as clinically relevant, but as a stress reaction to the dosing procedure.

Twenty-seven potential impurities were screened in silico or tested in follow up genotoxicity tests or repeated dose toxicity studies and did not raise relevant concerns.

2.3.6. Conclusion on the non-clinical aspects

The CHMP considers that the non-clinical data do not point to any major concerns and that the clinically relevant findings have been adequately addressed in the Quofenix product information.

The conducted toxicology programme is considered appropriate for the proposed clinical use of delafloxacin, as both clinical routes of administration (oral/IV) and the intended treatment duration of up to 2 weeks have been sufficiently studied in animals.

No final conclusions on the environmental risk assessment is currently possible and the CHMP considers the following measure to be necessary to address the non-clinical issues:

The applicant commits to complete Phase II of the Environmental Risk Assessment and provide the updated ERA including all study reports.

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 ID	Study objective(s)	Study design	Subjects; Gender; Age range	Dosage regimen; Route of administration	Delafloxacin formulation	Total No. of subjects entered/completed
M00-224	to determine the safety, tolerability and PK of single and multiple doses of oral delafloxacin to determine effects of food, sex and age on the PK of delafloxacin	Part I single-center, double-blind, randomised, parallel group, single-ascending dose study Part 2 *Food effect* single-center, double-blind, randomised, single-dose, 2-period, cross-over study *Female* single-center, double-blind, randomised, single-dose study *Elderly* single-center, double-blind, randomised, single-dose study Part 3 single-center, double-blind, randomised, parallel group, multiple-ascending dose	Part 1 healthy adult male subjects (fasted state) Part 2 *Food effect* healthy adult male subjects (fasted and fed state) *Female* healthy adult female subjects (fasted state) *Elderly* healthy adult male and female subject ≥ 65 years (fasted state) Part 3 healthy adult male subjects (fasted state)	Part 1 50 mg, 100 mg, 200 mg, 400 mg, 800 mg, 1200 mg and 1600 mg delafloxacin/ placebo, single-dose, oral Part 2 250 mg delafloxacin, single-dose, oral Part 3 100 mg, 200 mg, 400 mg, 800 mg and 1200 mg delafloxacin/placebo QD on Days 1-5, oral	formulation A	Part 1 56 subjects enrolled 56 subjects completed Part 2 *Food effect* 20 subjects enrolled 20 subjects completed *Female* 16 subjects enrolled 16 subjects completed *Elderly* 16 subjects enrolled 16 subjects completed Part 3 60 subjects enrolled 57 subjects completed
M01-492	to investigate metabolism and disposition of delafloxacin following a single oral dose	single-center, open-label, single-dose study	healthy male subjects (fasted state)	200 mg [^{14}C]-delafloxacin, single-dose, oral	formulation A	6 subjects enrolled 6 subjects completed
M01-301	to compare BA of formulations A and B under fasting conditions	single-center, single-dose, open-label, randomised, 2-period, cross-over study	healthy male and female subjects (fasted state)	200 mg delafloxacin, single dose; oral	formulation A formulation B	18 subjects enrolled 18 subjects completed
M02-422	to compare BA under	single-center,	healthy male and	200 mg delafloxacin,	formulation B	21 subjects enrolled

	fed (high-fat, low-fat) and fasting conditions	single-dose, open-label, 3-period, cross-over study	female subjects (fasted and fed state)	single dose; oral		18 subjects completed
M03-463	to compare BA of formulations A, B, C and D under fasting conditions	single-center, single-dose, open-label, randomised, 4-period, cross-over study	healthy male and female subjects (fasted state)	200 mg delafloxacin, single dose, oral	formulation A formulation B formulation C formulation D	24 subjects enrolled 24 subjects completed
RX-3341-101	to determine safety, tolerability and PK of single dose delafloxacin IV	single-center, double-blind, randomised, placebo-controlled, single-dose study Part 1 Ascending dose Part 2 Increasing infusion rate	healthy male and female subjects	Part 1 50 mg, 100 mg, 200 mg, 300 mg and 400 mg delafloxacin/ placebo, single-dose, IV (over 1 h) Part 2 300 mg delafloxacin, single-dose, IV (over 30 min)	formulation K	Part 1 27 subjects enrolled 26 subjects completed Part 2 16 subjects enrolled 16 subjects completed
RX-3341-102	to determine safety, tolerability and PK of single- and multiple-day IV dosing	single-center, double-blind, randomised, placebo-controlled Part 1 single-day dosing Part 2 multiple-day dosing	healthy male and female subjects	Part 1 300 mg and 600 mg delafloxacin/placebo, single-dose, IV Part 2 150 mg and 300 mg delafloxacin/ placebo, QD on Day 1, then BID on Days 2-10	formulation K	Part I 16 subjects enrolled 16 subjects completed Part II 24 subjects enrolled 16 subjects completed
RX-3341-103	to determine safety, tolerability and PK of 2 IV formulations of delafloxacin	single-center, double-blind, randomised study in 2 groups Group 1 single-dose, 2-treatment, cross-over study Group 2 multiple-dose, placebo-controlled study	healthy male and female subjects	Group 1 300 mg delafloxacin, single-dose, IV Group 2 300 mg or 450 mg delafloxacin/placebo QD on Day 1, then BID on Days 2-14, IV	Group 1 formulation K formulation L Group 2 formulation L	Group 1 12 subjects enrolled 12 subjects completed Group 2 20 subjects enrolled 18 subjects completed
RX-3341-104	to determine safety, tolerability and PK of 2 IV formulations of delafloxacin	Part 1 single-center, double-blind, randomised, single-dose, 2-treatment, cross-over study	healthy male and female subjects	Part 1 300 mg delafloxacin, single-dose, IV (over 1 h) Part 2 300 mg delafloxacin/ placebo QD on Day 1, then	Part 1 formulation L formulation M Part 2 formulation M	Part 1 12 subjects enrolled 11 subjects completed Part 2 12 subjects enrolled 11 subjects completed

		Part 2 single-center, double-blind, randomised, placebo-controlled, multiple-dose study		BID on Days 2-14, IV (over 1 h)		
RX-3341-1 06	to determine safety, tolerability and PK of 2 oral formulations of delafloxacin	Part 1 single-center, double-blind, randomised, single-dose, 2-treatment, cross-over study Part 2 single-center, double-blind, randomised, placebo-controlled, multiple dose study (cancelled by sponsor as formulation E did not increase BA over formulation A)	healthy male and female subjects (fasted state)	Part 1 400 mg delafloxacin, single-dose, oral	Part 1 formulation A formulation E	Part 1 16 subjects enrolled 16 subjects completed
RX-3341-1 07	to assess mass balance recovery and metabolite profiling of delafloxacin	single-center, open-label, non-randomised, single-dose study	healthy male subjects (fasted state)	300 mg [^{14}C]-delafloxacin, single-dose, IV	formulation M	6 subjects enrolled 6 subjects completed
RX-3341-1 08	to determine safety, tolerability and PK of 2 IV formulations of delafloxacin (relative to oral formulation) to determine MTD of formulation N	Part 1 single-center, double-blind, randomised, single IV dose, 2-treatment, cross-over study followed by an additional single oral dose Part 2 single-center, double-blind, randomised, placebo-controlled, single-ascending MTD dose	healthy male and female subjects (fasted state)	Part 1 300 mg delafloxacin IV (over 1 h); 300 mg delafloxacin, oral Part 2 450 mg, 600 mg, 750 mg, 900 mg and 1200 mg delafloxacin/placebo, IV (over 1 h)	Part 1 formulation A formulation M formulation N (intended commercial IV formulation) Part 2 formulation N (intended commercial IV formulation)	Part 1 12 subjects enrolled 12 subjects completed Part 2 50 subjects enrolled 50 subjects completed
RX-3341-1	to determine safety,	single-center,	healthy male and	875 mg augmentin QD on	formulation A	105 subjects enrolled

09	tolerability and PK of multiple doses of delafloxacin under fed and fasted conditions	open-label, randomised, multiple dose study	female subjects (fasted and fed state)	Day 1, then BID on Days 2-10, oral 400 mg delafloxacin QD on Day 1, then BID on Days 2-10		104 subjects completed
RX-3341-1 13	to determine safety, tolerability and PK of multiple doses of 5 delafloxacin formulations	single-center, multiple-dose, single-blind study	healthy male subjects (fasted state)	placebo Q12h BID for 2 days followed by 1 one 5 delafloxacin formulations QD on Day 3, then BID on Days 4-9, 400 mg oral or 300 mg IV (over 1 h)	formulation A formulation F formulation G formulation H formulation N (intended commercial IV formulation)	100 subjects enrolled 99 subjects completed
RX-3341-1 14	to determine safety, tolerability and PK of different oral delafloxacin formulations	single-center, open-label, 4-period, cross-over study	healthy male and female subjects (fasted state)	400 mg, 450 mg, 475 mg and 500 mg delafloxacin, oral	formulation I(a) formulation I(b) formulation I(c) formulation I(d)	20 subjects enrolled 20 subjects completed
RX-3341-1 15	Part 1 to compare BA of oral delafloxacin relative to IV delafloxacin Part 2 to determine exposure of 900 mg oral delafloxacin	Part 1 single-center, single-dose, open-label, randomised, 2-period, 2-sequence, cross-over study Part 2 single-center, single-dose, open-label, 1-period study	healthy male and female subjects (fasted state)	Part 1 300 mg delafloxacin solution , IV 450 mg delafloxacin, oral Part 2 900 mg delafloxacin, single-dose, oral	formulation J (intended commercial oral formulation)	Part 1 56 subjects enrolled 54 subjects completed Part 2 20 subjects enrolled 20 subjects completed
RX-3341-1 16	to compare BA of delafloxacin under fasting conditions, fed conditions (high fat) and fasting conditions with a high-fat meal 2 h post-dose	single-center, single-dose, open-label, randomised, 3-period, 6-sequence, cross-over study	healthy male and female subjects (fasted and fed state)	900 mg delafloxacin, single-dose, oral	formulation J (intended commercial oral formulation)	30 subjects enrolled 26 subjects completed
RX-3341-1 10	to assess the effect of renal impairment on the PK of delafloxacin (IV and oral)	single-center, open-label, parallel-group, single-dose, cross-over study	male and female subjects who are healthy or who have mild, moderate, severe and end-stage renal disease	400 mg delafloxacin, single-dose, oral 300 mg delafloxacin/placebo, single dose, oral	formulation A formulation N (intended commercial IV formulation)	44 subjects enrolled 42 subjects completed
ML-3341-1 12	to assess the effect of hepatic impairment on the PK of delafloxacin	multi-center, open-label, single-dose	male and female subjects who are healthy or who have	300 mg delafloxacin, single dose, IV	formulation N (intended commercial IV formulation)	39 subjects enrolled 36 subjects completed

	IV		mild, moderate or severe hepatic impairment			
ML-3341-118	to evaluate the effect of repeated doses of oral delafloxacin on PK profile of a single oral dose of midazolam	single-center, single- and multiple-dose, non-randomised, open-label, single-sequence, single-group drug-drug-interaction study	healthy male and female subjects	450 mg delafloxacin Q12h on Days 3-8, oral 5 mg midazolam on Day 1 and 8, oral	formulation J (intended commercial oral formulation)	22 subjects enrolled 22 subjects completed
M01-284	to evaluate if delafloxacin has any photosensitising potential	single-center, single-blind, placebo- and positive controlled, randomised, parallel group study	healthy male and female subjects	200 mg and 400 mg delafloxacin QD, oral 400 mg lomefloxacin QD, oral placebo QC, oral	formulation A	52 subjects enrolled 45 subjects completed
M01-365	to evaluate the effect of oral delafloxacin on the QT interval	multi-center, double-blind, randomised, placebo-controlled, multiple dose, 4-period, cross-over study	healthy male and female subjects	placebo on Day 1, then delafloxacin 200 mg, 800 mg and 1200 mg QD delafloxacin/placebo on Days 1-3, oral	formulation B	68 subjects enrolled 67 subjects completed
RX-3341-111	to assess ECG effects of IV delafloxacin	single-center, randomised, single-dose, positive-controlled, placebo-controlled, 4-period, cross-over study	healthy male and female subjects	300 mg and 900 mg delafloxacin, single-dose, IV (over 1 h) 400 mg moxifloxacin, single-dose, oral placebo, IV and oral	formulation N (intended commercial IV formulation)	52 subjects enrolled 51 subjects completed
RX-3341-201	to evaluate efficacy and safety of delafloxacin compared with tigecycline	Phase II, multi-center, double-blind, randomised, active-controlled study	male and female subjects with cSSSI	300 mg or 450 mg delafloxacin Q12h for 5 to 14 days, IV 100 mg tigecyclin followed by 50 mg Q12h for 5 to 14 days, IV	formulation L	150 patients enrolled 135 patients completed
RX-3341-202	to evaluate efficacy and safety of delafloxacin compared with linezolid and vancomycin	Phase II, multi-center, double-blind, randomised, stratified study	male and female subjects with ABSSSI	300 mg delafloxacin Q12h for 5 to 14 days, IV 600 mg linezolid Q12h for 5 to 14 days, IV 15 mg/kg vancomycin	formulation N (intended commercial IV formulation)	256 patients enrolled 210 patients completed

				Q12h for 5 to 14 days, IV		
RX-3341-3 02	to evaluate efficacy and safety of delafloxacin compared with vancomycin + aztrenoam	Phase III, multi-center, double-blind, randomised, active-controlled study	male and female subjects with ABSSSI	300 mg delafloxacin Q12h, IV (over 1 h) for 5 to 14 days + aztreonam placebo; IV 15 mg/kg vancomycin Q12h, IV for 5 to 14 days + 2 g aztreonam Q12h, IV	formulation N (intended commercial IV formulation)	660 patients enrolled 547 patients completed
RX-3341-3 03	to evaluate efficacy and safety of delafloxacin compared with vancomycin + aztrenoam	Phase III, multi-center, double-blind, randomised, active-controlled study	male and female subjects with ABSSSI	300 mg delafloxacin Q12h, IV (over 1 h) for 6 doses then 450 mg delafloxacin Q12h, oral for 2 to 11 days + aztreonam placebo 15 mg/kg vancomycin Q12h , IV for 5 to 14 days + 2 g aztreonam Q12h, IV	formulation J (intended commercial oral formulation) formulation N (intended commercial IV formulation)	850 patients enrolled 734 patients completed

2.4.2. Pharmacokinetics

The clinical development of delafloxacin commenced in 2001 with the development of an oral formulation up to Phase II study. In 2006 a programme was completed covering an oral and intravenous (IV) formulation. The aim of the oral formulation development was to achieve *in vivo* exposure equivalent to that of 300 mg delafloxacin IV to allow for switching between these two formulations. Based on the results of clinical exposure data, the applicant selected the 450 mg tablet as the to-be-marketed formulation that was evaluated in Phase II and Phase III studies in patients with acute bacterial skin and skin structure infections (ABSSSI).

A total of 23 Phase I studies have been conducted with 14 different formulations of delafloxacin (10 oral and 4 IV formulations; see Table 8).

Table 3: Oral and IV formulations of delafloxacin developed for clinical trials

Formulation	Formulation description	Administration
A	neat drug substance in capsule, 50 mg and 100 mg (Phase I capsule)	oral
B	wet granulation capsule, 100 mg (Phase II capsule)	oral
C	prototype wet granulation tablet, 200 mg	oral
D	prototype dry granulation tablet, 200 mg	oral
E	capsule formulation with vitamin E TPGS, 100 mg	oral
F	delafloxacin potassium salt in capsule, 100 mg	oral
G	Phase I capsule, 100 mg and 200 mg aluminium sulfate hydrate capsule	oral
H	delafloxacin meglumine bilayer tablet, 400 mg	oral
I(a) I(b) I(c) I(d)	tablet (wet granulation), 400 mg tablet (wet granulation), 450 mg tablet (wet granulation), 500 mg bilayer tablet (wet granulation), 475 mg	oral
J	tablet (wet granulation), 450 mg; **intended commercial formulation**	oral
K	solution containing Solutol HS-15, 300 mg	IV
L	solution containing Cavitron, 300 mg	IV
M	solution containing Captisol (no EDTA), 300 mg	IV
N	300 mg lyophilised, containing Captisol, **intended commercial formulation**	IV

Absorption

Following IV and oral administration to healthy subjects, delafloxacin is rapidly absorbed with T_{max} of 0.75 – 2 h. The absolute oral bioavailability of the to-be-marketed 450 mg delafloxacin tablet was estimated to be 58.8%.

- **Influence of food**

The influence of food on the bioavailability (BA) of delafloxacin has been evaluated at dosages of 250 mg and 400 mg of formulation A (neat drug substance in capsule), at 200 mg of formulation B (wet granulation capsule), and at 900 mg of the intended commercial tablet formulation (formulation J). Four clinical studies (M00-224, M02-422, RX-3341-109, RX-3341-115) demonstrated that administration of delafloxacin with food delays absorption (T_{max}) and reduces C_{max}. The impact of food on the total exposure depends on the formulation. AUC after administration of 900 mg of the intended commercial oral formulation was comparable when taken under fasted and fed conditions (geometric LS mean ratio: AUC_{0-t}: 101.79, $AUC_{0-\infty}$: 105.0). C_{max} of the to-be-marketed tablet formulation was about 20.5% reduced

after a high-fat meal taken prior to administration. Food taken 2 h after dosing did not have any effect on the relevant PK parameters.

- **Bioequivalence**

Study RX-3341-115

The aim of the oral formulation development was to achieve *in vivo* exposure equivalent to that of 300 mg delafloxacin IV to allow for switching between these two formulations. In Part 1 of study RX-3341-115 the bioavailability of the to-be-marketed oral formulation (450 mg compressed tablet) and IV formulation (300 mg lyophilised Captisol-containing formulation) were compared in healthy subjects. This was a single-dose, open-label, randomised, 2-period, 2-sequence study in 56 healthy male and female subjects in fasted state. The wash-out time between periods was 7 days. 54 subjects completed the study.

The overall exposure of delafloxacin (AUC) following administration of a single 450 mg tablet was bioequivalent to that following 300 mg IV infusion, although both AUC_{0-t} and $AUC_{0-\infty}$ were lower after oral treatment (84.5% and 87.7%, respectively; Table 9). There was a significant difference in C_{max} after administration of the 450 mg tablet and thus C_{max} did not meet bioequivalence criteria (51.5%-59.1%; Table 9). Median T_{max} of delafloxacin occurred at 0.82 h following the administration of the 450 mg tablet and at 1 h following 300 mg infused over 1 h. The mean $t_{1/2}$ of delafloxacin ranged from 10.90 h to 14.06 h across the two treatments.

Table 4: Statistical analysis of plasma pharmacokinetic parameters of delafloxacin after single oral administration of 450 mg delafloxacin (to-be-marketed tablet; treatment A) and IV infusion of 300 mg delafloxacin (to-be-marketed lyophilised Captisol-containing formulation; treatment B) over 1 h

Parameter (unit)	Treatment[a]	N	Geometric LS Means[c]	90% CI of the Geometric LS Means (A,B)	Ratio (%) of Geometric LS Means (A/B)[d]	90% CI of the Ratio (A/B)[e]
AUC_{0-inf} $(\mu g \cdot h/mL)$[b]	A	42	22.970	(21.614, 24.412)	87.680	(83.562, 92.001)
	B	49	26.198	(24.708, 27.778)		
AUC_{0-t} $(\mu g \cdot h/mL)$	A	55	22.239	(20.987, 23.567)	84.447	(80.898, 88.151)
	B	55	26.335	(24.852, 27.908)		
C_{max} $(\mu g/mL)$	A	55	5.797	(5.443, 6.173)	55.155	(51.496, 59.075)
	B	55	10.510	(9.869, 11.193)		

Abbreviations: CI, confidence interval; CV, coefficient of variation; IV, intravenous; LS, least square.

Note: A linear mixed-effect model on the natural logarithms (ln) of AUC_{0-inf}, AUC_{0-t} and C_{max} was performed with treatment, sequence, and period as fixed effects and subject nested within sequence as a random effect.

[a] Treatment A = delafloxacin 450-mg tablet.
Treatment B = delafloxacin 300 mg infused over 1 hour.

[b] n = 42 for Treatment A and n = 49 for Treatment B. Corresponding parameters were not calculated for some of the subjects because a linear regression line could not be fitted through the terminal phase.

[c] Least squares mean from analysis of variance. Least squares means were calculated by transforming the ln means back to linear scale, ie, geometric means.

[d] Ratio of least square means (expressed as a percentage). Ln-transformed difference was transformed back to linear scale to obtain the ratio of geometric least square means.

[e] The 90% CI for the ratio of metric means (expressed as a percentage). Ln-transformed confidence limits were transformed back to linear scale.

Distribution

Delafloxacin is well distributed with a mean volume of distribution at steady state (V_{ss}) of 30.2 l to 48.3 l across clinical studies with 300 mg delafloxacin IV (infused over 1 h) which is just below or in the range of total body water (~ 42 l). Protein binding in plasma ranged between 71-85%.

Metabolism

Metabolism accounts for ≤ 20% of the elimination of delafloxacin with glucuronidation being the primary metabolic pathway. Four metabolites of delafloxacin have been designated as M3, M5, M6A, and M7. The metabolites M3 and M5 have been identified as ester glucuronide metabolites of the parent drug. Metabolite M6A has been identified as an ether glucuronide of delafloxacin and M7 is an oxidative metabolite.

In vitro metabolism and pharmacokinetic data suggest that the UDP-glucuronosyltransferases UGT1A1, UG1A3 and UGT2B15 are involved in the glucuronidation of delafloxacin.

Elimination

Delafloxacin is excreted in both urine and faeces. After IV administration 64.5% and 28.4% of the administered dose were recovered in urine and faeces, respectively. After oral administration delafloxacin was almost equally distributed in urine (50.2%) and faeces (47.7%).

Dose proportionality and time dependencies

Simulations were carried out to evaluate dose proportionality (00432-1/PK-3341-009). Based on $AUC_{0-\infty}$, the lack of dose proportionality was reported at a dose of 500 mg IV (i.e., the point at which the 90% confidence interval is not fully contained within the range of 80-125%). No lack of dose proportionality was observed based upon C_{max}.

Intra- and inter-individual variability

Inter-individual variability (IIV) was estimated for almost all PK parameters of the developed population PK model (00432-1 / PK-3341-009) for delafloxacin; CL_{LN} (30% CV), CL_R (45.9% CV), Vc (38.9% CV), V_{max} (45.4% CV), K_m (60.7% CV), distributional clearance to the peripheral compartment 1 (CL_{D1}, 52.4% CV), volume of distribution for the peripheral compartments 1 and 2 (Vp1 55.8% CV and Vp2 27.5% CV). No IIV was found for distributional clearance to the peripheral compartments 2 (CL_{D2}). The model derived total exposure based on Bayesian estimates for ABSSSI patients in studies RX-3341-202, RX-3341-302, and RX-3341-303 on Day 1 varied from 41.5 µg*h/mL (35.3% CV) to 49.8 (30.9 %CV). Day 3 AUC_{0-24} ranged from 31.6 (41.4 %CV) to 52.2 (37.5 %CV).

Mean day 1 AUC_{0-24} and C_{max} for the ABSSSI patients from study RX-3341-202 (N=75) (*report 00242-1*) were 43.3 µg*h/mL (38.3% CV) and 0.259 µg/mL (71.2% CV), respectively.

Pharmacokinetics in target population

For the IV formulation PK samples were collected in both healthy volunteers and patients. Under the same dosing regimen, the overall exposure (AUC) of delafloxacin was comparable between healthy volunteers (Phase I studies) and patients with ABSSSI (Phase II and III studies).

For the oral formulation, a PK comparison is not available between healthy volunteers and patients. In the Phase III study RX-3341-303 patients switched from 300 mg delafloxacin IV twice daily to 450 mg delafloxacin orally twice daily at Day 4 of treatment. Blood samples for PK analysis were only collected at Day 3 of treatment, and thus patient PK data for the oral formulation were not obtained.

The population PK model was refined using pooled data after IV and PO administration of delafloxacin. Data from Phase 1, 2, and 3 studies (i.e. RX3341-104, -108, -110, -111, -114, -115, -116, -118, -202, -302, an -303) were used for population PK model development. The refined model is documented in 00526-3 (Date: 1st August 2019).

Special populations

Impaired renal function

Study RX-3341-110 is an open-label, parallel group, single dose, cross-over study in 44 male and female subjects to determine if altered renal function affects the plasma pharmacokinetics of delafloxacin. For this, the pharmacokinetics of delafloxacin administered as a 400 mg oral dose (formulation A; Table 8) and a 300 mg IV infusion (intended commercial formulation) in healthy subjects (eGFR>80 ml/min/1.73 m^2; group A) and subjects with mild (eGFR >50-80 ml/min/1.73 m^2; group B), moderate (eGFR >30-50 ml/min/1.73 m^2; group C), and severe renal impairment (eGFR ≤ 30 ml/min/1.73 m^2; group D) were compared. An additional treatment group (E) of subjects with end-stage renal disease (ESRD) received a 300 mg delafloxacin IV infusion (intended commercial formulation) before and after haemodialysis.

The intended commercial IV formulation of delafloxacin contains 2400 mg Captisol (sulfobutylether β-cyclodextrin; SBECD) per dose to improve drug solubility. In humans, SBECD is eliminated unchanged almost entirely by renal filtration, and thus SBECD accumulates in subjects with impaired renal function. To assess any potential effect of SBECD on delafloxacin PK, IV delafloxacin (containing Captisol), IV placebo containing Captisol and oral delafloxacin without Captisol, were administered to subjects in groups A-D. The 3 periods were separated by a wash-out-period of 14 days.

Subjects in group E participated in 2 treatment periods with a wash-out period of 14 days.

- Period 1: 300 mg delafloxacin (containing Captisol) 1 h IV infusion starting approximately 1 h before initiation of the last haemodialysis session of the week (E1)

- Period 2: 300 mg delafloxacin (containing Captisol) 1 h IV infusion starting within 1 h after completion of the last haemodialysis session of the week (E2)

Results:

Plasma PK data

After 300 mg IV dosing or 400 mg oral dosing, the total exposure (AUC) of delafloxacin increased consistently as the degree of renal impairment increased.

For delafloxacin IV, mean AUC_{0-t} for the severe renal impairment group was 2.1-fold higher than the exposure observed for the healthy group. Mean AUC_{0-t} for the ESRD group without haemodialysis after dosing (Group E2) was 4.1-fold higher than the exposure observed for the healthy group. C_{max} was similar for the healthy group and the mild and moderate renal impairment groups. Arithmetic mean C_{max} values for the severe renal impairment group and for group E2 were 2.1-fold and 6.4-fold higher, respectively, than the corresponding value observed for the healthy group (Table 10).

The elimination half-life ($t_{1/2}$) was also meaningfully increased only for the severe renal impairment group and the ESRD group without haemodialysis after dosing (group E2). Mean $t_{1/2}$ was 9.3 h for the healthy

group and increased to 15.0 h for the ESRD group without haemodialysis after dosing (group E2) (Table 10).

After the 400-mg oral delafloxacin dose, the healthy group had nearly the same total exposure as observed following the 300-mg delafloxacin/Captisol IV dose (23.64 µg*h/ml and 25.75 µg*h/ml, respectively). Mean AUC_{0-t} values for the moderate and severe renal impairment groups were approximately 1.5-fold higher than the corresponding value for the healthy group. Mean C_{max} varied little across the various renal function groups after oral dosing, with a slightly higher mean C_{max} of 7.2 µg/mL for the healthy group (Table 10).

Table 5: Mean ± CV plasma pharmacokinetic parameters of delafloxacin in subjects with normal renal function or mild, moderate or severe renal impairment or ESRD

Parameter (Units)	Group[a]					
	Group A Normal Renal Function (n = 8)	Group B Mild Renal Impairment (n = 8)	Group C Moderate Renal Impairment (n = 8)	Group D Severe Renal Impairment (n = 8)	Group E1 ESRD (n = 8)	Group E2 ESRD (n = 8)
300 mg IV						
AUC_t (µg·h/mL)	23.6 ± 5.48 (23)	31.0 ± 6.00 (19)	39.3 ± 10.4 (26)	49.6 ± 20.5 (41)	83.3 ± 101 (121)	96.7 ± 102 (105)
AUC_∞ (µg·h/mL)	22.6 ± 4.52[b] (20)	31.3 ± 5.95 (19)	38.4 ± 10.7[c] (28)	51.1 ± 20.9 (41)	84.3 ± 101 (119)	97.5 ± 102 (104)
C_{max} (µg/mL)	9.28 ± 2.35 (25)	9.80 ± 1.09 (11)	9.86 ± 2.53 (26)	19.5 ± 27.3 (140)	54.4 ± 124 (229)	59.9 ± 135 (225)
T_{max}[d] (h)	1.00 (0.66, 1.00)	1.00 (1.00, 1.08)	1.00 (1.00, 1.08)	1.00 (0.33, 1.10)	1.00 (1.00, 1.17)	1.00 (0.33, 1.02)
$t_{1/2}$ (h)	9.28 ± 4.33[b] (47)	10.7 ± 2.45 (23)	8.90 ± 2.98[c] (34)	14.2 ± 6.02 (43)	10.6 ± 5.01 (47)	15.0 ± 2.15 (14)
CL (L/h)	13.7 ± 2.62[b] (19)	9.92 ± 2.01 (20)	8.25 ± 1.89[c] (23)	6.59 ± 2.07 (32)	6.58 ± 4.35 (66)	5.09 ± 2.94 (58)
CL_u (L/h)	2.19 ± 0.51[b] (23)	1.87 ± 0.52 (28)	1.44 ± 0.44[c] (31)	1.30 ± 0.36 (28)	1.70 ± 1.28 (76)	1.30 ± 0.87 (67)
CL_{NR} (L/h)	7.37 ± 1.89[b] (26)	6.95 ± 1.63 (24)	6.90 ± 1.83[c] (27)	6.19 ± 1.91 (31)	3.08 ± 2.16[e] (70)	3.04 ± 0.66[f] (22)
400 mg Oral						
AUC_t (µg·h/mL)	25.8 ± 7.54 (29)	26.8 ± 8.39 (31)	36.9 ± 6.94 (19)	37.9 ± 10.2 (27)	–	–
AUC_∞ (µg·h/mL)	25.4 ± 8.01[c] (32)	28.3 ± 8.18[c] (29)	37.3 ± 7.03 (19)	39.5 ± 11.0 (28)	–	–
C_{max} (µg/mL)	7.16 ± 2.50 (35)	5.67 ± 1.94 (34)	6.00 ± 1.78 (28)	5.35 ± 1.33 (25)	–	–

Parameter (Units)	Group[a]					
	Group A Normal Renal Function (n = 8)	Group B Mild Renal Impairment (n = 8)	Group C Moderate Renal Impairment (n = 8)	Group D Severe Renal Impairment (n = 8)	Group E1 ESRD (n = 8)	Group E2 ESRD (n = 8)
T_{max}[d] (h)	1.00 (0.50, 1.50)	1.00 (0.50, 2.00)	1.00 (0.50, 3.00)	1.50 (0.50, 6.00)	–	–
$t_{1/2}$ (h)	15.4 ± 6.66[c] (43)	12.5 ± 2.73[c] (22)	10.5 ± 4.24 (41)	15.5 ± 5.23 (34)	–	–
CL / F (L/h)	17.6 ± 7.08[c] (40)	15.9 ± 7.57[c] (48)	11.0 ± 2.03 (18)	10.8 ± 2.77 (26)	–	–
CL_u / F (L/h)	2.87 ± 1.18[c] (41)	2.97 ± 1.42[c] (48)	1.93 ± 0.51 (27)	2.19 ± 0.67 (31)	–	–

CV = coefficient of variation; eGFR = estimated glomerular filtration rate; ESRD= end-stage renal disease; IV = intravenous; SD = standarddeviation

Note: For re-enrolled subjects, data collected from the original enrollment were not included in this table.

[a] Group A: healthy subjects (estimated glomerular filtration rate [eGFR] > 80 mL/min/1.73 m^2).
Group B: subjects with mild renal impairment (eGFR > 50 – 80 mL/min/1.73 m^2).
Group C: subjects with moderate renal impairment (eGFR > 30 – 50 mL/min/1.73 m^2).
Group D: subjects with severe renal impairment (eGFR ≤ 30 mL/min/1.73 m^2).
Group E1: subjects with ESRDon hemodialysis; 300 mg delafloxacin / Captisol® IV starting 1 hour before initiation of hemodialysis.
Group E2: subjects with ESRDon hemodialysis; 300 mg delafloxacin / Captisol® IV starting within 1 hour after completion of the hemodialysis.
[b] n = 6
[c] n = 7
[d] For T_{max}, the median (minimum, maximum) values are presented.
[e] n = 3 [f] n = 2

It was noted that three PK samples from one individual had to be excluded from the tabulated data since deviation was very high (>10-fold higher than the next highest subject's concentration at these time points), probably due to drawing from the infusion line. This explains the very high C_{max} mean values for ESRD patients reported in the summary statistics.

Table 6: Mean ±CV plasma pharmacokinetic parameters of SBECD in subjects with normal renal function or mild, moderate or severe renal impairment or ESRD

Parameter (Units)	Group[a]					
	Group A Normal Renal Function (n = 8)	Group B Mild Renal Impairment (n = 8)	Group C Moderate Renal Impairment (n = 8)	Group D Severe Renal Impairment (n = 8)	Group E1 ESRD (n = 8)[b]	Group E2 ESRD (n = 8)
	300 mg IV					
AUC_t (µg·h/mL)	375 ± 44.5 (12)	494 ± 157 (32)	816 ± 216 (27)	1976 ± 607 (31)	3184 ± 1975 (62)	11165 ± 3538 (32)
AUC_∞ (µg·h/mL)	387 ± 44.7 (12)	508 ± 161 (32)	852 ± 217 (25)	2083 ± 659 (32)	–	29565 ± - (-)

Parameter (Units)	Group[a]					
	Group A Normal Renal Function (n = 8)	Group B Mild Renal Impairment (n = 8)	Group C Moderate Renal Impairment (n = 8)	Group D Severe Renal Impairment (n = 8)	Group E1 ESRD (n = 8)[b]	Group E2 ESRD (n = 8)
C_{max} (μg/mL)	177 ± 24.7 (14)	167 ± 16.8 (10)	191 ± 51.4 (27)	323 ± 358 (111)	946 ± 2004 (212)	1322 ± 2880 (218)
T_{max}[d] (h)	1.00 (1.00, 1.08)	1.00 (1.00, 1.08)	1.00 (1.00, 1.13)	1.00 (0.33, 1.10)	1.00 (1.00, 1.17)	1.05 (0.33, 1.17)
$t_{1/2}$ (h)	1.76 ± 0.15 (9)	2.51 ± 0.83 (33)	3.99 ± 0.77 (19)	10.3 ± 2.99 (29)	–	65.6[c]± - (-)
CL (L/h)	6.28 ± 0.79 (13)	5.08 ± 1.32 (26)	3.00 ± 0.82 (27)	1.26 ± 0.38 (30)	–	0.08[c]± - (-)
CL_{NR} (L/h)	0.92 ± 0.37 (40)	0.42 ± 1.22 (290)	0.09 ± 0.62 (683)	0.11 ± 0.20 (176)	–	–
Placebo IV						
AUC_t (μg·h/mL)	359 ± 48.7 (14)	427 ± 85.8 (20)	760 ± 208 (27)	1878 ± 731 (39)	–	–
AUC_∞ (μg·h/mL)	371 ± 48.8 (13)	446 ± 103 (23)	803 ± 207 (26)	1989 ± 804 (40)	–	–
C_{max} (μg/mL)	174 ± 25.8 (15)	161 ± 16.9 (11)	181 ± 37.8 (21)	191 ± 37.8 (20)	–	–
T_{max}[d] (h)	1.00 (0.33, 1.00)	1.00 (1.00, 1.08)	1.00 (1.00, 1.08)	1.00 (1.00, 1.08)	–	–
$t_{1/2}$ (h)	1.74 ± 0.17 (10)	2.38 ± 0.63 (27)	3.96 ± 0.75 (19)	9.69 ± 2.97 (31)	–	–
CL (L/h)	6.57 ± 0.86 (13)	5.60 ± 1.12 (20)	3.15 ± 0.73 (23)	1.38 ± 0.50 (36)	–	–
CL_{NR} (L/h)	1.13 ± 1.16 (102)	0.00 ± 5.87[e] (0)	0.28 ± 0.57 (203)	0.25 ± 0.27 (109)	–	–

Note: For re-enrolled subjects, data collected from the original enrollment were not included in this table.

[a] Group A: healthy subjects (estimated glomerular filtration rate [eGFR] >80 mL/min/1.73 m²).
Group B: subjects with mild renal impairment (eGFR >50-80 mL/min/1.73 m²).
Group C: subjects with moderate renal impairment (eGFR >30-50 mL/min/1.73 m²).
Group D: subjects with severe renal impairment (eGFR ≤30 mL/min/1.73 m²).
Group E1: subjects with ESRD on hemodialysis; 300-mg delafloxacin/Captisol IV starting 1 hour before initiation of hemodialysis.
Group E2: subjects with ESRD on hemodialysis; 300-mg delafloxacin/Captisol IV starting within 1 hour after completion of the hemodialysis.

[b] The $t_{1/2}$ could not be estimated for the ESRD group. Several dependent parameters could not be generated.

[c] n = 1.

[d] For T_{max}, the median (minimum, maximum) values are presented.

[e] CL_{NR} for Captisol placebo Group B was –0.94 (–625.0). Values presented as zeros in the table.

Statistics for plasma PK data of SBECD are shown in Table 11. A significant increase of total SBECD exposure was observed in the severe renal impairment and ESRD groups compared to the healthy control group. Arithmetic mean AUC_{0-t} for the severe renal impairment group was about 5-fold higher than the AUC_{0-t} of the healthy group while the increase for the ESRD group without haemodialysis after dosing (Group E2) was about 30-fold higher. However, for the healthy group and the mild, moderate, and severe renal impairment groups that received both the delafloxacin/Captisol IV infusion and the placebo/Captisol IV infusion, the arithmetic mean AUC_{0-t} values appeared to be similar.

Urine PK data

After the 300-mg delafloxacin/Captisol IV dosing, the fraction of the delafloxacin dose excreted in urine during 48 h after dosing declined from 45.3% for the healthy group to 5.5% for the severe renal impairment group. The vast majority of the urinary excretion of delafloxacin occurred in the first 12 h after dosing. The CL_{cr} decreased from 6.03 l/h for the healthy group to 0.40 l/h for the severe renal impairment group. The CL_{cr} after oral dosing was similar to the values and pattern observed for the IV dosing and decreased from 5.09 l/h for the healthy group to 0.29 l/h for the severe renal impairment group.

As expected, CL_{cr} of SBECD decreased with decreasing renal function. Mean CL_{cr} was 5.43 l/h for the healthy group and declined to 1.13 l/h for the severe renal impairment group. The mean CL_{cr} of SBECD was similar for the delafloxacin/Captisol administration and the placebo/Captisol administration.

Dialysate PK data

For delafloxacin, when haemodialysis occurred 1 h after delafloxacin/Captisol IV infusion in the ESRD group, the mean fraction of administered delafloxacin recovered in the dialysate (Frem%0-4) was 19.2%. Mean CL_d was 4.21 l/h.

For SBECD, when haemodialysis occurred 1 h after the delafloxacin/Captisol IV infusion in the ESRD group, the mean fraction of administered SBECD recovered in the dialysate (Frem%0-4) was 56.1%. Mean CL_d was 4.74 L/h.

PopPK

The impact of renal impairment, independent of weight or sex indicates that patients with severe renal impairment and patients with ESRD are expected to have substantial increases in delafloxacin exposure if given the full clinical dose of 300 mg IV Q12h. Simulations were conducted for patients with different status of renal impairment and reduced doses were proposed for severely renal impaired patients (00432-1). With the reduced dose of 200 mg IV Q12h in this patient population, simulated AUC was between AUC values of patients with normal renal functions and those with mildly impaired renal function (00432-1).

Oral administration of 450 mg (report 00517): For the simulated patient population which was generated using bootstrapping to reflect patients in Studies RX-3341-202, RX-3341-302, and RX-3341-303 (n=3,913), median free-drug and total-drug plasma AUC values on day 1 were 6.43 (min 2.07, max 22.9) and 40.2 (min 12.9, max 143) mg*h/L, respectively. The median CL_{Cr} was 95.2 (min 21, max 244) mL/min/1.73 m^2.

00432-2 (PK-3341-015): Patients with normal renal function, mild or moderate impairment received 300 mg IV Q12h followed by 450 mg PO Q12h while patients with severe renal impairment or end-stage renal disease received 200 mg IV Q12h followed by 450 mg PO Q24h delafloxacin. For the simulated patient population which was generated using bootstrapping to reflect patients in studies RX-3341-202, RX-3341-302, and RX-3341-303 (n=3,913), median (min, max) free drug plasma AUC values on Days 1 and 4 were 6.99 (2.32, 22.9) and 7.03 (1.51, 25.8), respectively. The median (min, max) CL_{Cr} was 95.2 (21, 244) mL/min/1.73 m^2.

Delafloxacin was administered to simulated patients with normal renal function, mild and moderate renal impairment as 300 mg IV Q12h on Days 1-3 and 450 mg PO Q12h on Day 4. Simulated patients with severe renal impairment and ESRD received delafloxacin 200 mg IV Q12h on Days 1 to 3 followed by 450 mg PO Q12h on Day 4 (00432-2 addendum1 / PK-3341-021).

Overall, AUC values range roughly from 36 to 57 µg*h/mL (total-drug) and 6 to 9 µg*h/mL (free-drug), respectively, for patients with normal renal function and mild or moderate impaired renal function (00517, 00432-2, and 00432-2 addendum1). AUC values in patients with severe renal function or end-stage renal disease tend to rise 2-fold after oral administration of 450 mg Q12h compared to 450 mg Q24h (e.g. total AUC 34 to 68 µg*h/mL).

The impact of dialysis on delafloxacin exposure in patients with end-stage renal disease was quantified by adjusting the simulated exposures in those patients using the distribution ratio of AUC_{0-24} when delafloxacin was administered just before and after dialysis in Study RX-3341-110. This study showed that AUC_{0-24} was approximately 20% lower when delafloxacin was administered just before dialysis.

The refined model (report 00526-1, date: 10 December 2018) reveals that after IV administration of 300 mg Q12h patients with mild and moderate renal impairment and patients with ESRD receiving a reduced IV dose of 200 mg Q12h are expected to have up to about 2-fold higher exposure compared to patients with normal renal function (report 00526-1). After oral administration of 450 mg Q12h, patients with mild to severe renal impairment and ESRD are expected to have approximately up to 2- to 3.5-fold increase in AUC compared to patients with normal renal function (report 00526-1).

Simulations were performed in order to evaluate the differences in expected exposure (AUC) when delafloxacin is administered with or without dialysis (report 00526-1). The impact of dialysis on delafloxacin exposure in patients with ESRD was quantified to be approximately 20% at Day 1 as well as at Day 4, following 3 days of delafloxacin Q12h administration.

In the PoP-PK model, ~~only the~~ renal impairment was identified as the only intrinsic factor warranting dose adjustment. The other covariates such as age, gender, weight and disease status have not shown to significantly impact delafloxacin exposure.

Disease status: Disease status (patients vs. healthy) was not a statistically significant predictor of the IIV in delafloxacin PK (00432-1).

Impaired hepatic function

Study ML-3341-112 was a multi-centre, open-label study to evaluate the PK profile of a single 1-hour infusion of 300 mg delafloxacin (intended commercial formulation) in healthy subjects and subjects with mild, moderate, or severe hepatic impairment. A total of 39 male and female subjects were enrolled and stratified into groups based on hepatic function as defined by the Child-Pugh classification system.

AUC_{0-t} in subjects with mild, moderate and severe hepatic impairment increased by 1.1 to 1.4-fold compared to healthy subjects. For C_{max} either no change (mild impairment) or just a slight reduction (10% for moderate impairment and 8% for severe impairment) was observed.

Drug-Drug-Interactions

Similar to other fluoroquinolones, delafloxacin is minimally metabolised by CYP450 and undergoes direct glucuronidation. Delafloxacin neither inhibits or induces CYP450, nor inhibit drug transporters at clinically relevant concentrations.

In *in vitro* studies, delafloxacin was shown to be a substrate for BCRP (efflux ratio of 8.86) and a possible substrate for P-gp (efflux ratio of 2.1). A clinical drug-drug interaction (DDI) study to evaluate the *in vivo* DDI potential between delafloxacin and P-gp and/or BCRP inhibitors has not been conducted.

The effect of delafloxacin on midazolam was studied *in vivo* indicating that delafloxacin is not a CYP3A inducer.

2.4.3. Pharmacodynamics

Mechanism of action

Delafloxacin, like other fluoroquinolones, is a novel anionic fluoroquinolone antibiotic that inhibits DNA synthesis in bacteria by binding to bacterial type II topoisomerases DNA gyrase and topoisomerase IV. Since delafloxacin shows a similar affinity for both types of enzymes, it is depicted as a dual-targeting fluoroquinolone. A key feature of delafloxacin is its unique chemical structure among the fluoroquinolone class antibiotics. These chemical properties seem to correlate with a highly improved potency relative to other fluoroquinolones against Gram-positive bacteria and an enhanced activity in acidic environments.

Spectrum of antimicrobial activity

The *in vitro* activity of delafloxacin against selected clinically prevalent Gram-positive and Gram-negative pathogens including anaerobes has been determined via both preclinical profiling studies and surveillance studies.

Delafloxacin was shown to have potent *in vitro* activity for bacteria traditionally related to ABSSSI such as several staphylococci or streptococci. Compared to levofloxacin and other antibiotics delafloxacin had an overall enhanced activity against Gram-positive isolates. Additionally, potent activity was also demonstrated against strains with quinolone resistance like MRSA. Delafloxacin was also shown to be active against Gram-negative isolates, although activity was decreased in isolates with high fluoroquinolone-resistance rates.

The spectrum of activity of delafloxacin also includes potent activity against the atypical pathogens (*L. pneumophila*, Legionella spp., *M. pneumoniae*, *M. fermentans*, *M. genitalium*; *M. hominis*, *Ureaplasma* spp., *Chlamydophila trachomatis*, and *Chlamydophila pneumoniae)*. Delafloxacin also demonstrates *in vitro* activity against *B. anthracis*, *Y. pestis*, *B. mallei* and *B. pseudomallei*, bacteria that can cause naturally acquired infections but may also be used as biological weapons.

Bactericidal and intracellular activity / PAE

In *in vitro* studies delafloxacin was bactericidal against several staphylococci species including MSSA and MRSA strains as well as against other clinical Gram-positive and Gram-negative isolates.

Resistance mechanisms

Delafloxacin had a low rate of spontaneous mutations leading to resistance in the *in vitro* single-step mutational studies and a comparable occurrence of resistance development in multiple-steps mutational studies with regard to the tested comparator fluoroquinolones. In the clinical studies, no emergence of resistance was observed.

Animal studies

The activity of delafloxacin was evaluated in several infection models against ABSSSI target pathogens and other relevant pathogenic bacteria. The data of most importance in this application were those used to support the PK/PD analyses.

Pharmacodynamic interactions with other medicinal products or substances

The provided studies demonstrated that delafloxacin shows no positive or negative interactions with other antibiotics and thus a co-administration with the tested agents is thought to have no impact. Macrolides which could be indicated in case of ABSSSI were not tested for antimicrobial interaction to delafloxacin due to potential adverse reactions. Furthermore, concomitant administration of both antibiotic classes is not recommended for the management of ABSSSI according to current guidelines

Relationship between plasma concentration and effect

The proposed dose regimen for IV treatment of ABSSSI is 300 mg delafloxacin every 12 hours by 60 minutes-infusion for 5 to 14 days. It is planned that a switch to the proposed oral dose can be done at the discretion of the physician as stated in the product information.

The proposed oral (PO) treatment of ABSSSI is 450 mg delafloxacin every 12 hours for a total duration of 5 to 14 days.

These dose regimens for Phase 2 and 3 studies were selected based on *in vitro* microbiological testing, *in vivo* animal models of infection with PK/PD analysis, target attainment analysis using MCS, clinical exposure -response modelling, and clinical experience. The refinement of the popPK models and PTA analyses has been achieved in an iterative manner as more human PK data became available from clinical studies.

Non-clinical PK-PD targets for efficacy were determined using data from a neutropenic murine thigh infection model. The AUC/MIC ratio based on free-drug plasma data were found to be the most predictive of efficacy (r^2=0.74 for *S. aureus*). These findings are in line with PK-PD relationship for other fluoroquinolones.

The free-drug plasma AUC/MIC ratio target associated with net bacterial stasis and 1-$\log_{10}$ CFU reductions from baseline for *S. aureus* were 9.3 and 14.3, respectively.

Clinical efficacy-response relationship could not be established due to high percentage of successful clinical response in clinical efficacy studies. The high percentages of clinical success (improved + cured) overall (86.6 to 98.7% across endpoints and populations) and distribution of $fAUC_{24}$/MIC ratios observed relative to the murine non-clinical targets suggest that patients achieved delafloxacin exposures on the plateau of the PK/PD relationships for efficacy.

Based on a refined popPK model (00562-3), MCS were conducted to determine % PTA by MIC values for *S. aureus* on Days 1 and 4 among delafloxacin dose regimens (IV, IV-to-PO, and PO).

Following the IV dosing regimen of 300 mg delafloxacin IV Q12h for simulated patients with normal renal function, mild or moderate renal impairment or 200 mg IV Q12h for patients with severe renal impairment or ESRD the percent probabilities of PK/PD target attainment at a MIC value of 0.25 µg/mL based on the median fAUC/MIC ratio target associated with net bacterial stasis was nearly 100% on Days 1 and 4 in all populations, respectively. At the MIC value of 0.5 µg/mL, percent probabilities of PK - PD target attainment on Days 1 and 4 were 88.4% and 90.7% for the clinical trial population, respectively.

For the IV to PO dosing regimen for delafloxacin (300 mg IV, Q12h on Days 1 to 3 followed by 450 mg PO, Q12h on Day 4 [normal renal function and mild/moderate renal impairment] or 200 mg IV, Q12h on Days 1 to 3 followed by 450 mg PO, Q12h on Day 4 [severe renal impairment or ESRD]), the % PTAs for all patients (including those with varying degrees of renal function) on Day 1 and 4 at a MIC_{90} value of 0.25 µg/mL associated with net bacterial stasis were 99.8% and 99.7 %, respectively. At a MIC value of 0.5 µg/mL, percent probabilities of PK - PD target attainment on Days 1 and 4 were 88.4% and 82.3%, respectively.

Percent probabilities of target attainment for the oral dosing regimen of 450 mg delafloxacin PO Q12h for the clinical trial population (including patients with normal renal function as well as mild/moderate/severe renal impairment or patients with ESRD) were 99.5% and 99.7% on Day 1 and 4 at MIC_{90} value of 0.25 µg/mL associated with net bacterial stasis, respectively.

The % PTA for *E. coli* following IV dosing at stasis which was predicted by simulations was 98% at a MIC value of 0.25 µg/mL. For a $1\text{-}log_{10}$ bacterial reduction, the % PTA was 99% for MICs up to and including 0.12 µg/mL.

The % PTA for *P. aeruginosa* following IV dosing were ≥ 97.3% for stasis ($fAUC_{24}$/MIC ratio target of 3.81) at a MIC value of 1 µg/mL, and 99.9% for 1-log10 CFU reduction ($fAUC_{24}$/MIC ratio target of 5.02) at a MIC value of 0.5 µg/mL.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetics and pharmacodynamics of delafloxacin as oral and intravenous formulation has been well characterised in 23 Phase I studies.

AUC after administration of 900 mg of the intended commercial oral formulation was comparable when taken under fasted and fed conditions, but a high-fat meal taken 30 min before delafloxacin administration delayed absorption (T_{max}) and reduced C_{max} (90% CI: 73.13, 86.44).

Bioequivalence between the to-be-marketed 450 mg tablet and the to-be-marketed 300 mg IV infusion was demonstrated under fasting conditions in terms of AUC. However, both AUC_{0-t} and $AUC_{0-\infty}$ were at the lower end of the confidence interval after oral administration (mean AUC_{0-t}: 84.5% (CI: 80.90; 88.15), mean $AUC_{0-\infty}$: 87.7% (CI: 83.56; 92.00)) and this difference could impact on efficacy when using the oral formulation alone or switching from IV to oral formulation. Mean C_{max} was about 45% reduced after administration of the 450 mg tablet under fasting conditions compared to C_{max} after intravenous infusion. As the PK parameters of IV and oral formulations were not studied in a bioequivalence study under fed conditions, a direct comparison of the influence of food on C_{max} is not possible. However, the results of studies RX-3341-115 (bioequivalence study) and RX-3341-116 (food effect study) indicate that the difference in C_{max} may be even higher between the two formulations when the 450 mg tablet is taken with a meal. Nevertheless, since the relevant PK-PD index of delafloxacin is $fAUC_{24}$/MIC a decrease in C_{max} is not expected to affect the probability of target attainment.

A population PK model was developed describing data from Phase 1, 2, and 3 studies after IV administration of delafloxacin and served as basis for various simulations (00432-1 / PK-3341-009). This initial model has been updated using pooled data after IV and PO administration. The final model 0526-3 served as basis for PKPD target attainment analysis.

In the PopPK model renal impairment was identified as the only intrinsic factor warranting dose adjustment.

In patients with mild and moderate renal impairment mean AUC_{0-t} was 1.3-fold and 1.7-fold higher, respectively, compared to healthy subjects. The CHMP agreed that no dose adjustment is required in

those patients (as reflected in the product information). The safety assessment for patients with mild and moderate renal impairment included in the Phase II study RX-3341-201 and the Phase III studies RX-3341-302 and RX-3341-303 did not identify any additional TEAEs compared to other patients.

Based on the results from study RX-3341-110 and the popPK analysis the applicant proposed to reduce the delafloxacin dose in patients with severe renal impairment (to 200 mg IV every 12 h. Alternatively patients should receive 450 mg delafloxacin orally every 12 hours. For delafloxacin IV, mean AUC_{0-t} for the severe renal impairment group was 2.1-fold higher than the exposure observed for the healthy group. After oral administration of 400 mg delafloxacin in patients with severe renal impairment mean AUC_{0-t} was about 1.5-fold higher than the corresponding value of the healthy group, mean C_{max} was about 25% decreased. A dose reduction of the IV formulation for patients with severe renal impairment is therefore considered adequate.

With respect to patients with severe renal impairment, simulated AUCs after dosing with 200 mg delafloxacin revealed that exposure will be in the same range as for patients with normal to moderate renal function receiving a 300 mg dose. The model used to simulate the exposure underpredicted the concentrations in severe renal impairment, resulting in lower predicted AUCs compared to expected observed data. But even taking this into account, it is still agreed that exposures after 200 mg dosing IV in severe renal impairment will result in exposures in the range of that seen in the clinical trials. Differences in C_{max} values between renal function groups, associated with safety, were less pronounced. The CHMP therefore agreed with the recommendation to reduce the delafloxacin dose in patients with severe renal impairment (to 200 mg IV every 12 h and that alternatively patients should receive 450 mg delafloxacin orally every 12 hours.

For the ESRD group without haemodialysis after dosing (Group E2), mean AUC_{0-t} was 4.1-fold higher and mean C_{max} values for group E2 were 6.4-fold higher than the corresponding values observed for the healthy group. Additionally, the elimination half-life ($t_{1/2}$) increased from 9.3 h for the healthy group to 15 h for E2. In order to determine the dose recommendation in patients with ESRD, the CHMP took into account data on SBECD exposure.

Delafloxacin for IV administration is formulated with SBECD which is primarily excreted by glomerular filtration in the kidney. Consistently, SBECD exposure was shown to increase with decreased renal function in study RX-3341-110, but SBECD seems not to affect delafloxacin PK. Mean SBECD AUC_{0-t} of patient with severe renal impairment was about 5-fold higher, while AUC_{0-t} increased about 30-fold in ESRD patients after haemodialysis (group E2). Accumulation of SBECD at supra-clinical concentrations has resulted in renal vacuolation and appearance of pulmonary foamy macrophages in animal studies (Luke et al., 2010: review on the basic and clinical pharmacology of sulfobutylether-ß-cyclodextrin, *J Pharm Sci* 99: 3291-3301). However, SBECD-associated toxicity in humans that would prevent its use has not been described so far. Nevertheless, there are other IV drugs approved that contain SBECD.

Study RX-3341-110 showed that SBECD is removed from blood by haemodialysis. However, haemodialysis is usually performed intermittently (every 2 or 3 days) in ESRD patients and thus SBECD is expected to accumulate extensively on interdialytic days which raises a potential safety concern. Based on the available data, no dose recommendation for ESRD patients can be supported. In addition, predicted exposures of SBECD in ESRD patients were high and clinical safety data in these patients are lacking. Therefore, the applicant agreed to not further pursue the recommendation of IV delafloxacin dosing in ESRD patients and to modify the product information accordingly. The CHMP considered that the dose reduction of 200 mg IV in patients with severe renal impairment remains appropriate and agreed, but the risk of renal damage secondary to SBECD accumulation in patients with severe renal impairment is seen as an important potential risk necessitating close monitoring and is therefore included in the RMP.

In *in vitro* studies, delafloxacin was shown to be a substrate for BCRP and a possible substrate for P-gp. However, a clinical drug-drug interaction (DDI) study to evaluate the *in vivo* DDI potential between

delafloxacin and P-gp and/or BCRP inhibitors has not been conducted. The applicant argues that inhibition of these transporters would likely increase delafloxacin C_{max} modestly due its good oral bioavailability (58.8%), and the increases in exposure would likely not be clinically relevant due to the safety of delafloxacin at oral doses up to 1200 mg/day (study M00-224) and IV doses of 450 mg Q12h (study RX-3341-103). This was agreed by the CHMP. In clinical trials 28 patients received a P-gp/BCRP inhibitor concomitantly (from start of delafloxacin to EOT). 17 of these patients experienced at least one TAE; 4 of them were serious but were not considered to be treatment-related by the applicant. Post-hoc analyses indicates that the PK of delafloxacin is not impacted by the presence of P-gp or BCRP inhibitors.

The spectrum of antimicrobial activity has been assessed via susceptibility testing in both preclinical profiling studies and surveillance studies. Several surveillance studies from different regions in the period of 2014 to 2018 were compared and analysed, accordingly. Delafloxacin showed a good activity against several gram-positive as well as gram-negative pathogens.

In vitro experiments were conducted to evaluate the bactericidal effect of delafloxacin and its ability to concentrate inside cells with antibacterial activity. The impact on the proposed breakpoints of the post-antibiotic effect and the delayed re-growth of bacteria following exposure to an antibiotic should be observed in order to investigate the possibility of resistance development. The CHMP recommended that this data should be submitted as a post-authorisation measure by the end of February 2020.

Concerning the testing of resistance mechanisms, no resistance development was detected in clinical studies. However, the development of resistance to delafloxacin will be monitored by the applicant post-authorisation.

With regard to the aspect of cross-resistance which is commonly observed between fluoroquinolones, a summarising comment on cross-resistance of delafloxacin with other antibiotics was implemented in the product information.

The selection of the IV dosing regimen (300 mg IV Q12h) for the clinical efficacy studies has been adequately justified and predicted to be effective via MCS, PK/PD target attainment analysis and a review of delafloxacin exposure data obtained from patients enrolled in a Phase 2 ABSSSI study (RX-3341-202). The oral dose regimen (450 mg PO Q12h) was selected based on the fact that the 450 mg tablet was shown to be bioequivalent to the IV dose. PTA analyses of several oral dosing regimens revealed that a dosing regimen of 450 mg PO Q12h should be sufficiently effective in all of the simulated patient populations even with renal impairment.

With regard to the evaluation of the PK/PD relationship for efficacy the dosing regimens of IV, IV-to- PO and PO only for patients with ABSSSI were evaluated. Based on a popPK model, MCS were conducted to determine %PTA by MIC values for *S. aureus* on Day 1 and 4 among delafloxacin dose regimens (IV, IV-to-PO, and PO). Results of the PTA analyses for the different dosing regimens revealed sufficient coverage (>90%) of the target associated with net bacterial stasis for the different patient populations at a MIC representing the clinical breakpoint of 0.25 µg/mL. Thus, the presented data are supportive for the proposed dosing recommendations. Therefore, the PK/PD target attainment in simulated patients receiving delafloxacin for all of the proposed dosing regimens are considered acceptable. In the context of the exposure-response analysis for clinical endpoints the applicant analysed different efficacy endpoints with regard to successful clinical responses. In relation to the primary efficacy endpoint in the pivotal trials (Investigator-assessed outcome of clinical cure at the FU visit) no relationship between Investigator-assessed clinical response at FU and fAUC/MIC ratio could be identified.

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

The final susceptibility testing breakpoints established by the EUCAST were:

Organism	MIC breakpoints (mg/L)	
	Susceptible (S ≤)	Resistant (R >)
Staphylococcus aureus	0.25	0.25
Streptococcus pyogenes	0.03	0.03
Streptococcus dysgalactiae	0.03	0.03
Streptococcus agalactiae	0.03	0.03
Streptococcus anginosus group	0.03	0.03
Escherichia coli	0.125	0.125

2.4.5. Conclusions on clinical pharmacology

With regard to pharmacokinetics and pharmacodynamics the documentation of delafloxacin is considered satisfactory.

Data generated under fasted and fed conditions support the conclusion that delafloxacin can be taken with or without food.

In patients with ESRD, the accumulation of delafloxacin in the two to three days in between two dialysis sessions with Q12h dosing still remains unknown but may be pronounced in these patients. No PK data in this period are available and model predictions for this period were not possible according to the applicant and would be very uncertain given the performance of the model for this subpopulation. Overall, with the available data, no dose recommendation for ESRD patients is therefore possible. In addition, predicted exposures of SBECD in ESRD patients were high and clinical safety data in these patients are lacking.

With respect to patients with severe renal impairment, simulated AUCs after dosing with 200 mg IV delafloxacin revealed that exposure will be in the same range as for patients with normal to moderate renal function receiving a 300 mg dose, even taking the underprediction by the model for this subpopulation into account. Differences in C_{max} values between renal function groups, associated with safety, were less pronounced. Regarding the oral formulation, the justification for keeping the 450 mg oral dosage in patients with severe renal impairment is supported by popPK model.

In conclusion, the applicant agreed not to recommend the use of IV and oral delafloxacin dosing in ESRD patients in the product information while in patients with severe renal impairment, the recommended IV dose is reduced to 200 mg IV every 12 hours. No dose adjustment is necessary in patients with severe renal impairment for the oral formulation. The risk of renal damage secondary to SBECD accumulation in patients with severe renal impairment is seen as an important potential risk necessitating close monitoring and is therefore included in the RMP.

2.5. Clinical efficacy

Clinical documentation to support this application includes one Phase 2 dose finding study, two pivotal Phase 3 studies and one supportive Phase 2 study (please refer to the table below).

Table 7: Overview of Delafloxacin Clinical Key Studies in Adults in Support of ABSSSI Indication

	RX-3341-201 (Study 201)	RX-3341-202 (Study 202)	RX-3341-302 (Study 302)	RX-3341-303 (Study 303)
Phase; Year Completed	Phase II; 2008	Phase II; 2011	Phase III; 2014	Phase III; 2016

		RX-3341-201 (Study 201)	RX-3341-202 (Study 202)	RX-3341-302 (Study 302)	RX-3341-303 (Study 303)
Population		Adults with cSSSI (pre 2010 definition)	Adults with ABSSSI (required lesion size ≥ 75cm^2) and at least 1 systemic sign of infection	Adults with ABSSSI (required lesion size ≥ 75cm^2) and at least 2 systemic signs of infection	Adults with ABSSSI (required lesion size ≥ 75cm^2) and at least 2 systemic signs of infection
Comparator (N)		Tigecycline (50)	Linezolid (77), Vancomycin (98) (optional aztreonam)	Vancomycin + aztreonam (329)	Vancomycin + aztreonam (427)
Delafloxacin Dose / Route (N)		300 mg IV Q12h (49), 450 mg IV Q12h (51)	300 mg IV Q12h (81)	300 mg IV Q12h (331)	300 mg IV Q12h for 6 doses with switch to 450 mg oral Q12h (423)
Duration of Therapy		5 - 14 d	5 - 14 d	5 - 14 d	5 - 14 d
Time points	OR	NA	48 - 72 h	48 - 72 h	48 - 72 h
	EOT	NA	NA	Assessment collected	Assessment collected
	FU	NA	Day 14	Day 14	Day 14
	LFU	NA	Day 21 - 28	Day 21 - 28	Day 21 - 28
	TOC	14 - 21 days post last dose	NA	• PTE • PTE$_{7-14*}$ • PTE$_{6-15*}$	• PTE • PTE$_{7-14*}$ • PTE$_{6-15*}$
Stratification Factors and Enrollment Limits at Randomization		Infection Type	Infection Type and Prior Antibiotics Enrollment limited to: Prior antibiotics − 30%, Abscesses − 30%	Infection Type Enrollment limited to: Prior antibiotics − 25%, Abscesses − 25%, Wounds − 35%	Infection Type and BMI (< or ≥ 30 kg/m^2). Enrollment limited to: Prior Antibiotics − 25%, Abscesses − 25%, Wounds − 30%, BMI ≥ 30 mg/kg^2 − ≤ 50%
Primary Endpoint		Investigator outcome (traditional definition with complete or near resolution of signs and symptoms as cure)	Investigator assessment of cure only (cure was classified as a success and all other responses were classified as failures [i.e., improved, failure, and indeterminate]).	Investigator assessment at FU (Day 14 + 1 from randomization).	Investigator assessment at FU (Day 14 + 1 from randomization).

EOT: End of Treatment; FU: Follow-up; LFU: Late Follow-up; OR: objective response; TOC: Test of Cure; PTE: Post Treatment Evaluation (as for EMA SAP); PTE$_{7-14}$: PTE within the 7 - 14 window post EOT; PTE$_{6-15}$: PTE within the 6 - 15 window post EOT
* PTE$_{7-14}$ and PTE$_{6-15}$ were performed by the applicant as additional analyses.

2.5.1. Dose response study

<u>Phase 2 study RX-3341-201</u>

Study RX 3341-201 was a randomised, double blind, Phase II, multicentre study comparing the efficacy and safety of IV delafloxacin to that of IV tigecycline when used to treat adults with cSSSI. In total, 150 patients were randomly assigned, in a 1 : 1 : 1 ratio, to delafloxacin 300 mg Q12h, delafloxacin 450 mg Q12h, or tigecycline 100 mg initially, followed by 50 mg Q12h. Treatment was given for 5 to 14 days, based on the investigator's judgment. The primary efficacy endpoint was clinical response in the CE population at TOC visit (14 to 21 days after the final dose of study drug). Clinical cure was defined as resolution of baseline signs and symptoms of cSSSI or improvement to an extent that no additional antibiotic treatment is necessary.

Table 8: Clinical Response of Delafloxacin at Test of Cure in Study RX 3341 201

	Delafloxacin 300 mg	Delafloxacin 450 mg	Tigecycline 100 / 150 mg
Clinically Evaluable (CE)	94% (33 / 35)	93% (37 / 40)	91% (31 / 34)
Intent-to-Treat (ITT)	88% (43 / 49)	90% (46 / 51)	82% (41 / 50)
Clinical Response by Pathogen for CE Population			
S. aureus	96% (21 / 22)	93% (25 / 27)	90% (18 / 20)
MRSA	93% (13 / 14)	95% (19 / 20)	86% (12 / 14)
MSSA	100% (8 / 8)	86% (6 / 7)	100% (6 / 6)

Source: Study RX-3341-201 Table 14.2.1.1, Table 14.2.1.2 and Table 14.2.1.4

The clinical cure rate in CE population was comparable between delafloxacin arms and tigecycline arm. In the ITT population the clinical cure rate was numerically higher in the delafloxacin arms compared to the tigecycline arm. Regarding safety more AEs were reported for the 450 mg delafloxacin group compared to the lower dose. In particular, higher incidences of gastrointestinal disorders (450 mg delafloxacin: 43.1% vs. 300 mg delafloxacin: 24.5%) and low serum glucose values (450 mg delafloxacin: n=9 vs. 300 mg delafloxacin: n=3) were detected.

As a conclusion, the 300 mg IV dose of delafloxacin, given its clinical and microbiological effect and its tolerability profile, was selected to be evaluated in the next Phase II and larger Phase III studies.

Overall, the selection of the 300 mg IV dose based on the efficacy and safety results of phase II studies seems to be appropriate.

2.5.2. Main studies

Two pivotal phase III studies were performed by the applicant. Study RX-3341-302 investigated the efficacy of IV delafloxacin vs vancomycin + aztreonam in the treatment of patients with ABSSSI for 5 to 14 days (n= 660) and was conducted in the years 2013-2014. Study RX-3341-303 investigated the efficacy of IV (3 days) followed by oral delafloxacin vs vancomycin + aztreonam in the treatment of patients with ABSSSI for overall 5 to 14 days (n= 850) and was conducted between 2014 and 2016.

Study titles

Study RX-3341-302 title: A Phase 3, Multicenter, Randomized, Double-Blind, Active-Controlled Study to Evaluate the Efficacy and Safety of Delafloxacin Compared With Vancomycin + Aztreonam in Patients With Acute Bacterial Skin and Skin Structure Infections

Study RX-3341-303 title: A Phase 3, multicenter, randomized, double-blind, active-controlled study to evaluate the efficacy and safety of IV and oral delafloxacin compared with vancomycin + aztreonam in patients with acute bacterial skin and skin structure infections

Methods

Study participants

Main inclusion criteria

Eligible patients in pivotal studies RX-3341-302 and RX-3341-303 were male or female ≥18 years of age with a diagnosis of ABSSSI, i.e., an infection involving skin and/or subcutaneous tissues of at least 1 of the following 4 types (only the primary infection type was followed for study purposes):

- Cellulitis/erysipelas: diffuse skin infection, minimum surface area of 75 cm^2
- Wound infection: infection characterised by purulent drainage from a traumatic or surgical wound with surrounding redness of a minimum surface area of 75 cm^2
- Major cutaneous abscess: infection characterised by a collection of pus within the dermis or deeper that is accompanied by redness of a minimum surface area of 75 cm^2
- Burn infection: infection characterised by purulent drainage that is accompanied by redness of a minimum surface area of 75 cm^2, patients with burn infections were only enrolled if the area of the burn comprised ≤10% of the patient's body surface as determined by the investigator

AND at least 2 of the following signs of systemic infection:

- Lymph node enlargement due to the present infection
- Documented fever ≥38°C/100.4°F taken orally (or the equivalent value for the temperature recording method used)
- Lymphangitis
- Elevated white blood cells (WBCs) of ≥10 000 cells/μL in the 48 hours prior to first dose of study drug
- Elevated C-reactive protein (>10 × upper limit of normal [ULN]) in the 48 hours prior to first dose of study drug
- Purulent or seropurulent drainage or discharge

Main exclusion criteria included:

- Medical history of significant hypersensitivity or allergic reaction to quinolones, beta-lactams, vancomycin, or vancomycin derivatives according to the judgment of the investigator.
- Women who were pregnant or lactating.
- Any chronic or underlying skin condition at the site of infection that might complicate the assessment of response (e.g., atopic dermatitis or eczema). Any other skin condition that, in the opinion of the investigator, would interfere with objective measurement of the ABSSSI under treatment.
- Infection associated with a prosthetic joint or the removal of a prosthetic joint, or infection involving other prosthetic materials or foreign bodies (e.g., catheter tunnels) unless that other prosthetic material was removed within 24 hours after starting study drug.

- Infection associated with any of the following: Human or animal bite (insect bites were not considered animal bites), Osteomyelitis, Decubitus ulcer, Diabetic foot ulcer, Septic arthritis, Mediastinitis, Sternal wound, Necrotizing fasciitis, anaerobic cellulitis, or synergistic necrotizing cellulitis, Myositis, Tendinitis, Endocarditis, Toxic shock syndrome, Sustained shock, Gangrene or gas gangrene, Burns covering ≥10% of body surface area, Severely impaired arterial blood supply to an extremity with an ABSSSI, Current evidence of deep vein thrombosis or superficial thrombophlebitis, Any infection types with poor circulatory status in the opinion of the investigator

- Receipt of systemic antibiotic therapy in the 14 days before enrolment unless one of the following was documented:

  The patient received at least 48 hours of antibiotic therapy for ABSSSI AND the clinic notes or photographs documented the clinical progression of ABSSSI (i.e., not by patient history alone).

  The patient recently (Study RX-3341-302: within 7 days; Study RX-3341-303: within 14 days) completed a treatment course with an antibacterial drug for an infection other than ABSSSI and the drug did not have activity against bacterial pathogens that cause ABSSSI.

  The patient received only 1 dose of either a single, potentially effective, short-acting (Study RX-3341-302: half-life ≤12 hours; Study RX-3341-303: half-life ≤12 hours or dosed every 12 hours or more frequently) antimicrobial drug or a short-acting antimicrobial drug regimen for treatment of the ABSSSI under study before enrolment (Patients who received 1 dose of either a single, potentially effective, short-acting antimicrobial drug or regimen for treatment of the ABSSSI under study in the 14 days before study entry were limited to no more than 25% of total randomly assigned patients)

- Severely compromised immune systems

- Known history of Child-Pugh Class B or C liver disease.

- Alanine aminotransferase (ALT) >3 × ULN.

- Patients with end-stage renal disease on haemodialysis or peritoneal dialysis or creatinine clearance of ≤30 mL/minute using the Cockcroft-Gault formula.

- Body weight Study RX-3341-302: >140 kg; Study RX-3341-303: >200 kg.

Treatments

Study RX-3341-302

Delafloxacin, 300 mg IV every 12 hours for infusion over 1 hour **or** vancomycin, 15 mg/kg IV every 12 hours (based on actual body weight) administered over 2 hours and aztreonam, 2 g IV every 12 hours over 30 minutes; treatment duration minimum 5 days (10 doses), maximum 14 days (28 doses). Aztreonam or matching placebo treatment was to be stopped after baseline cultures were confirmed negative for gram-negative pathogens.

Study RX-3341-303

Delafloxacin, 300 mg, IV, every 12 hours for 6 doses; followed by delafloxacin, 450 mg orally, given every 12 hours (without regard to food) for an additional 4 to 22 doses **or** vancomycin hydrochloride, 15 mg/kg (based on actual body weight) or according to local standard of care, IV, for 10 to 28 doses and aztreonam, 1 or 2 g, IV; treatment duration minimum 5 days (10 doses), maximum 14 days (28 doses).

Aztreonam or matching placebo treatment was to be stopped after baseline cultures were confirmed negative for gram-negative pathogens.

Objectives

In both pivotal trials, the primary endpoint was the investigator's clinical assessment at the FU Visit (i.e., Day 14 + 1 from randomisation) with duration of treatment lasting up to 14 days for both delafloxacin and the comparator arm. The analysis was performed considering the outcome of cure and of clinical success on the ITT and CE populations.

The TOC visit was timed 14 + 1 day from randomisation. Taking the treatment duration of 5 to 14 days into account, the TOC visit was performed between day 0 and day 9 after the last day of treatment. In order to be compliant with the addendum to the guideline, the applicant defined several additional analyses as sensitivity analysis. A new definition of investigator assessment at PTE was introduced within a window of 7 - 14 and 6 - 15 days after EOT (PTE_{7-14} - PTE_{6-15}); all the assessments outside that window were considered missing, and therefore counted as failure. If, instead, both the assessments are within the defined window after EOT the earliest one (i.e., FU visit) was taken.

Clinical cure was defined as complete resolution of all baseline signs and symptoms of ABSSSI at EOT, FU, and LFU visits; however, if erythema was the only sign of infection remaining at EOT or FU visit, and the erythema was absent at LFU visit, then the case was classified as a cure at EOT (derived), FU (derived), and LFU visits.

The primary analysis was performed for the ITT and CE population. The endpoint was prespecified for noninferiority testing with a margin of 10%.

Secondary objectives were as follows:

Study RX-3341-302

To evaluate the clinical efficacy of delafloxacin compared with vancomycin + aztreonam by assessing:

- the investigator-assessed response of signs and symptoms of infection at the LFU visit
- the objective clinical response of the reduction of erythema of ≥30% at 48 to 72 hours
- the investigator-assessed response of signs and symptoms of infection in MRSA patients at the FU visit
- the reduction in pain at EOT as measured by ePRO
- the microbiological response in MRSA patients
- the microbiological response in all patients

To evaluate the safety of delafloxacin compared with vancomycin + aztreonam

Study RX-3341-303

To evaluate the clinical efficacy of delafloxacin compared with vancomycin + aztreonam by assessing

- the investigator-assessed response of signs and symptoms of infection at the Follow-up Visit
- the investigator-assessed response of signs and symptoms of infection in patients with a baseline BMI ≥ 30 kg/m2 at the Follow-up Visit
- the investigator-assessed response of signs and symptoms of infection at the Late Follow-up Visit
- the microbiological response
- the sustained clinical efficacy at the Late Follow-up Visit
- the clinical efficacy at 48 to 72 hours after initiation of treatment

To evaluate the safety of delafloxacin compared with vancomycin + aztreonam

Sample size

In both pivotal studies a sample size of 660 randomly assigned patients (330 per treatment group) was calculated provided greater than 90% power to demonstrate the noninferiority of delafloxacin with respect to the objective response rate of vancomycin + aztreonam with a noninferiority margin of 10%.

Randomisation

Patients who met all of the inclusion criteria and none of the exclusion criteria were randomly assigned to 1 of 2 treatment groups in a 1:1 ratio to receive either delafloxacin or vancomycin + aztreonam.

Randomization was stratified by type of infection and designed so that no more than 25% of enrolled patients were treated for a major cutaneous abscess, and no more than 35% (Study RX-3341-302) or 30% (Study RX-3341-303) of enrolled patients were treated for wound infections. The remaining infection types (cellulitis/erysipelas or burn infection) were not limited. Patients who had received 1 dose of either a single, potentially effective, short-acting antimicrobial drug or regimen for treatment of the ABSSSI under study in the 14 days before study entry were limited to no more than 25% of total randomly assigned patients.

In study RX-3341-303 randomisation was also stratified by baseline BMI (< 30 kg/m2 and ≥ 30 kg/m^2). Patients with a BMI ≥ 30 kg/m^2 comprised at least 40% but no more than 50% of the enrolled population.

Statistical methods

Analysis Sets

- ITT Analysis Set: Includes all patients who were randomly assigned to treatment. Patients were grouped and analysed according to their assigned treatment.

- MITT Analysis Set: Includes all patients in the ITT analysis set who had a bacterial pathogen identified at baseline that was known to cause ABSSSI. Patients were analysed according to their assigned treatment.

- CE Analysis Sets: There are several CE analysis sets, each based on the time of assessment. The sets include all patients in the ITT analysis set who had a relevant (at the specific timepoint) non-missing assessment, an ABSSSI, who received $\geq 80\%$ of their assigned treatment, had the required clinical assessments within the appropriate window, did not receive systemic antibacterial therapy with activity against the causative pathogens through the time period in question, and had no protocol deviations that would have affected efficacy assessments through the time period in question. Patients were analysed according to their assigned treatment.

- ME Analysis Sets: There are several ME analysis sets, which include all patients in the MITT analysis set who also met the criteria for the corresponding CE analysis set for either objective or investigator-assessed response. Patients in the ME analysis sets were analysed according to their assigned treatment.

Primary analysis

The primary efficacy endpoint was the investigator-assessed response of signs and symptoms of infection at the Follow-up Visit. Levels of the endpoint were classified as cure, improved, success, failure, or indeterminate. Indeterminate responses were considered failures in the ITT and MITT analyses and

excluded from the CE and ME analysis sets. For all efficacy analyses, patients were analysed in the treatment group to which they were randomly assigned. Patients who received the study drug other than the study drug to which they were randomly assigned were not included in the CE and ME analysis sets. The primary efficacy analysis was performed on the ITT and the CEFUI analysis sets.

Cure rate was defined as cure rate= cure / (cure + failure), with as improved, failure, indeterminate (excluded for CEFUI) and missing classified failure.

The null (H0) and alternative (Ha) hypotheses to be tested in order to establish the non-inferiority of delafloxacin were:

H0: $P_d - P_v \leq -0.10$

Ha: $P_d - P_v > -0.10$

where P_v and P_d are the probabilities of the investigator assessed cure for vancomycin + aztreonam and delafloxacin, respectively.

Superiority was tested for secondary hypotheses (H0: $P_d - P_v \leq 0$; Ha: $P_d - P_v > 0$).

A two-sided 95% CI for non-inferiority testing was computed based on the difference in sample responder rates for vancomycin + aztreonam and using a non-stratified method proposed by Miettinen and Nurminen. If the lower limit (LL) of the two-sided 95% CI was greater than -0.10, it was concluded that delafloxacin is noninferior to vancomycin + aztreonam. If noninferiority was met superiority was tested. If the LL of the two-sided 95% CI is greater than 0, then delafloxacin will be declared superior to vancomycin + aztreonam.

Secondary analyses

Secondary analyses were performed using non-stratified Miettinen and Nurminen methodology for binary endpoints and a mixed models repeated measures (MMRM) analysis for the reduction in pain endpoint. Other continuous secondary efficacy measures were analysed using an analysis of covariance (ANCOVA) model with treatment, infection type, site of infection, and prior antimicrobial therapy as main effects and the baseline measure as the covariate. All secondary statistical tests and confidence intervals were two-sided with a testwise type I error rate at alpha = 0.05.

Multiplicity

If the NI of delafloxacin was declared in the primary analysis the secondary endpoints (ITT analysis set or for the MEFUI analysis set) were tested for superiority in a hierarchical approach. No interim analysis was performed in the studies.

Sensitivity analysis

Sensitivity analyses of the primary analysis of the primary endpoint were performed to investigate the robustness of the primary efficacy results.

Subgroups analysis

An initial exploration of homogeneity of efficacy across subgroups was undertaken by constructing two-sided 95% CIs for the treatment groups' differences in rates of the primary efficacy endpoint, similar to the primary efficacy analysis using Miettinen and Nurminen methodology without stratification. Pre-specified subgroups included demographic stratification (age category, sex, diabetes, BMI groups, ethnicity, race category and region), baseline infection type, prior antibiotics use, bacteraemia at baseline, quartiles of baseline erythema area, major surgical procedures.

Results

Participant flow and recruitment

Study RX-3341-302

A total of 660 patients comprised the ITT analysis set (enrolled from 34 sites in 7 countries – United states, Croatia, Hungary, Israel, Latvia, Spain, Ukraine).

The following tables provide an overview of the disposition of patients in the ITT analysis set.

Table 9: Participant workflow - Study RX-3341-302
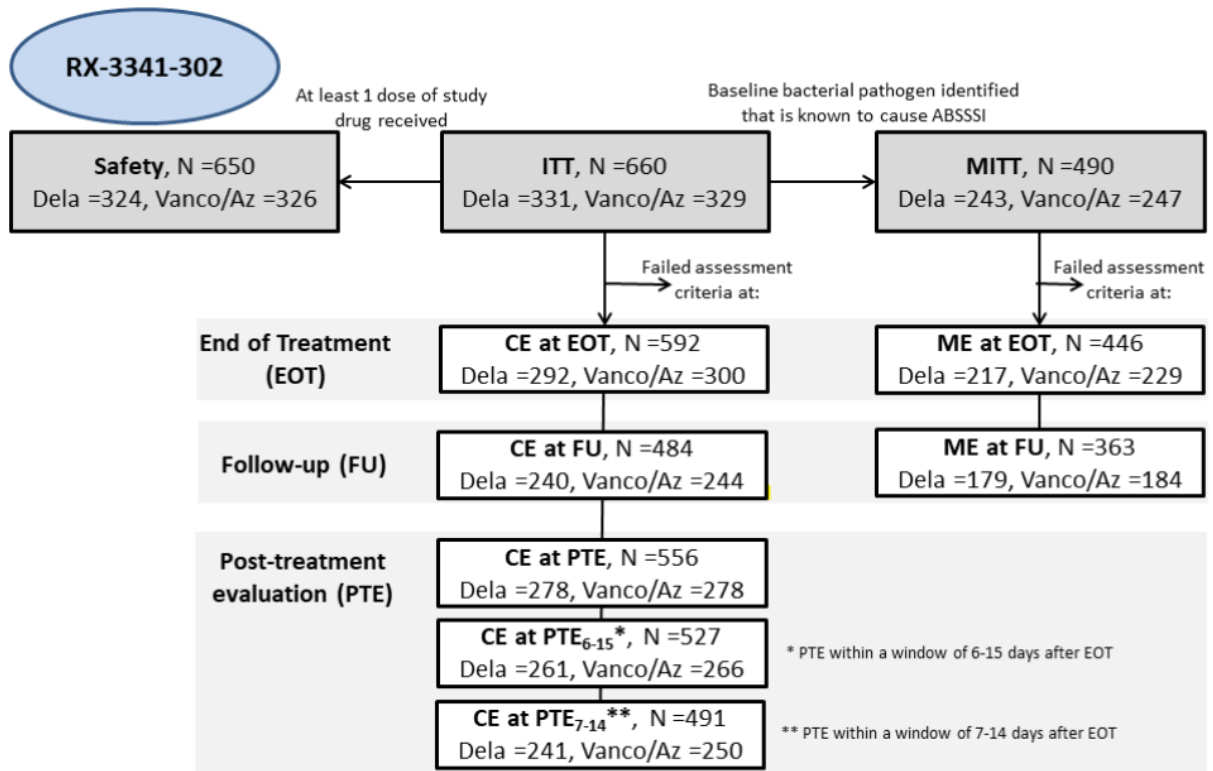
Table 10: Patient Disposition, All Patients - Study RX-3341-302

	Delafloxacin (N=331)	Vancomycin + Aztreonam (N=329)	Total (N=660)
	n (%)	n (%)	n (%)
ITT analysis set	331 (100.0)	329 (100.0)	660 (100.0)
Completed study (LFU visit; ITT analysis set)	276 (83.4)	271 (82.4)	547 (82.9)
Completed the FU visit (ITT analysis set)	286 (86.4)	287 (87.2)	573 (86.8)
Completed the Telephone Call FU (ITT analysis set)	289 (87.3)	282 (85.7)	571 (86.5)
Safety analysis set	324 (97.9)	326 (99.1)	650 (98.5)
MITT analysis set	243 (73.4)	247 (75.1)	490 (74.2)
Primary reason for withdrawal from study (ITT analysis set)			
Adverse event	3 (0.9)	9 (2.7)	12 (1.8)
Death	1 (0.3)	1 (0.3)	2 (0.3)
Lack of efficacy	3 (0.9)	1 (0.3)	4 (0.6)
Lost to follow-up	24 (7.3)	29 (8.8)	53 (8.0)
Noncompliance with study drug	2 (0.6)	2 (0.6)	4 (0.6)
Physician decision	2 (0.6)	0	2 (0.3)
Protocol violation	0	0	0
Study terminated by sponsor	0	0	0
Withdrawal by patient	15 (4.5)	9 (2.7)	24 (3.6)
The patient took a concomitant medication that might affect patient safety or study assessments/objects	0	0	0
Other	5 (1.5)	6 (1.8)	11 (1.7)
Number of patients excluded from MITT analysis set	88 (26.6)	82 (24.9)	170 (25.8)

Abbreviations: FU, follow-up; ITT, intent to treat; LFU, late follow-up; MITT, microbiological intent to treat.
Note: Reason for exclusion from the MITT analysis set is for no baseline-eligible pathogen present.
Source Data: Posttext Table 14.1.1.1, Posttext Table 14.1.1.2, Posttext Table 14.1.2.1.

Study RX-3341-303

A total of 850 patients comprised the ITT analysis set (enrolled from 76 sites in North America, Europe, Asia and Latin America).

The following tables provide an overview of the disposition of patients in the ITT analysis set.

Table 11: Participant workflow - Study RX-3341-303

Flowchart: Study RX-3341-303

At least 1 dose of study drug received → **Safety**, N =842; Dela =417, Vanco/Az =425

ITT, N =850; Dela =423, Vanco/Az =427

Baseline bacterial pathogen identified that is known to cause ABSSSI → **MITT**, N =552; Dela =275, Vanco/Az =277

End of Treatment (EOT)
Failed assessment criteria
CE at EOT, N =771; Dela =391, Vanco/Az =380
ME at EOT, N =503; Dela =258, Vanco/Az =245

Follow-up (FU)
CE at FU, N =682; Dela =353, Vanco/Az =329
ME at FU, N =443; Dela =231, Vanco/Az =212

Post-treatment evaluation (PTE)
CE at PTE, N =737; Dela =377, Vanco/Az =360
CE at PTE$_{6-15}$*, N =685; Dela =353, Vanco/Az =332   * PTE within a window of 6-15 days after EOT
CE at PTE$_{7-14}$**, N =631; Dela =326, Vanco/Az =305   ** PTE within a window of 7-14 days after EOT

Table 12: Patient Disposition, All Patients – Study RX-3341-303

Disposition Category	Delafloxacin (N = 423)	Vancomycin + Aztreonam (N = 427)	Total (N = 850)
Total number of patients (n [%]) who completed:			
Follow-up Visit	385 (91.0)	381 (89.2)	766 (90.1)
Study (Late Follow-up Visit)	366 (86.5)	368 (86.2)	734 (86.4)
Telephone Call Follow-up	376 (88.9)	374 (87.6)	750 (88.2)
Primary reasons for withdrawal from study, n (%)			
Lost to follow-up	25 (5.9)	24 (5.6)	49 (5.8)
AE	8 (1.9)	12 (2.8)	20 (2.4)
Withdrawal by patient	8 (1.9)	9 (2.1)	17 (2.0)
Lack of efficacy	3 (0.7)	6 (1.4)	9 (1.1)
Physician decision	4 (0.9)	2 (0.5)	6 (0.7)
Protocol violation	4 (0.9)	2 (0.5)	6 (0.7)
Noncompliance with study drug	2 (0.5)	1 (0.2)	3 (0.4)
Death	0	1 (0.2)	1 (0.1)
Other	3 (0.7)	2 (0.5)	5 (0.6)
Total number of patients (n [%]) who completed:			
Study drug	386 (91.3)	387 (90.6)	773 (90.9)
At least 10 doses of study drug	391 (92.4)	378 (88.5)	769 (90.5)
Prematurely discontinued from study drug	31 (7.3)	38 (8.9)	69 (8.1)
Never administered study drug	6 (1.4)	2 (0.5)	8 (0.9)
Primary reasons for withdrawal from study drug, n (%)			
AE	8 (1.9)	12 (2.8)	20 (2.4)
Withdrawal by patient	7 (1.7)	6 (1.4)	13 (1.5)
Lost to follow-up	4 (0.9)	9 (2.1)	13 (1.5)
Lack of efficacy	4 (0.9)	7 (1.6)	11 (1.3)
Physician decision	3 (0.7)	0	3 (0.4)
Noncompliance with study drug	2 (0.5)	1 (0.2)	3 (0.4)
Protocol violation	1 (0.2)	1 (0.2)	2 (0.2)
Death	0	0	0
Other	2 (0.5)	2 (0.5)	4 (0.5)

Abbreviations: AE, adverse event; ITT, intent-to-treat.
Source: End-of-Text Table 14.1.2.1.

Conduct of the study

Study RX-3341-302

Overall, 8 patients experienced 9 significant protocol deviations. The following table outlines the number of patients with significant protocol deviations in the ITT analysis set.

Table 13: Number of Patients With Significant Protocol Deviations, ITT Analysis

	Delafloxacin (N=331) n (%)	Vancomycin + Aztreonam (N=329) n (%)	Total (N=660) n (%)
Informed consent	0	0	0
Inclusion/exclusion criteria violated	0	1 (0.3)	1 (0.2)
Dosing or randomization errors	3 (0.9)	4 (1.2)	7 (1.1)
Procedural errors	1 (0.3)	0	1 (0.2)
Administration of prohibited concomitant medications	0	0	0
Other	0	0	0

Abbreviation: ITT, intent to treat.
Source Data: Posttext Table 14.1.2.4.

There were an additional 20 patients (10 patients in the delafloxacin treatment group and 10 patients in the vancomycin + aztreonam treatment group) who had protocol deviations that impacted evaluability but that were not considered significant. These protocol deviations were all related to procedural errors.

Overall, the occurrence of protocol deviations was balanced across treatment arms for the entire study population.

Study RX-3341-303

Overall, 34 patients experienced significant protocol deviations. The following table outlines the number of patients with significant protocol deviations in the ITT analysis set.

Table 14: Number of Patients With Significant Protocol Deviations, ITT Analysis

Deviation	Delafloxacin (N = 423)	Vancomycin + Aztreonam (N = 427)	Total (N = 850)
	n (%) of Patients With Significant Protocol Deviations[a]		
Informed consent	0	3 (0.7)	3 (0.4)
Inclusion/exclusion criteria violation	3 (0.7)	8 (1.9)	11 (1.3)
Dosing or randomization error	13 (3.1)	7 (1.6)	20 (2.4)
Procedural error	0	0	0
Administration of prohibited concomitant medication	0	0	0
Other	0	0	0

Abbreviation: ITT, intent-to-treat.

[a] A significant protocol deviation was defined as nonadherence to the protocol that resulted in a significant additional risk to the patient when the patient, principal investigator, or subinvestigator had failed to adhere to significant protocol requirements.

Source: End-of-Text Table 14.1.2.5.

Baseline data

The following tables provide information about demographics and other baseline characteristics.

Table 15: Demographics and Other Baseline Characteristics − Phase III studies, ITT Analysis Set

	RX-3341-302		RX-3341-303		Phase III Efficacy Analysis Set	
	Delaflox acin Q12h (N = 331)	Vancom ycin (Aztreon am) (N = 329)	Delaflox acin (N = 423)	Vancom ycin (Aztreon am) (N = 427)	Delaflox acin (N = 754)	Vancom ycin (Aztreon am) (N = 756)
Age (Year)						
N	331	329	423	427	754	756
Mean (SD)	46.3 (13.91)	45.3 (14.44)	51.2 (15.98)	50.2 (16.03)	49.0 (15.29)	48.1 (15.54)
Median	47.0	46.0	51.0	50.0	49.0	48.0
Min, Max	18, 94	19, 90	18, 89	19, 93	18, 94	19, 93
Age Categories (Year), n (%)						
≤ 65	309 (93.4)	309 (93.9)	344 (81.3)	352 (82.4)	653 (86.6)	661 (87.4)
> 65	22 (6.6)	20 (6.1)	79 (18.7)	75 (17.6)	101 (13.4)	95 (12.6)
> 75	7 (2.1)	10 (3.0)	35 (8.3)	31 (7.3)	42 (5.6)	41 (5.4)
Sex, n (%)						
Male	206 (62.2)	209 (63.5)	262 (61.9)	276 (64.6)	468 (62.1)	485 (64.2)
Female	125 (37.8)	120 (36.5)	161 (38.1)	151 (35.4)	286 (37.9)	271 (35.8)
Race, n (%)						
American Indian or Alaska Native	5 (1.5)	2 (0.6)	12 (2.8)	7 (1.6)	17 (2.3)	9 (1.2)
Asian	1 (0.3)	1 (0.3)	11 (2.6)	15 (3.5)	12 (1.6)	16 (2.1)
Black or African American	27 (8.2)	19 (5.8)	13 (3.1)	18 (4.2)	40 (5.3)	37 (4.9)
Native Hawaiian or other Pacific Islander	1 (0.3)	2 (0.6)	2 (0.5)	2 (0.5)	3 (0.4)	4 (0.5)
White	297 (89.7)	304 (92.4)	348 (82.3)	355 (83.1)	645 (85.5)	659 (87.2)
Other	0	1 (0.3)	37 (8.7)	30 (7.0)	37 (4.9)	31 (4.1)
Region, n (%)[a]						
Europe	63 (19.0)	55 (16.7)	165 (39.0)	173 (40.5)	228 (30.2)	228 (30.2)
North America	268 (81.0)	274 (83.3)	202 (47.8)	196 (45.9)	470 (62.3)	470 (62.2)
Asia	0	0	9 (2.1)	14 (3.3)	9 (1.2)	14 (1.9)
Latin America	0	0	47 (11.1)	44 (10.3)	47 (6.2)	44 (5.8)

	RX-3341-302		RX-3341-303		Phase III Efficacy Analysis Set	
	Delaflox acin Q12h (N = 33 1)	Vancom ycin (Aztreon am) (N = 329)	Delaflox acin (N = 423)	Vancom ycin (Aztreon am) (N = 427)	Delaflox acin (N = 754)	Vancom ycin (Aztreon am) (N = 756)
Weight (kg)						
N	331	329	423	427	754	756
Mean (SD)	82.9 (19.41)	81.4 (19.08)	87.4 (22.92)	89.1 (23.65)	85.4 (21.55)	85.8 (22.09)
Median	80.6	79.4	83.9	86.0	82.5	82.9
Min, Max	42.1, 140.0	43.8, 148.3	30.8, 198.5	45.8, 185.0	30.8, 198.5	43.8, 185.0
BMI (kg/m^2)						
N	331	329	423	427	754	756
Mean (SD)	28.4 (6.42)	27.9 (6.36)	30.4 (7.44)	30.7 (7.54)	29.5 (7.08)	29.5 (7.18)
Median	27.2	26.7	29.7	30.0	28.8	28.3
Min, Max	16.5, 52.0	17.3, 52.8	15.3, 65.8	17.3, 68.0	15.3, 65.8	17.3, 68.0
BMI Categories (kg/m^2), n (%)						
< 30	211 (63.7)	235 (71.4)	212 (50.1)	213 (49.9)	423 (56.1)	448 (59.3)
≥ 30	120 (36.3)	94 (28.6)	211 (49.9)	214 (50.1)	331 (43.9)	308 (40.7)
Diabetes, n (%)						
Yes	30 (9.1)	27 (8.2)	53 (12.5)	54 (12.6)	83 (11.0)	81 (10.7)
No	301 (90.9)	302 (91.8)	370 (87.5)	373 (87.4)	671 (89.0)	675 (89.3)

Note: BMI (Body mass index) is calculated as (body weight in kilograms) / (height in meters)^2.
[a] Europe includes Latvia, Hungary, Estonia, Moldova, Slovakia, Romania, Bulgaria, Georgia, Spain, Croatia, Israel. North America includes United States. Asia includes Taiwan, Korea. Latin America includes Peru, Argentina, Mexico, Chile, Brazil.
Source: ITT Analysis Set (Table 14.1.3.1 of TL - SCE)

Table 16: Location and Description of ABSSSI at Baseline – Phase III studies, ITT Analysis Set

	RX-3341-302		RX-3341-303		Phase III Efficacy Analysis Set	
	Delafloxaci n (N = 331)	Vancomycin (Aztreonam) (N = 329)	Delafloxaci n (N = 423)	Vancomycin (Aztreonam) (N = 427)	Delafloxaci n (N = 754)	Vancomycin (Aztreonam) (N = 756)
Baseline infection type, n(%)						
Major cutaneous abscess	84 (25.4)	83 (25.2)	106 (25.1)	106 (24.8)	190 (25.2)	189 (25.0)
Burn infection	3 (0.9)	2 (0.6)	4 (0.9)	3 (0.7)	7 (0.9)	5 (0.7)
Wound infection	116 (35.0)	116 (35.3)	111 (26.2)	112 (26.2)	227 (30.1)	228 (30.2)

	RX-3341-302		RX-3341-303		Phase III Efficacy Analysis Set	
	Delafloxacin (N = 331)	Vancomycin (Aztreonam) (N = 329)	Delafloxacin (N = 423)	Vancomycin (Aztreonam) (N = 427)	Delafloxacin (N = 754)	Vancomycin (Aztreonam) (N = 756)
Cellulitis / erysipelas	128 (38.7)	128 (38.9)	202 (47.8)	206 (48.2)	330 (43.8)	334 (44.2)
Consolidated anatomical site of infection group 2, n (%)						
Head / neck / face	12 (3.6)	12 (3.6)	15 (3.5)	19 (4.4)	27 (3.6)	31 (4.1)
Back	9 (2.7)	8 (2.4)	11 (2.6)	12 (2.8)	20 (2.7)	20 (2.6)
Thorax	9 (2.7)	8 (2.4)	11 (2.6)	5 (1.2)	20 (2.7)	13 (1.7)
Upper extremities	108 (32.6)	119 (36.2)	106 (25.1)	97 (22.7)	214 (28.4)	216 (28.6)
Lower extremities	135 (40.8)	131 (39.8)	226 (53.4)	250 (58.5)	361 (47.9)	381 (50.4)
Abdomen	21 (6.3)	13 (4.0)	22 (5.2)	21 (4.9)	43 (5.7)	34 (4.5)
Pubic / perineum / groin	6 (1.8)	6 (1.8)	7 (1.7)	8 (1.9)	13 (1.7)	14 (1.9)
Buttocks	34 (10.3)	38 (11.6)	31 (7.3)	22 (5.2)	65 (8.6)	60 (7.9)
Erythema size digital (cm^2)						
N	326	328	421	426	747	754
Mean (SD)	294.8 (308.34)	319.1 (314.03)	341.5 (312.89)	364.4 (391.70)	321.1 (311.57)	344.7 (360.46)
Median	190.7	214.0	248.2	222.8	215.7	218.3
Min, Max	32.6, 2381.3	40.2, 2666.0	6.5, 2236.7	0.0, 2714.3	6.5, 2381.3	0.0, 2714.3
Induration size digital (cm^2)						
N	325	329	421	426	746	755
Mean (SD)	94.1 (208.66)	120.7 (219.57)	116.1 (205.29)	159.3 (288.69)	106.5 (206.91)	142.5 (261.38)
Median	47.4	55.5	51.8	59.1	48.6	56.5
Min, Max	0.0, 2318.6	0.0, 1786.2	0.0, 1612.0	0.0, 2050.6	0.0, 2318.6	0.0, 2050.6

<u>Study drug exposure and days between time points</u>

Most patients received study drug for 4 to <8 days (study RX-3341-302: delafloxacin group 69.8% vs. vancomycin + aztreonam group 73.3%; study RX-3341-303: delafloxacin group 59.9% vs. vancomycin + aztreonam group 61.4%). In study RX-3341-302 less patients received study drug for 8 to 14 days compared to study RX-3341-303 (RX-3341-302: delafloxacin group 19.1% vs. vancomycin + aztreonam group 17.9%; study RX-3341-303: delafloxacin group 35.7% vs. vancomycin + aztreonam group 32%).

In study RX-3341-302 in 65.9% of the patients the TOC visit (FU visit) was investigated 7 to 14 days after EOT. In study RX-3341-303 in 58.6% the TOC visit was performed 7 to 14 days after EOT.

Baseline Pathogens

Study RX-3341-302

Table 17: Eligible Pathogens Identified at Baseline from Site of Infection Occurring in at Least 2% of Cultures From Either Treatment Group, MITT Analysis Set – Study RX-3341-302

	Delafloxacin (N=243) n (%)	Vancomycin + Aztreonam (N=247) n (%)
Gram-positive organisms		
Staphylococcus aureus[a]	159 (65.4)	165 (66.8)
MRSA	78 (32.1)	91 (36.8)
MSSA	82 (33.7)	74 (30.0)
Staphylococcus epidermidis	20 (8.2)	18 (7.3)
Streptococcus intermedius	15 (6.2)	18 (7.3)
Streptococcus anginosus	11 (4.5)	13 (5.3)
Streptococcus constellatus	9 (3.7)	10 (4.0)
Staphylococcus lugdunensis	7 (2.9)	3 (1.2)
Streptococcus pyogenes	7 (2.9)	5 (2.0)
Staphylococcus haemolyticus	6 (2.5)	2 (0.8)
Streptococcus agalactiae	6 (2.5)	2 (0.8)
Streptococcus mitis/oralis	6 (2.5)	3 (1.2)
Clostridium perfringens	5 (2.1)	2 (0.8)
Staphylococcus hominis	4 (1.6)	5 (2.0)
Gram-negative organisms		
Klebsiella pneumoniae	11 (4.5)	11 (4.5)
Enterobacter cloacae	6 (2.5)	2 (0.8)
Escherichia coli	5 (2.1)	9 (3.6)
Haemophilus parainfluenzae	2 (0.8)	5 (2.0)
Pseudomonas aeruginosa	2 (0.8)	5 (2.0)

Abbreviations: MITT, microbiological intent to treat; MRSA, methicillin-resistant *Staphylococcus aureus*, MSSA, methicillin-susceptible *Staphylococcus aureus*.

[a] Patients with both MRSA and MSSA were counted only once in *Staphylococcus aureus*.

Source Data: Posttext Table 14.2.5.1.

Table 18: Pathogens Identified From Site of Infection at Baseline in > 2% of Patients (MITT Analysis Set) – Study RX-3341-303

Baseline Pathogen	No. (%) of Pathogens	
	Delafloxacin (N = 275)	Vancomycin + Aztreonam (N = 277)
Gram-positive organisms		
Staphylococcus aureus[a]	160 (58.2)	158 (57.0)
MRSA	66 (24.0)	50 (18.1)
MSSA	96 (34.9)	108 (39.0)
Staphylococcus epidermidis	25 (9.1)	32 (11.6)
Streptococcus pyogenes	16 (5.8)	12 (4.3)
Streptococcus intermedius	13 (4.7)	12 (4.3)
Streptococcus anginosus	12 (4.4)	10 (3.6)
Staphylococcus haemolyticus	9 (3.3)	6 (2.2)
Enterococcus faecalis	8 (2.9)	13 (4.7)
Streptococcus agalactiae	8 (2.9)	10 (3.6)
Streptococcus mitis/oralis	7 (2.5)	2 (0.7)
Staphylococcus hominis	5 (1.8)	6 (2.2)
Staphylococcus lugdunensis	4 (1.5)	6 (2.2)
Streptococcus dysgalactiae	4 (1.5)	8 (2.9)
Gram-negative organisms		
Klebsiella pneumoniae	10 (3.6)	12 (4.3)
Escherichia coli	9 (3.3)	11 (4.0)
Enterobacter cloacae	8 (2.9)	9 (3.2)
Pseudomonas aeruginosa	8 (2.9)	6 (2.2)
Proteus mirabilis	6 (2.2)	8 (2.9)

Abbreviations: MITT, microbiological intent to treat; methicillin-resistant *Staphylococcus aureus*, MSSA, methicillin-susceptible *Staphylococcus aureus*.

[a] Patients with both MRSA and MSSA were counted only once for *S aureus*.

Source Data: End-of-Text Table 14.2.5.1.

Outcomes and estimations

Investigator assessed response at Follow-up visit

Table 19 Investigator Assessed Response at the Follow up Visit – Phase III studies

	RX-3341-302		RX-3341-303		Phase III Efficacy Analysis Set	
	Delafloxacin	**Vancomycin (Aztreonam)**	**Delafloxacin**	**Vancomycin (Aztreonam)**	**Delafloxacin**	**Vancomycin (Aztreonam)**
ITT Analysis Set	**N = 331**	**N = 329**	**N = 423**	**N = 427**	**N = 754**	**N = 756**
Cure, n / N (%)	172 (52.0)	166 (50.5)	244 (57.7)	255 (59.7)	416 (55.2)	421 (55.7)
Difference (95% CI)	1.5 (−6.1, 9.1)		−2.0 (−8.6, 4.6)		−0.5 (−5.5, 4.5)	
Success: Cure + improved, n / N (%)	270 (81.6)	274 (83.3)	369 (87.2)	362 (84.8)	639 (84.7)	636 (84.1)
Difference (95% CI)	−1.7 (−7.6, 4.1)		2.5 (−2.2, 7.2)		0.8 (−2.8, 4.5)	
MITT Analysis Set	**N = 243**	**N = 247**	**N = 275**	**N = 277**	**N = 518**	**N = 524**
Cure, n / N (%)	126 (51.9)	118 (47.8)	158 (57.5)	163 (58.8)	284 (54.8)	281 (53.6)
Difference (95% CI)	4.1 (−4.8, 12.9)		−1.4 (−9.6, 6.8)		1.1 (−4.9, 7.1)	
Success: Cure + improved, n / N (%)	204 (84.0)	209 (84.6)	247 (89.8)	233 (84.1)	451 (87.1)	442 (84.4)
Difference (95% CI)	−0.7 (−7.2, 5.8)		5.7 (0.1, 11.4)		3.0 (−1.3, 7.3)	
CEFUI Analysis Set	**N = 240**	**N = 244**	**N = 353**	**N = 329**	**N = 593**	**N = 573**
Cure, n / N (%)	142 (59.2)	142 (58.2)	220 (62.3)	224 (68.1)	362 (61.0)	366 (63.9)
Difference (95% CI)	1.0 (−7.8, 9.7)		−5.8 (−12.9, 1.4)		−3.1 (−8.6, 2.5)	
Success: Cure + improved, n / N (%)	233 (97.1)	238 (97.5)	340 (96.3)	319 (97.0)	573 (96.6)	557 (97.2)
Difference (95% CI)	−0.5 (−3.7, 2.7)		−0.6 (−3.5, 2.2)		−0.6 (−2.7, 1.6)	
MEFUI Analysis Set	**N = 179**	**N = 184**	**N = 231**	**N = 212**	**N = 410**	**N = 396**
Cure, n / N (%)	104 (58.1)	101 (54.9)	141 (61.0)	144 (67.9)	245 (59.8)	245 (61.9)
Difference (95% CI)	3.2 (−7.0, 13.3)		−6.9 (−15.7, 2.1)		−2.5 (−9.2, 4.2)	
Success: Cure + improved, n/N (%)	175 (97.8)	181 (98.4)	226 (97.8)	207 (97.6)	401 (97.8)	388 (98.0)
Difference (95% CI)	−0.6 (−4.2, 2.7)		0.2 (−2.9, 3.5)		−0.2 (−2.5, 2.2)	

Note: Difference = Difference in cure/success rates (Delafloxacin treatment group minus vancomycin + aztreonam treatment group). Confidence intervals are calculated using Miettinen and Nurminen method without stratification for individual studies and stratified by studies for Phase III Efficacy Analysis Set analysis.
Source: ITT at Follow-up Analysis Set (Table 14.2.2.1 of TL - SCE), MITT at Follow-up Analysis Set (Table 14.2.2.3 of TL - SCE), CEFUI Analysis Set (Table 14.2.2.2 of TL - SCE), and MEFUI Analysis Set (Table 14.2.2.4 of TL - SCE)

Investigator assessed response at PTE, PTE_{7-14} and PTE_{6-15}

The following table reports the investigator assessed response at the PTE and at PTE7-14 and PTE6-15 (described in the EMA SCE - SAP), that supported the outcome for the primary endpoint at FU.

Table 20: Investigator Assessed Response at the PTE, PTE7-14 and PTE6-15 − Phase III studies

	RX-3341-302		RX-3341-303		Phase III Efficacy Analysis Set	
	Delafloxacin	Vancomycin (Aztreonam)	Delafloxacin	Vancomycin (Aztreonam)	Delafloxacin	Vancomycin (Aztreonam)
ITT at PTE Analysis Set	**N = 331**	**N = 329**	**N = 423**	**N = 427**	**N = 754**	**N = 756**
Cure, n / N (%)	182 (55.0)	178 (54.1)	262 (61.9)	277 (64.9)	444 (58.9)	455 (60.2)
Difference (95% CI)	0.9 (-6.7, 8.5)		-2.9 (-9.4, 3.5)		-1.3 (-5.5, 3.8)	
Success: Cure + improved, n / N (%)	274 (82.8)	278 (84.5)	369 (87.2)	365 (85.5)	643 (85.3)	643 (85.1)
Difference (95% CI)	-1.7 (-7.4, 4.0)		1.8 (-2.9, 6.4)		0.2 (-4.9, 5.1)	
ITT at PTE_{7-14} Analysis Set	**N = 331**	**N = 329**	**N = 423**	**N = 427**	**N = 754**	**N = 756**
Cure, n / N (%)	160 (48.3)	170 (51.7)	226 (53.4)	238 (55.7)	386 (51.2)	408 (54.0)
Difference (95% CI)	-3.3 (-10.9, 4.3)		-2.5 (-9.2, 4.1)		-2.9 (-5.9, 3.1)	
Success: Cure + improved, n / N (%)	240 (72.5)	249 (75.7)	324 (76.6)	308 (72.1)	564 (74.8)	557 (73.7)
Difference (95% CI)	-3.2 (-9.9, 3.5)		4.5 (-1.4, 10.3)		1.1 (-4.1, 5.6)	
ITT at PTE_{6-15} Analysis Set	**N = 331**	**N = 329**	**N = 423**	**N = 427**	**N = 754**	**N = 756**
Cure, n / N (%)	174 (52.6)	174 (52.9)	245 (57.9)	255 (59.7)	419 (55.6)	429 (56.7)
Difference (95% CI)	-0.3 (-7.9, 7.3)		-2.0 (-8.6, 4.6)		-1.3 (-5.4, 3.7)	
Success: Cure + improved, n / N (%)	259 (78.2)	265 (80.5)	350 (82.7)	339 (79.4)	609 (80.8)	604 (79.9)
Difference (95% CI)	-2.3 (-8.5, 3.9)		3.4 (-1.9, 8.6)		0.9 (-4.5, 5.5)	
CE at PTE Analysis Set	**N = 278**	**N = 278**	**N = 377**	**N = 360**	**N = 655**	**N = 638**
Cure, n / N (%)	176 (63.3)	174 (62.6)	257 (68.2)	260 (72.2)	433 (66.1)	434 (68.0)
Difference (95% CI)	0.7 (-7.3, 8.7)		-4.1 (-10.6, 2.6)		-2.0 (-6.2, 4.1)	

	RX-3341-302		RX-3341-303		Phase III Efficacy Analysis Set	
	Delafloxacin	**Vancomycin (Aztreonam)**	**Delafloxacin**	**Vancomycin (Aztreonam)**	**Delafloxacin**	**Vancomycin (Aztreonam)**
Success: Cure + improved, n / N (%)	268 (96.4)	272 (97.8)	363 (96.3)	347 (96.4)	631 (96.3)	619 (97.0)
Difference (95% CI)	-1.4 (-4.6, 1.5)		-0.1 (-3.0, 2.8)		-0.7 (-5.7, 5.2)	
CE at PTE$_{7-14}$ Analysis Set	**N = 241**	**N = 250**	**N = 326**	**N = 305**	**N = 567**	**N = 555**
Cure, n / N (%)	155 (64.3)	167 (66.8)	220 (67.5)	224 (73.4)	375 (66.1)	391 (70.5)
Difference (95% CI)	-2.5 (-10.9, 5.9)		-6.0 (-13.0, 1.2)		-4.4 (-7.6, 3.6)	
Success: Cure + improved, n / N (%)	235 (97.5)	244 (97.6)	317 (97.2)	294 (96.4)	552 (97.4)	538 (96.9)
Difference (95% CI)	-0.1 (-3.2, 3.0)		0.8 (-2.0, 3.9)		0.4 (-5.3, 6.4)	
CE at PTE$_{6-15}$ Analysis Set	**N = 261**	**N = 266**	**N = 353**	**N = 332**	**N = 614**	**N = 598**
Cure, n/N (%)	169 (64.8)	172 (64.7)	239 (67.7)	240 (72.3)	408 (66.4)	412 (68.9)
Difference (95% CI)	0.1 (-8.1, 8.2)		-4.6 (-11.4, 2.3)		-2.6 (-6.4, 4.3)	
Success: Cure + improved, n/N (%)	253 (96.9)	260 (97.7)	343 (97.2)	322 (97.0)	596 (97.1)	582 (97.3)
Difference (95% CI)	-0.8 (-4.0, 2.2)		0.2 (-2.5, 3.0)		-0.3 (-5.4, 5.8)	

Note: Difference = Difference in cure / success rates (Delafloxacin treatment group minus vancomycin + aztreonam treatment group). Confidence intervals are calculated using Miettinen and Nurminen method without stratification for individual studies and stratified by studies for Phase III Efficacy Analysis Set analysis.
Source: Study RX-3341-302 Table 14.2.2.12, Table 14.2.2.13, Study RX-3341-303 Table 14.2.2.15, Table 14.2.2.16
TLF - EMA - SCE for Phase III Efficacy analysis set: T1.1.1a ,T1.1.1b, T1.1.2a, T1.1.2b, T1.1.3a, T1.1.3b, T1.1.4a, T1.1.4b, T2.1.1a, T2.1.1b, T2.1.2a, T2.1.2b, T2.1.3a, T2.1.3b, T2.1.4a, T2.1.4b,
TLF - EMA - SCE for RX-3341-302: T1.1.1a ,T1.1.1b, T1.1.2a, T1.1.2b, T1.1.3a, T1.1.3b, T1.1.4a, T1.1.4b
TLF - EMA - SCE for RX-3341-303: T1.1.1a ,T1.1.1b, T1.1.2a, T1.1.2b, T1.1.3a, T1.1.3b, T1.1.4a, T1.1.4b

Ancillary analyses

Responder rate by region

The following table displays the response rate by region in Phase III Efficacy Analysis sets.

Table 21: Responder rate by region – Phase III studies

Type Time Point	RX-3341-302		RX-3341-303		Phase III Efficacy Analysis Set	
	Responder Rate (%)[a]	**Difference (95% CI)[b,c]**	**Responder Rate (%)[a]**	**Difference (95% CI)[b,c]**	**Responder Rate (%)[a]**	**Difference (95% CI)[b,c]**
Region: Europe	N_{dela} = 63, N_{vanco} = 55		N_{dela} = 165, N_{vanco} = 173		N_{dela} = 228, N_{vanco} = 228	
Cure						
FU	85.7, 70.9	14.8 (0.0,29.9)	67.9, 69.9	-2.1 (-11.9, 7.8)	72.8, 70.2	2.3 (-10.4, 7.8)
PTE	87.3, 74.5	12.8 (-1.4, 27.4)	71.5, 75.1	-3.6 (-13.1, 5.8)	75.9, 75.0	0.6 (-11.3, 6.9)
PTE$_{7-14}$	73.0, 70.9	2.1 (-14.0, 18.5)	58.8, 60.1	-1.3 (-11.8, 9.1)	62.7, 62.7	-0.4 (-10.2, 7.6)
PTE$_{6-15}$	81.0, 74.5	6.4 (-8.7, 21.8)	66.1, 67.6	-1.6 (-11.6, 8.5)	70.2, 69.3	0.5 (-10.3, 7.7)
Region: North America	N_{dela} = 268, N_{vanco} = 274		N_{dela} = 202, N_{vanco} = 196		N_{dela} = 470, N_{vanco} = 470	
Cure						
FU	44.0, 46.4	-2.3 (-10.7, 6.1)	46.5, 49.5	-3.0 (-12.7, 6.9)	45.1, 47.7	-2.6 (-6.7, 4.2)
PTE	47.4, 50.0	-2.6 (-11.0, 5.8)	51.0, 53.1	-2.1 (-11.8, 7.7)	48.9, 51.3	-2.4 (-6.9, 4.3)
PTE$_{7-14}$	42.5, 47.8	-5.3 (-13.6, 3.1)	47.5, 49.5	-2.5 (-12.2, 7.3)	44.7, 48.5	-4.1 (-7.8, 3.1)
PTE$_{6-15}$	45.9, 48.5	-2.6 (-11.0, 5.8)	49.5, 50.0	-1.0 (-10.8, 8.8)	47.4, 49.1	-1.9 (-6.6, 4.4)
Region: Asia	N_{dela} = 9, N_{vanco} = 14					
Cure						
FU	NA	NA	55.6, 64.3	-8.7 (-46.8, 30.3)	NA	NA
PTE	NA	NA	55.6, 71.4	-15.9 (-52.6, 23.1)	NA	NA
PTE$_{7-14}$	NA	NA	33.3, 57.1	-23.8 (-57.8, 18.3)	NA	NA
PTE$_{6-15}$	NA	NA	44.4, 57.1	-12.7 (-49.6, 28.0)	NA	NA
Region: Latin America	N_{dela} = 47, N_{vanco} = 44					

Type Time Point	RX-3341-302		RX-3341-303		Phase III Efficacy Analysis Set	
	Responder Rate (%)[a]	Difference (95% CI)[b,c]	Responder Rate (%)[a]	Difference (95% CI)[b,c]	Responder Rate (%)[a]	Difference (95% CI)[b,c]
Cure						
FU	NA	NA	70.2, 63.6	6.6 (-12.8, 25.6)	NA	NA
PTE	NA	NA	76.6, 75.0	1.6 (-16.1, 19.5)	NA	NA
PTE$_{7-14}$	NA	NA	63.8, 65.9	-2.1 (-21.4, 17.5)	NA	NA
PTE$_{6-15}$	NA	NA	68.1, 72.7	-4.6 (-23.1, 14.3)	NA	NA

<u>Response rate per disease entity</u>

The following table displays the responder rate per disease entity in Phase III Efficacy Analysis sets.

Table 22: Responder rate in patients per disease entity – Phase III studies

Type Time Point	RX-3341-302		RX-3341-303		Phase III Efficacy Analysis Set	
	Responder Rate (%)[a]	Difference (95% CI)[b,c]	Responder Rate (%)[a]	Difference (95% CI)[b,c]	Responder Rate (%)[a]	Difference (95% CI)[b,c]
Burn Infection	N_{dela} = 3, N_{vanco} = 2		N_{dela} = 4, N_{vanco} = 3		N_{dela} = 7, N_{vanco} = 5	
Cure						
FU	100.0, 0.0	100.0 (2.0, 100.0)	75.0, 100.0	-25.0 (-72.3, 43.8)	85.7, 60.0	26.5 (-49.4, 52.3)
PTE	100.0, 0.0	100.0 (2.0, 100.0)	75.0, 100.0	-25.0 (-72.3, 43.8)	85.7, 60.0	26.5 (-49.4, 52.3)
PTE$_{7-14}$	100.0, 0.0	100.0 (2.0, 100.0)	75.0, 100.0	-25.0 (-72.3, 43.8)	85.7, 60.0	26.5 (-49.4, 52.3)
PTE$_{6-15}$	100.0, 0.0	100.0 (2.0, 100.0)	75.0, 100.0	-25.0 (-72.3, 43.8)	85.7, 60.0	26.5 (-49.4, 52.3)
Cellulitis / erysipelas	N_{dela} = 128, N_{vanco} = 128		N_{dela} = 202, N_{vanco} = 206		N_{dela} = 330, N_{vanco} = 334	
Cure						
FU	67.2, 60.9	6.3 (-5.5, 17.9)	59.9, 63.1	-3.2 (-12.6, 6.2)	62.7, 62.3	0.4 (-7.3, 6.9)
PTE	71.1, 64.1	7.0 (-4.5, 18.4)	65.3, 69.9	-4.6 (-13.6, 4.5)	67.6, 67.7	0.1 (-8.0, 6.5)

Type Time Point	RX-3341-302		RX-3341-303		Phase III Efficacy Analysis Set	
	Responder Rate (%)[a]	Difference (95% CI)[b,c]	Responder Rate (%)[a]	Difference (95% CI)[b,c]	Responder Rate (%)[a]	Difference (95% CI)[b,c]
PTE$_{7-14}$	64.1, 60.9	3.1 (-8.7, 14.9)	53.5, 57.3	-3.8 (-13.4, 5.8)	57.6, 58.7	-1.1 (-8.1, 5.9)
PTE$_{6-15}$	68.8, 63.3	5.5 (-6.2, 17.0)	59.4, 63.1	-3.7 (-13.1, 5.8)	63.0, 63.2	-0.2 (-7.6, 6.6)
Major Cutaneous Abscess	N_{dela} = 84, N_{vanco} = 83		N_{dela} = 106, N_{vanco} = 106		N_{dela} = ,190N_{vanco} = 189	
Cure						
FU	52.4, 48.2	4.2 (-10.9, 19.1)	64.2, 57.5	6.6 (-6.5, 19.5)	58.9, 53.4	5.5 (-6.6, 11.6)
PTE	53.6, 51.8	1.8 (-13.3, 16.7)	67.9, 61.3	6.6 (-6.3, 19.3)	61.6, 57.1	4.5 (-6.8, 11.7)
PTE$_{7-14}$	40.5, 48.2	-7.7 (-22.5, 7.4)	63.2, 53.8	8.5 (-4.8, 21.5)	53.2, 51.3	1.3 (-8.0, 9.9)
PTE$_{6-15}$	50.0, 50.6	-0.6 (-15.6, 14.5)	67.9, 56.6	10.4 (-2.7, 23.2)	60.0, 54.0	5.5 (-6.1, 12.1)
Wound Infection	N_{dela} = 116, N_{vanco} = 116		N_{dela} = 111, N_{vanco} = 112		N_{dela} = 227, N_{vanco} = 228	
Cure						
FU	33.6, 41.4	-7.8 (-20.0, 4.7)	46.8, 54.5	-7.6 (-20.5, 5.5)	40.1, 47.8	-7.7 (-11.5, 3.8)
PTE	37.1, 45.7	-8.6 (-21.1, 4.1)	49.5, 58.0	-8.5 (-21.3, 4.6)	43.2, 51.8	-8.6 (-12.1, 3.6)
PTE$_{7-14}$	35.3, 44.8	-9.5 (-21.8, 3.2)	43.2, 53.6	-10.3 (-23.1, 2.8)	39.2, 49.1	-9.9 (-12.8, 2.5)
PTE$_{6-15}$	35.3, 44.0	-8.6 (-21.0, 4.0)	45.0, 55.4	-10.3 (-23.1, 2.8)	40.1, 49.6	-9.4 (-12.4, 2.9)

<u>Obese patients</u>

The following table outlines the responder rate in obese patients in Phase III Efficacy Analysis sets.

Table 23: Responder rate in obese patients – Phase III studies

Type Time Point	RX-3341-302		RX-3341-303		Phase III Efficacy Analysis Set	
	Responder Rate (%)[a]	Difference (95% CI)[b,c]	Responder Rate (%)[a]	Difference (95% CI)[b,c]	Responder Rate (%)[a]	Difference (95% CI)[b,c]
Obese patients (BMI ≥ 30 kg/m²)	N_{dela} = 120, N_{vanco} = 94		N_{dela} = 211, N_{vanco} = 214		N_{dela} = 331, N_{vanco} = 308	
Cure						
FU	56.7, 44.7	12.0 (-1.5, 25.1)	58.8, 59.3	-0.6 (-9.9, 8.7)	58.0, 54.9	3.5 (-4.1, 11.1)
PTE	60.0, 47.9	12.1 (-1.3, 25.2)	64.9, 65.9	-1.0 (-10.0, 8.1)	63.1, 60.4	3.4 (-8.1, 6.7)
PTE_{7-14}	52.5, 45.7	6.8 (-6.7, 20.0)	56.4, 57.5	-1.1 (-10.5, 8.3)	55.0, 53.9	1.5 (-8.1, 6.2)
PTE_{6-15}	56.7, 46.8	9.9 (-3.6, 23.0)	60.2, 61.7	-1.5 (-10.7, 7.8)	58.9, 57.1	2.3 (-8.4, 6.2)

Summary of main efficacy results

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.

Table 24: Summary of efficacy for trial RX-3341-302

Title:			
A Phase 3, Multicenter, Randomized, Double-Blind, Active-Controlled Study to Evaluate the Efficacy and Safety of Delafloxacin Compared With Vancomycin + Aztreonam in Patients With Acute Bacterial Skin and Skin Structure Infections			
Study identifier	NCT01811732		
Design	Phase 3, randomized, double-blind, multi-center, comparative efficacy and safety study to evaluate IV delafloxacin compared to IV vancomycin + aztreonam in the treatment of adult patients with ABSSSI.		
	Duration of main phase:		28 days
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Non-inferiority in the ITT and CE population, Non-inferiority margin -10%		
Treatments groups	Delafloxacin		300 mg IV every 12 hours administered over 1 hour, for a minimum of 5 days (10 doses) and a maximum of 14 days (28 doses); Lot #12DEL1
	Vancomycin + Aztreonam		<u>Vancomycin:</u> 15 mg/kg IV every 12 hours (based on actual body weight) administered over 2 hours, for a minimum of 5 days (10 doses) and a maximum of 14 days (28 doses); Lot #23405DD <u>Aztreonam:</u> 2 g IV every 12 hours administered over 30 minutes, treatment until baseline cultures were confirmed negative for gram-negative pathogens; Lot #2M50306, #2L70570, and #3B75669
Endpoints and definitions	Primary endpoint	Non-inferiority	Investigator's clinical assessment at the FU Visit (i.e., Day 14 + 1 from randomization) with duration of treatment lasting up to 14 days. The analysis was performed considering the outcome of cure (complete resolution of all signs and symptoms) and of clinical success (patients reported as cured or improved where no further antibiotics are required) on the ITT and CE populations.

	Secondary endpoints	descriptive	To evaluate the clinical efficacy of delafloxacin compared with vancomycin + aztreonam by assessing:
			- the investigator-assessed response of signs and symptoms of infection at the LFU visit - the objective clinical response of the reduction of erythema of ≥30% at 48 to 72 hours - the investigator-assessed response of signs and symptoms of infection in MRSA patients at the FU visit - the reduction in pain at EOT as measured by ePRO - the microbiological response in MRSA patients - the microbiological response in all patients To evaluate the safety of delafloxacin compared with vancomycin + aztreonam

Database lock	30 August 2014; Study period 25 April 2013 – 6 June 2014

Results and Analysis

Analysis description	Primary Analysis		
Analysis population and time point description	ITT: Includes all patients who were randomly assigned to treatment. CE at FU visit: Includes all patients in the ITT analysis set who had a relevant (at the specific timepoint) non-missing assessment, an ABSSSI, who received ≥ 80% of their assigned treatment, had the required clinical assessments within the appropriate window, did not receive systemic antibacterial therapy with activity against the causative pathogens through the time period in question, and had no protocol deviations that would have affected efficacy assessments through the time period in question.		
Effect estimate per comparison	Treatment group	Delafloxacin	Vancomycin + Aztreonam	
	Number of subjects	ITT: 331 CE at FU visit:240	329 244	
	Cure at FU in ITT n/N (%)	172 (52.0)	166 (50.5)	
	Difference (95% CI)	1.5 (−6.1, 9.1)		
	Success at FU in ITT: Cure + improved n/N (%)	270 (81.6)	274 (83.3)	
	Difference (95% CI)	−1.7 (−7.6, 4.1)		
	Cure at FU in CE n/N (%)	142 (59.2)	142 (58.2)	
	Difference (95% CI)	1.0 (−7.8, 9.7)		

| | | Success at FU in CE: Cure + improved n/N (%) | 233 (97.1) | 238 (97.5) | |
| | | Difference (95% CI) | −0.5 (−3.7, 2.7) | | |

Analysis description	Secondary analysis
Analysis population and time point description	In addition to ITT and CE: MITT: Includes all patients in the ITT analysis set who had a bacterial pathogen identified at baseline that was known to cause ABSSSI. ME: There are several ME analysis sets, which include all patients in the MITT analysis set who also met the criteria for the corresponding CE analysis set for either objective or investigator-assessed response.
Descriptive Statistics and Estimate Variability	For results of the secondary endpoints see section outcomes and estimation.

Table 25: Summary of efficacy for trial RX-3341-303

Title:	
A Phase 3, multicenter, randomized, double-blind, active-controlled study to evaluate the efficacy and safety of IV and oral delafloxacin compared with vancomycin + aztreonam in patients with acute bacterial skin and skin structure infections	
Study identifier	NCT01984684
Design	Phase 3, randomized, double-blind, double-dummy, multi-center, comparative efficacy and safety study to evaluate I.V. followed by oral delafloxacin compared to I.V. vancomycin + aztreonam in the treatment of adult patients with ABSSSI.

Design	Duration of main phase:	28 days
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable

Hypothesis	Non-inferiority in the ITT and CE population, Non-inferiority margin -10%	
Treatments groups	Delafloxacin	Delafloxacin, 300 mg, IV, every 12 hours for 6 doses (Lot Nos. 13DE009H, 13DE009J, 13DE011E, 13DE0121, 13DE012G, 13DE012H); followed by delafloxacin, 450 mg orally, given every 12 hours for an additional 4 to 22 doses (Lot Nos. 12DEL1 13DEL1, 14DEL1)
	Vancomycin + Aztreonam	Vancomycin: 15 mg/kg IV every 12 hours (based on actual body weight) administered over 2 hours, for a minimum of 5 days (10 doses) and a maximum of 14 days (28 doses); Lot 2704503, 2734809, 154271A, 31305DD Aztreonam: 2 g IV every 12 hours administered over 30 minutes, treatment until baseline cultures were confirmed negative for gram-negative pathogens; Lot AAA2794, AAC6524, 3B75669, 4B81416, 3G74346

Endpoints and definitions	Primary endpoint	Non-inferiority	Investigator's clinical assessment at the FU Visit (i.e., Day 14 + 1 from randomization) with duration of treatment lasting up to 14 days. The analysis was performed considering the outcome of cure (complete resolution of all signs and symptoms) and of clinical success (patients reported as cured or improved where no further antibiotics are required) on the ITT and CE populations.
	Secondary endpoints	descriptive	To evaluate the clinical efficacy of delafloxacin compared with vancomycin + aztreonam by assessing: ▪ the investigator-assessed response of signs and symptoms of infection at the Follow-up Visit ▪ the investigator-assessed response of signs and symptoms of infection in patients with a baseline BMI ≥ 30 kg/m2 at the Follow-up Visit ▪ the investigator-assessed response of signs and symptoms of infection at the Late Follow-up Visit ▪ the microbiological response ▪ the sustained clinical efficacy at the Late Follow-up Visit ▪ the clinical efficacy at 48 to 72 hours after initiation of treatment To evaluate the safety of delafloxacin compared with vancomycin + aztreonam
Database lock	N/A; Study period 2 May 2014 – 29 January 2016		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT: Includes all patients who were randomly assigned to treatment. CE at FU visit: Includes all patients in the ITT analysis set who had a relevant (at the specific timepoint) non-missing assessment, an ABSSSI, who received ≥ 80% of their assigned treatment, had the required clinical assessments within the appropriate window, did not receive systemic antibacterial therapy with activity against the causative pathogens through the time period in question, and had no protocol deviations that would have affected efficacy assessments through the time period in question.		
Effect estimate per comparison	Treatment group	Delafloxacin	Vancomycin + Aztreonam	
	Number of subjects	ITT: 423 CE at FU visit:353	427 329	
	Cure at FU in ITT n/N (%)	244 (57.7)	255 (59.7)	
	Difference (95% CI)	−2.0 (−8.6, 4.6)		

	Success at FU in ITT: Cure + improved n/N (%)	369 (87.2)	362 (84.8)	
	Difference (95% CI)	2.5 (−2.2, 7.2)		
	Cure at FU in CE n/N (%)	220 (62.3)	224 (68.1)	
	Difference (95% CI)	−5.8 (−12.9, 1.4)		
	Success at FU in CE: Cure + improved n/N (%)	340 (96.3)	319 (97.0)	
	Difference (95% CI)	−0.6 (−3.5, 2.2)		
Analysis description	**Secondary analysis**			
Analysis population and time point description	In addition to ITT and CE: MITT: Includes all patients in the ITT analysis set who had a bacterial pathogen identified at baseline that was known to cause ABSSSI. ME: There are several ME analysis sets, which include all patients in the MITT analysis set who also met the criteria for the corresponding CE analysis set for either objective or investigator-assessed response.			
Descriptive Statistics and Estimate Variability	For results of the secondary endpoints see section outcomes and estimation.			

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

The applicant performed pooled analysis of phase III data and phase II plus phase III data and compared efficacy results of meaningful studies.

Clinical studies in special populations

There were no efficacy studies in special populations.

Supportive study

Phase II study RX-3341-202

Study RX 3341-202 was a stratified, randomized, double blind, Phase II, multicentre study conducted in the US comparing the efficacy and safety of IV delafloxacin to that of IV linezolid and IV vancomycin in the treatment of ABSSSI. This study was initiated prior to the release of the current EMA guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, when the presence of only one systemic sign of infection was required to be enrolled. A total of 256 adult patients were randomly assigned, in a 1:1:1 ratio, to delafloxacin IV 300 mg Q12h, linezolid IV 600 mg Q12h, or vancomycin IV 15 mg/kg Q12h. Subjects whose microbiological cultures grew Gram-negative bacteria could have had aztreonam added to their treatment regimen at the discretion of the investigator. Treatment was given for 5 to 14 days, based on the investigator's judgment.

Subjects aged 18 and above, who had a diagnosis of ABSSSI, defined as cellulitis/erysipelas, wound infection, major cutaneous abscess, or burn infection, of a minimum surface area of 75 cm^2; had lymph node enlargement caused by the present infection or at least one of the following symptoms of systemic infection: fever ≥ 38°C, lymphangitis, white blood cell (WBC) count ≥ 15,000 cells/μL, or CRP > 5.0 mg/L; and who required and was a suitable candidate for IV antibiotic therapy.

Randomization was stratified by category of infection with no more than 30% of enrolled subjects having cutaneous abscess. The remaining infection types were not limited but were stratified for balance between treatment groups. Randomization was also stratified equally across treatment groups by prior antibiotic therapy exclusion criteria, and subjects with prior antibiotic therapy were limited overall to ≤ 30%.

Clinical response was determined at Follow-up (Day 14 ± 1) and Late Follow-up (Day 21 to 28) based on the investigator's assessment of the signs and symptoms of infection. Microbiological response was determined for subjects in the microbiologically evaluable (ME) population at the Follow-up and Late Follow-up assessments at both the subject and pathogen levels.

The investigator assessed outcomes were classified as cure, improved, failure and indeterminate. Cure was defined as the complete resolution of all baseline signs and symptoms of ABSSSI at FU and LFU. However, if erythema was the only sign of infection remaining at FU, and the erythema was absent at LFU, then the case was classified as a cure. Improved was defined as some symptoms remaining, but the patient had improved to an extent that no additional antibiotic treatment was necessary. However, improved responses were considered failures for purposes of the primary analysis. The primary endpoint, clinical response in the ITT population, was determined by the success rate based on the investigator's assessment at the Follow-up visit and expressed as (cure) / (cure + failure) in percentage, in which "cure" was classified as success, and improved, indeterminate, and failure responses were treated as failures.

A total of 210 (82.0%) subjects completed the study: 69 (85.2%) in the delafloxacin group, 63 (81.8%) in the linezolid group, and 78 (79.6%) in the vancomycin group. Overall, the most frequent reasons for withdrawal were lost to follow-up (22 [47.8%] subjects), other reasons (10 [21.7%] subjects), and subject withdrew consent (9 [19.6%]). Across the 3 treatment groups, demographic characteristics (age, sex, ethnicity group, race, height, weight, and BMI) were generally similar. A majority of subjects were men (59.4%), Caucasian (76.2%), and not Hispanic or Latino (77.7%). The mean age of subjects was 43.2 years (range, 18-91 years); and the mean BMI (SD) was 29.5 kg/m2 (6.58).

At Baseline, 175 of 256 (68.4%) subjects had at least 1 pathogen and 29 of 256 (11.3%) subjects had multiple pathogens. Among the delafloxacin, linezolid, and vancomycin treatment groups, a similar percentage of subjects had at least 1 pathogen at Baseline (63.0%, 74.0%, and 68.4%, respectively); whereas a higher percentage of subjects in the linezolid group (19.5% [15 of 77]) had multiple pathogens at Baseline than in the delafloxacin (7.4% [6 of 81]) and vancomycin (8.2% [8 of 98]) groups. Overall, 205 gram-positive pathogens (58 in the delafloxacin group, 83 in the linezolid group, and 74 in the vancomycin group), 6 gram-negative pathogens (4 in the delafloxacin group, 0 in the linezolid group, and 2 in the vancomycin group), and 3 anaerobes (2 in the delafloxacin group and 1 in the linezolid group) were isolated. The most common pathogen was *S. aureus* (177 isolates: 119 MRSA; 58 MSSA) in all 3 treatment groups (48 isolates [36 MRSA; 12 MSSA] in the delafloxacin group, 65 isolates [45 MRSA; 20 MSSA] in the linezolid group, and 64 isolates [38 MRSA; 26 MSSA] in the vancomycin group). Of the 256 subjects overall, 159 (62.1%) had at least 1 S. aureus pathogen: 106 (41.4%) subjects had at least 1 MRSA pathogen and 53 (20.7%) subjects had at least 1 MSSA pathogen.

In the following table the cure rates at FU visit are presented:

Table 26: Cure Rate, Stratified by Baseline Infection Category, Using Investigator Assessment (ITT Population) in Study RX-3341-202

	Treatment Group		
	Delafloxacin IV n / Total (%) N = 81	Linezolid IV n / Total (%) N = 77	Vancomycin IV n / Total (%) N = 98
All Patients	57 (70.4)	50 (64.9)	53 (54.1)
Difference (95% CI) vs. Delafloxacin [a]		5.4% (−9.1, 20.0)	16.3% (2.3, 30.3)
P - Value [b]		0.496	0.031

CI = confidence interval; IWRS = interactive web response system.
Note: Success rate was expressed as (cure) / (cure + failure) in percentage and was based on the investigator's assessment at the Follow-up visit. Cure was treated as success, and improved, indeterminate, and failure responses were treated as failures.
[a] Treatment effects and their CIs were based on the overall difference in proportions. Differences were between delafloxacin and linezolid (D - L) and delafloxacin and vancomycin (D - V).
[b] This p-value of nonzero correlation from Cochran – Mantel - Haenszel statistics stratified by baseline infection categories indicates the significance of association between treatments and clinical responses (success vs. failure).
Source: Study RX-3341-202 Table 14.2.2.1.1a

A total of 125 patients were in the microbiologically evaluable (ME) population across the 3 treatment arms. Consistent with the clinical response assessment, patients receiving delafloxacin had higher microbiological eradication rates than patients in the linezolid or vancomycin arms.

Table 27: Microbiological Efficacy Response (Microbiologically Evaluable Population) in Study RX-3341-202

Microbiological Response, n (%)	Delafloxacin IV	Linezolid IV	Vancomycin IV	Overall
Response Category				
N	34	39	52	125
Documented Eradicated	0	0	0	0
Presumed Eradicated	30 (88.2)	32 (82.1)	42 (80.8)	104 (83.2)
Documented Persisted	0	1 (2.6)	0	1 (0.8)
Presumed Persisted	4 (11.8)	6 (15.4)	10 (19.2)	20 (16.0)
Superinfection	0	0	0	0
New Infection	0	0	0	0

Source: Study RX-3341-202 Table 14.2.19.1

Given the statistically superior result in the investigator assessment of cure at FU in the overall ITT population, subgroups were analysed to assess factors that contributed to this difference. In a post hoc analysis, non-obese patients (BMI < 30 kg/m^2) showed no statistically significant difference in cure rate between delafloxacin and the other 2 agents. However, for obese patients (BMI ≥ 30 kg/m^2), who comprised 42% of the study population, the proportion of patients with the investigator assessment of cure was significantly higher for delafloxacin (78.8%) than for vancomycin (48.8%; mean difference from delafloxacin: 30.0%; 95% confidence interval (CI), 9.3%, 50.7%). It was numerically higher for delafloxacin compared to linezolid but not statistically different (linezolid outcome 58.8%).

2.5.3. Discussion on clinical efficacy

This application concerns delafloxacin, a new fluoroquinolone, for the treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI) in adults. The efficacy of delafloxacin was evaluated in two pivotal Phase III studies (RX-3341-302 [IV] and RX-3341-303 [IV to oral]) and one supportive Phase II study (RX-3341-202 [IV].

Design and conduct of pivotal studies

The Phase III studies RX-3341-302 and RX-3341-303 were multi-centre, randomized, double blind efficacy and safety studies (Study RX-3341-303 in addition double-dummy). Study RX-3341-302 investigated IV formulation of delafloxacin, whereas study RX-3341-303 investigated oral and IV formulation of delafloxacin.

Inclusion/exclusion criteria

In both pivotal studies specific definitions of ABSSSI infection types (cellulitis/erysipelas, wound infection, major cutaneous abscess, burn infection) with prespecified minimum surface area of 75 cm2 and definition of at least two of signs of systemic inflammation were included as inclusion criteria to ensure that only severely infected patients were included into the studies.

For burn infections the maximum extent was further specified in the inclusion criteria. Patients with burn infections were only enrolled if the area of the burn comprised ≤ 10% of the patient`s body surface as determined by the investigator.

Randomisation was stratified by type of infection and designed so that no more than 25% of enrolled patients were treated for a major cutaneous abscess, and no more than 35% (Study RX-3341-302) or 30% (Study RX-3341-303) of enrolled patients were treated for wound infections. The remaining infection types (cellulitis/erysipelas or burn infection) were not limited.

The exclusion of patients with diabetic foot, which would be considered a complicated infection, is in line with the recommendation in the Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (EMA/CHMP/351889/2013) where diabetic foot infections are advised to be evaluated in separate dedicated studies.

Overall, inclusion and exclusion criteria are in line with the recommendations in the Addendum and therefore acceptable. Patients included on the basis of these criteria meet the requirements for ABSSSI.

Treatments

Study RX-3341-302 investigated 300 mg IV delafloxacin every 12 hours for a minimum of 5 days and a maximum of 14 days, whereas study RX-3341-303 investigated 300 mg IV delafloxacin every 12 hours for 6 doses followed by 450 mg oral delafloxacin, given every 12 hours (without regard to food) for an additional 4 to 22 doses with the same treatment duration as in study RX-3341-302 (5-14 days).

In both studies, vancomycin + aztreonam were chosen as comparator. Aztreonam was added for treatment of Gram-negative ABSSSI and was to be stopped after baseline cultures were confirmed negative for Gram-negative pathogens.

Vancomycin is a well-established antibiotic that has been used as comparator in several cSSTI studies. Even if vancomycin may not be the optimal choice of treatment of MSSA and streptococci and linezolid would have been the more appropriate comparator, it is considered acceptable as a high proportion of MRSA is aimed at. Weight-based dosage of vancomycin and used dosage of aztreonam are in line with approved dosages in the EU.

Primary endpoint

In both pivotal trials, the primary endpoint was the investigator's clinical assessment at the FU Visit (i.e., Day 14 + 1 from randomization) with duration of treatment lasting up to 14 days for both delafloxacin and the comparator arm. The analysis was performed considering the outcome of cure and of clinical success on the ITT and CE populations.

According to the Addendum as primary analysis clinical outcome documented at a TOC visit timed from randomisation so that it occurs within a window of approximately 7-14 days after the last day of treatment would be an acceptable primary endpoint. In the pivotal studies the TOC visit was timed 14 + 1 day from randomisation, which is not in line with this recommendation. Taking the treatment duration of 5 to 14 days into account, the TOC visit was performed between day 0 and day 9 after the last day of treatment. The applicant addressed this point in its application dossier. In order to be compliant with the EMA antibacterial guideline, the applicant defined several additional analyses as sensitivity analysis. A new definition of investigator assessment at PTE was introduced within a window of 7 - 14 and 6 - 15 days after EOT (PTE7-14 - PTE6-15); all the assessments outside that window were considered missing, and therefore counted as failure. If, instead, both the assessments are within the defined window after EOT the earliest one (i.e., FU visit) was taken. Overall, the used time point of TOC visit is not optimal. Nevertheless, since finally the results of the additional sensitivity analysis at PTE7-14 and PTE6-15 supported the results of the primary analysis the approach as used in the pivotal studies is acceptable.

Clinical cure was defined as complete resolution of all baseline signs and symptoms of ABSSSI at EOT, FU, and LFU visits; however, if erythema was the only sign of infection remaining at EOT or FU visit, and the erythema was absent at LFU visit, then the case was classified as a cure at EOT (derived), FU (derived), and LFU visits.

Clinical success was defined as a response of cure or improved where the investigator felt that no further antibiotics were needed.

The primary analysis was performed for the ITT and CE population. This is in accordance with current recommendations in the antibacterial guideline where it is suggested that the all-treated population and the clinically evaluable population should be viewed as co-primary. For the primary efficacy endpoint it is further stated that the endpoint was prespecified for non-inferiority testing with a margin of 10%. The non-inferiority margin of 10 % is in line with the recommendation in the Addendum to the guideline.

Statistical methods

Statistical methods used for the primary analysis are considered adequate. Non-inferiority of the new treatment compared to a comparator treatment was assessed using an appropriate confidence interval approach without stratification. The approach to address multiplicity is unproblematic in the pivotal studies with a hierarchical approach used for secondary endpoints. There was no multiplicity due to interim analysis.

Study protocol amendments and changes to analysis plans are acceptable had no relevant impact on the interpretation of results. Missing data is not a major problem in both pivotal studies, 86% to 91% of patients completed the studies at clinical follow-up in the study arms of the ITT population (94% to 95% in the CEFUI population). The applicant also addressed the problem that patients were excluded from the CEFUI population if the investigator clinical assessment at follow up was not available with a post-treatment evaluation analysis. The originally provided analyses in the clinically evaluable population, conducted as standard "per-protocol" analysis, with varied windowing for the visits for Study -303 indicated that delafloxacin cannot be considered non-inferior to the comparator in the study, while the ITT analysis allows concluding that delafloxacin is non-inferior to the comparator. As the ITT analysis can generally be considered anti-conservative for equivalence or non-inferiority trials it is usually required

that the analyses in the "per-protocol" and ITT populations lead to similar conclusions for a robust interpretation of results. The per-protocol set is defined by post randomisation (intercurrent) events and may be biased or difficult to interpret. In study -303, there was a larger proportion of patients excluded in the vancomycin + aztreonam arm compared to the delafloxacin arm.

The applicant provided two additional analyses that addressed the issue. The first analysis was performed as proposed by the CHMP in form of a sensitivity analysis, evaluating non-inferiority using a principle stratum analysis to test the causal treatment effect for patients who would be part of the clinical evaluable population under both delafloxacin and vancomycin + aztreonam (using a "Survivor Average Causal Effect (SACE) as in Lou YL and Sun W, J Biopharm Stat 2018). The second analysis is an additional analysis using a hypothetical strategy to impute excluded observations in the clinically evaluable population. Results show that for study -303 non-inferiority could be concluded in a range of scenarios in the sensitivity analysis and that results are closer to the non-inferiority margin with imputed observations compared to the original "per protocol" analysis (although based on the missing at random assumption). Results of the analyses also confirm the robustness of the Study -302 results.

Baseline data

Baseline data were comparable between treatment arms. In both pivotal studies most patients were aged ≤ 65 years and Whites. More than half of patients were male. When comparing pivotal studies, in study RX 3341-303 more patients were aged >65 years, more patients were from Europe, more patients had a BMI ≥ 30 and slightly more patients had diabetes compared to study RX 3341-302.

The baseline infection type was comparable between delafloxacin and vancomycin + aztreonam groups. Less than 30% of patients had a major cutaneous abscess and less than 1% had a burn infection as base line infection in delafloxacin and vancomycin + aztreonam groups. In study RX 3341-302 more patients with wound infection were included into the study compared to study RX 3341-303 (35% vs. 26%), whereas study RX 3341-302 included less patients with cellulitis/erysipelas as base line infection (39% vs. 48%).

Overall, the most common location of the infection site was the lower and upper extremities. The distribution by anatomical site was similar between the delafloxacin group and the vancomycin + aztreonam group for sites of infection.

The mean (SD) size of the erythema, using digital methods, was slightly smaller in the delafloxacin treatment groups compared with the vancomycin + aztreonam treatment groups (RX 3341-302: 294.8 cm2 vs. 319.1 cm2; RX 3341-303: 341.5 cm2 vs. 364.4 cm2). However, there was a wide range in the measurements of erythema area. Similarly, the mean size of the induration, using digital methods, tended to be smaller in the delafloxacin treatment group compared with the vancomycin + aztreonam treatment group and there was a wide range in the measurements of induration area.

More than 55% of the patients had 3 or more systemic signs of infection in both treatment groups. Overall, the most frequent systemic sign reported was lymph node enlargement due to present infection with similar numbers between the 2 treatment groups. The other frequently reported systemic sign was the presence of purulent or seropurulent drainage or discharge with similar numbers between the 2 treatment groups. Approximately half of the patients had the systemic sign of elevated white blood cell (WBC) ≥ 10,000 cells/µL. Overall, fewer than 50% of the patients reported the systemic sign of elevated C reactive protein, fever ≥ 38ºC/100.4ºF, lymphangitis, or bacteraemia.

Overall, baseline disease characteristics are in line with the recommendation in the Addendum and severity of disease was supported by baseline data.

In study RX-3341-302 in 65.9% of the patients the TOC visit (FU visit) was investigated 8 to 14 days after EOT (as recommended in the Addendum). In study RX-3341-303 in 58.6% the TOC visit was performed 8 to 14 days after EOT.

The percentage of patients who had the FU visit within 3 days and within 6 days from EOT was higher in the study RX-3341-303 versus study RX-3341-302 (i.e.: 17.8% vs 11.4% within 3 days and 40.2% vs 25.6% within 6 days, respectively); however, there was no difference in the distribution of patients by treatment arm.

The pathogens isolated at baseline reflected the most commonly detected causal pathogens for ABSSSI. Baseline pathogens were in general comparable between treatment groups.

Efficacy data and additional analyses of pivotal studies

Primary EP

Study RX 3341-302 (delafloxacin IV):

In the ITT population the cure rate at FU visit was 52.0% in the delafloxacin group and 50.5% in the vancomycin + aztreonam group. In the CE population (CEFUI) the cure rates at FU visit were comparable as well (delafloxacin 59.2% vs. vancomycin + aztreonam 58.2%). The cure rates are relatively low compared to some other studies in ABSSSI. However, this could be explained by early time point of FU visit and strict definition of clinical cure (complete resolution of all baseline signs and symptoms of ABSSSI at FU). Non-inferiority of delafloxacin to vancomycin + aztreonam has been demonstrated, since the lower limit of the two-sided 95% confidence interval was above the pre-specified margin -10% for the primary endpoint in both the ITT (-6.1%) and CE (-7.8%) population.

The success rates (cure + improved where the investigator felt that no further antibiotics were needed in the respective populations) in the ITT population at FU were 81.6% in the delafloxacin group an 83.2% in the vancomycin + aztreonam group (95% CI -7.6, 4.1). In the CE-Population the success rates were 97.1% in the delafloxacin group and 97.5% in the vancomycin + aztreonam group (95% CI -3.7, 2.7).

The reasons for clinical failure at FU visit were generally well balanced between treatment groups in the study.

Cure rates at FU visit in the MITT and ME population as well as cure rates in the ITT and CE population at PTE, PTE7-14 and PTE6-15 were comparable between delafloxacin and vancomycin + aztreonam group. The results of these sensitivity analyses support the results of the primary analysis.

Study RX 3341-303 (delafloxacin IV 6 doses followed by oral):

The cure rates at FU visit in the ITT population were 57.7% in the delafloxacin group and 59.7% in the vancomycin + aztreonam group, which were slightly higher rates compared to study RX 3341-302. For the ITT population the lower limit of the two-sided 95% confidence interval was above the pre-specified margin -10% (-8.6%).

In the CE population (CEFUI) the cure rates at FU visit were 62.3% (delafloxacin) vs. 68.1% (vancomycin + aztreonam), 95% CI -12.9, 1.4. The lower limit of the 95% CI was below the non-inferiority (NI) margin (-10%).

The success rates (cure + improved where the investigator felt that no further antibiotics were needed in the respective populations) in the ITT population at FU were 87.2% in the delafloxacin group an 84.8% in the vancomycin + aztreonam group (95% CI –2.2, 7.2). In the CE-Population the success rates were 96.3% in the delafloxacin group and 97.0% in the vancomycin + aztreonam group (95% CI -3.5, 2.2).

The reasons for clinical failure at FU visit were generally well balanced between treatment groups in the study.

The cure rates in the MITT population (all patients in the ITT analysis set who had a bacterial pathogen identified at baseline that was known to cause ABSSSI) were comparable (delafloxacin 57.5% vs. vancomycin + aztreonam 58.8% (95% CI -9.6, 6.8). However, in the ME population (all patients in the MITT analysis set who also met the criteria for the CE analysis set for either objective or investigator-assessed response) the cure rate in the delafloxacin group was slightly lower compared to vancomycin + aztreonam group (61.0% vs. 67.9%, 95% CI -15.7, 2.1), which are in line with the results of the cure rates in the CE population.

In addition, in the ITT population the cure rates at PTE, PTE7-14 and PTE6-15 were comparable between delafloxacin and vancomycin + aztreonam group. However, in the CE population the cure rates at PTE, PTE7-14 and PTE6-15 tended to be in disfavour of delafloxacin. Overall, these sensitivity analyses supported that non-inferiority can be concluded for the ITT population; however, non-inferiority could not formally be concluded for the CE population.

The applicant was requested to further discuss possible implications of the early TOC visit on the results of the primary analysis. It was quantified how many patients had the FU assessment outside the window of 7 - 14 days after EOT, and in particular, how many patients had an earlier time of FU assessment which has been categorised as FU at < 3 days from EOT and < 6 days from EOT and of early TOC visit on the results of the primary analysis. The percentage of patients who had the FU visit within 3 days and within 6 days from EOT was higher in the study RX-3341-303 versus study RX-3341-302 (i.e.: 17.8% vs 11.4% within 3 days and 40.2% vs 25.6% within 6 days, respectively); however, there was no difference in the distribution of patients by treatment arm.

Furthermore, shift tables of clinical assessment from FU to LFU for patients with FU visit < 3 and ≤6 days from EOT were provided. In the vast majority of cases the investigator's assessment at FU < 3 days and ≤6 days from EOT was confirmed at the subsequent LFU visit.

Considering the FU assessment ≤ 3 days from EOT, only two patients per each treatment arm in study RX-3341-302, and 14 and 11 patients in the delafloxacin and vancomycin arm in study RX-3341-303, respectively, were evaluated at the earlier assessment as improved whereas the outcome could have potentially been assessed as cure if the TOC was performed later, being cure recorded at the LFU.

However, only one patient allocated to vancomycin in each pivotal study was assessed as cure at this much earlier assessment, while at later FU visit the response was de-escalated to improved. Finally, in study RX-3341-302 only one patient on delafloxacin and one patient on vancomycin treatment arm had the earlier assessment (improved and cure, respectively) without any confirmatory later assessment.

Regarding the FU assessment ≤6 days from EOT, similar results were obtained for the evaluation of the impact of early assessments on the clinical response. A total of 22 and 45 patients in RX-3341-302 study and in RX-3341-03 study respectively, similarly distributed between the treatment arms, were evaluated at the earlier assessment as improved whereas the outcome could have potentially been recorded as cure if the TOC was performed later. The number of patients who have been assessed as cured at FU and then de-escalated to improved at LFU was negligible in both studies.

Overall, the analysis supported that the FU assessment performed earlier than the window of 7 - 14 days after the EOT had a negligible effect on the evaluation of the primary endpoint in both pivotal studies.

Results of two additional analysis showed that for study -303 non-inferiority could be concluded in a range of scenarios in the sensitivity analysis and that results are closer to the non-inferiority margin with imputed observations compared to the original "per protocol" analysis (although based on the missing at random assumption). Results of the analyses also confirmed the robustness of the Study -302 results.

Furthermore, additional analysis supported that no relationship between exposure and clinical response could be identified. In addition, no relevant differences of the predicted plasma exposures (measured at day 1 and day 3 after IV delafloxacin) in those who did and did not fail between studies RX-3341-302 and RX-3341-303 were detectable.

Subgroup analyses in studies RX 3341-302 and RX 3341-303

Eradication rates as presented by the applicant were in general high and comparable between treatment groups. Eradication rates of delafloxacin for MRSA were 100% (58/58) in study RX 3341-302 and 96% (48/50) in study RX 3341-303.

In both studies cure rates were considerably higher at FU visit in patients in Europe (study RX 3341-302: delafloxacin 85.7%, vancomycin + aztreonam 70.9%, n=118; study RX 3341-303: delafloxacin 67.9%, vancomycin + aztreonam 69.9%; n=338) compared to North America (study RX 3341-302: delafloxacin 44.0%, vancomycin + aztreonam 46.4%, n=542; study RX 3341-303: delafloxacin 46.5%, vancomycin + aztreonam 49.5%; n=398).

In study RX 3341-302 cure rate at FU visit in women was considerably higher in delafloxacin group (58.4%) compared to vancomycin + aztreonam (47.5%). In men cure rates were slightly lower in delafloxacin group (48.1% vs. 52.2%). In study RX 3341-303 cure rate at FU visit in women was comparable between treatment groups. In men the cure rate was slightly lower in the delafloxacin group (54.6% vs. 58.7%). In both studies cure rates at FU visit were considerably higher in women compared to men.

In study RX 3341-302 the cure rate at FU visit in patients with renal impairment (CL_{cr} < 90 mL/min) was higher in the delafloxacin group (delafloxacin 60.4% (n=53); vancomycin + aztreonam 52.7% (n=55)), whereas in study RX 3341-303 the cure rates were comparable (delafloxacin 68.1% (n=69); vancomycin + aztreonam 68.7% (n=67)). In addition, the number of patients with different degree of renal impairment in pivotal studies and respective cure rates was provided. Overall, 167 patients with mild renal impairment ($CL_{cr} \geq 60$ mL/min and CL_{cr} < 90 mL/min), 75 patients with moderate renal impairment ($CL_{cr} \geq 30$ mL/min and CL_{cr} < 60 mL/min) and four patients with severe renal impairment (CL_{cr} < 30 mL/min) were included in the pivotal studies RX-3341-302 and RX-3341-303. In the Phase III pool cure rates in the delafloxacin group were numerically higher in patients with mild and moderate renal impairment compared to cure rate in patients with normal renal function. When comparing delafloxacin group and vancomycin + aztreonam group, the cure rate in patients with mild renal impairment was comparable and in patients with moderate renal impairment, the cure rate was numerically higher in delafloxacin group. Since only four patients with severe renal impairment were included into pivotal studies, no conclusion about efficacy in this population is possible. Overall, efficacy of delafloxacin in mild and moderate renal impaired patients seems to be adequate. The data available in patients with severe renal impairment is too limited to draw a conclusion regarding efficacy.

Cure rates at FU visit in patients with cellulitis/erysipelas were higher in delafloxacin group compared to comparator group in study RX 3341-302 (delafloxacin: 67.2% n=128; vancomycin + aztreonam: 60.9% n=128), whereas in study RX 3341-303 cure rates at FU visit were slightly lower in delafloxacin group compared to comparator group (delafloxacin 59.9% n=202 vs. vancomycin + aztreonam 63.1% n=202).

In patients with major abscess cure rates at FU visit were higher in delafloxacin group compared to vancomycin + aztreonam group in both pivotal studies (study RX 3341-302: delafloxacin 52.4% n=84; vancomycin + aztreonam 48.2% n=83; study RX 3341-303: delafloxacin 64.2% n=106; vancomycin + aztreonam 57.5% n=106).

In contrast, in case of wound infection cure rates were considerably lower in delafloxacin group compared to comparator group in both pivotal studies (study RX 3341-302: delafloxacin 33.6% n=116; vancomycin + aztreonam 41.4% n=116; study RX 3341-303: delafloxacin 46.8% n=111; vancomycin + aztreonam

54.5% n=112). However, further analysis indicated that a different treatment effect for the cure rate in patients with wound infection could not be statistically claimed. Furthermore, it was highlighted that in terms of success rate (cured or improved) the differences at FU between treatment arms in patients with wound infection were negligible in the RX-3341-302 study and the rate of success was even higher in patients treated with delafloxacin in the RX-3341-303 study. In addition, the cure rates in patients treated with delafloxacin were also similar to those in patients treated with vancomycin + aztreonam when the analysis considered the assessment at the LFU.

Phase II study RX 3341-202 was investigated to evaluate efficacy and safety of delafloxacin (IV) compared to treatment with IV linezolid or IV vancomycin in patients with ABSSSI. In comparison with pivotal studies in study RX 3341-202 the presence of only one systemic sign of infection was necessary to be enrolled. However, further analysis indicated that in this Phase II study in a substantial proportion of patients two or more systemic signs of infection were detectable which suggest that a sufficiently ill study population was investigated.

The TOC visit was performed on day 14 ± 1 after initiation of treatment, which relates to day 0-9 after EOT. Definition of cure was acceptable.

In general, baseline characteristics were comparable. There were small differences in mean age. In the delafloxacin group mean age was 39.7 years, whereas in linezolid group mean age was 44.8 years and in the vancomycin group the mean age was 44.8 years. Regarding the baseline infection slightly more cases of wound infection compared to comparator groups were detectable (delafloxacin 48.1%, linezolid 41.6%, vancomycin 44.9%). Furthermore, the total area of infection was slightly smaller in the delafloxacin group. Baseline pathogens were as expected for ABSSSI.

Cure rates at TOC visit (ITT population) were numerically higher in the delafloxacin group (70.4%) compared to linezolid group (64.9%) and significantly higher compared to vancomycin group (54.1%).

Overall, it can be concluded that results of phase II study RX 3341-202 support efficacy of delafloxacin IV in patients with ABSSSI.

Surveillance studies to monitor the susceptibility of representative clinical isolates against delafloxacin were conducted between 2014-2017 in the EU (including Israel) and USA, as part of the SENTRY Antimicrobial Surveillance Program in which the activity of delafloxacin is compared to numerous broad-spectrum agents when tested against contemporary clinical isolates collected in European and United States medical centres.

Delafloxacin is depicted as a dual-targeting fluoroquinolone showing similar affinity to the bacterial type II topoisomerases DNA gyrase and topoisomerase IV and thus might exhibit an advantageous resistance profile compared to other fluoroquinolones. Thus, the conduct of surveillance studies as a statutory requirement to determine if resistance to delafloxacin has developed in target organisms specific to the indication in the label for ABSSSI is regarded necessary. Accordingly, the applicant confirmed that all data on resistance surveillance retrieved from SENTRY Antimicrobial Surveillance Program and future surveillance programs will be presented and discussed in future PSURs in the context of efficacy.

2.5.4. Conclusions on the clinical efficacy

In study RX-3341-302 non-inferiority of delafloxacin (IV) has been demonstrated (which was further supported by results of phase 2 study RX 3341-202).

In study RX-3341-303 (IV followed by oral delafloxacin), non-inferiority of delafloxacin towards vancomycin + aztreonam for the primary endpoint clinical cure at FU visit has only been demonstrated for the ITT population. In the CE population the lower limit of the 95% CI was below the non-inferiority (NI)

margin (-10%) which was further supported by sensitivity analysis. The CHMP considered it acceptable to consider the single primary population ITT (all randomised patients) for primary analysis and to regard the CE population as secondary.

In study RX-3341-303 the success rates (cure + improved where the investigator felt that no further antibiotics were needed in the respective populations) at FU visit were comparable between treatment groups in both the ITT and CE population. Furthermore, non-inferiority of delafloxacin towards vancomycin + aztreonam for the endpoint success at FU visit has been demonstrated for both the ITT and CE population.

Furthermore, the applicant provided two additional analyses where results showed that for study -303 non-inferiority could be concluded in a range of scenarios in the sensitivity analysis and that results are closer to the non-inferiority margin with imputed observations compared to the original "per protocol" analysis (although based on the missing at random assumption).

In addition, no relevant differences of the predicted plasma exposures (measured on day 1 and day 3 after IV delafloxacin) in those who did and did not fail between studies RX-3341-302 and RX-3341-303 were detectable which support the conclusion of non-inferiority.

Overall, non-inferiority of IV as well as IV followed by oral delafloxacin is concluded.

Development of resistance is regarded as efficacy concern and should be closely monitored during post-marketing period. Any information that becomes available to the applicant on emerging resistance, changing patterns of resistance or new mechanisms of resistance to the antibacterial agent should be notified promptly to EU regulators with a discussion of the possible implications for the product information. The applicant should follow up and report this issue in the Periodic Safety Update Reports. In this regard, the applicant confirmed that all data on resistance surveillance retrieved from SENTRY Antimicrobial Surveillance Program and future surveillance programs will be presented and discussed in future PSURs in the context of efficacy.

2.6. Clinical safety

Delafloxacin has been evaluated in 30 completed Phase I to Phase III clinical studies comprising a total of 2658 delafloxacin-treated subjects. Safety data from the delafloxacin clinical program have been assessed using the following analysis sets:

- Integrated Phase I Safety analysis set (including 20 Phase I studies)

- Phase II and III Safety Pooled Analysis Set (including two Phase II and two Phase III studies: RX-3341-201, RX-3341-202, RX-3341-302 and RX-3341-303; includes 1840 subjects with ABSSSI who received delafloxacin or comparator, of these 868 patients who received multiple doses of delafloxacin 300 mg IV/ 450 mg oral delafloxacin Q12h)

- Non-integrated studies (three studies evaluated delafloxacin in indications AECB (M01-298), CAP (M01-344) and urogenital gonorrhoea (ML-3341-304) in doses that were not used in the ABSSSI studies, one Phase I study in subjects with renal impairment (RX-3341-110), one Phase I study in subjects with hepatic impairment (ML-3341-112) and one Phase I drug interaction study (ML-3341-118) with midazolam). Additionally, one Phase II study (RX-3341-201) included in the Phase II and III Safety Analysis Set also enrolled 51 subjects who received 450 mg IV delafloxacin Q12h for 5 to 14 days. The data from these subjects are not included in the pooled analysis set since the 450 mg IV dose provides higher exposure than the to-be-marketed 300 mg IV dose.

In addition, six of the Phase I studies performed in special populations were discussed individually:

- Photosensitivity Study (M01-284)
- 2 Cardiac Safety Studies (M01-365, RX-3341-111)
- Renal Impairment Study (RX-3341-110)
- Hepatic Impairment Study (ML-3341-112)
- Drug Interaction Study (ML-3341-118)

Patient exposure

The table below summarises the study drug exposure. A total of 2658 subjects have been exposed to delafloxacin in the studies presented below.

Table 28: Study Drug Exposure

	Oral Delafloxacin			IV Delafloxacin		All Doses and Regimens (N = 2658) n
	< 400 mg (N = 576) n	400 - 500 mg (N = 934) n	> 500 mg (N = 456) n	≤ 300 mg (N = 1173) n	> 300 mg (N = 162) n	
Phase I Safety Analysis Set	235	288	152	232	111	814
Phase II and III Safety Analysis Set		417		868		868
Non-Integrated Studies						
M01-298	138	69				207
M01-344	203	106				309
ML-3341-304			304			304
RX-3341-110		32		34		44
ML-3341-112				39		39
ML-3341-118		22				22
RX-3341-201 non-integrated arm					51	51

In Phase I Safety Analysis Set, exposure ranged from 1 to 14 days, with a mean of 4.6 days. Most subjects (74.9%) received ≤ 10 doses, with 25.1% receiving 11 to 28 doses.

In Phase II and III Safety Analysis Set, delafloxacin exposure ranged from 0.5 to 14.0 days, with a mean of 6.8 days. Most patients (59.2%) received 11 to 28 doses of delafloxacin, with 40.7% receiving ≤ 10 doses.

Adverse events

Phase II and III Safety Analysis Set

Table 29: Overall Summary of Treatment-Emergent Adverse Events – Phase II and III Safety Analysis Set

	Pooled Phase III studies		Pooled Phase II studies		Phase II and III Safety Analysis Set	
	Delafloxacin (N = 741) n (%)	Vancomycin (Aztreonam) (N = 751) n (%)	Delafloxacin (N = 127) n (%)	Pooled Comparators (N = 221) n (%)	Delafloxacin (N = 868) n (%)	All Comparators (N = 972) n (%)
Total number of TEAEs	775	879	233	486	1008	1365
Patients with any TEAE	334 (45.1)	358 (47.7)	80 (63.0)	151 (68.3)	414 (47.7)	509 (52.4)
Patients with any related TEAE	164 (22.1)	196 (26.1)	58 (45.7)	105 (47.5)	222 (25.6)	301 (31.0)
Patients with any TEAE presented by maximum severity						
Mild	198 (26.7)	206 (27.4)	44 (34.6)	96 (43.4)	242 (27.9)	302 (31.1)
Moderate	110 (14.8)	131 (17.4)	33 (26.0)	38 (17.2)	143 (16.5)	169 (17.4)
Severe	26 (3.5)	21 (2.8)	3 (2.4)	17 (7.7)	29 (3.3)	38 (3.9)
Patients with any serious TEAE	27 (3.6)	26 (3.5)	5 (3.9)	11 (5.0)	32 (3.7)	37 (3.8)
Patients with any related serious TEAE	2 (0.3)	4 (0.5)	0	0	2 (0.2)	4 (0.4)
Patients with any TEAE leading to premature study drug discontinuation	13 (1.8)	26 (3.5)	1 (0.8)	11 (5.0)	14 (1.6)	37 (3.8)
Patients with any related TEAE leading to premature study drug discontinuation	6 (0.8)	18 (2.4)	0	5 (2.3)	6 (0.7)	23 (2.4)
Patients with any TEAE leading to death	1 (0.1)	3 (0.4)	0	0	1 (0.1)	3 (0.3)

The table below presents a summary of TEAEs which occurred in >2% of patients in either treatment group in pooled Phase II and III studies.

Table 30: Treatment-Emergent Adverse Events with Incidence of Preferred Term ≥ 2% in Either Treatment Arm of All Skin Studies by System Organ Class and Preferred Term – Phase II and III Safety Analysis Set

System organ class Preferred Term	Pooled Phase III studies		Pooled Phase II studies		Phase II and III Safety Analysis Set	
	Delafloxacin (N = 741) n (%)	Vancomycin (Aztreonam) (N = 751) n (%)	Delafloxacin (N = 127) n (%)	Pooled Comparators (N = 221) n (%)	Delafloxacin (N = 868) n (%)	All Comparators (N = 972) n (%)

System organ class Preferred Term	Pooled Phase III studies		Pooled Phase II studies		Phase II and III Safety Analysis Set	
	Delafloxacin (N = 741) n (%)	Vancomycin (Aztreonam) (N = 751) n (%)	Delafloxacin (N = 127) n (%)	Pooled Comparators (N = 221) n (%)	Delafloxacin (N = 868) n (%)	All Comparators (N = 972) n (%)
Total number of TEAEs with incidence of preferred term ≥ 2%	319	328	71	169	390	497
Patients with at least one TEAE with incidence of preferred term ≥ 2%	195 (26.3)	201 (26.8)	44 (34.6)	94 (42.5)	239 (27.5)	295 (30.3)
Gastrointestinal disorders	107 (14.4)	68 (9.1)	36 (28.3)	62 (28.1)	143 (16.5)	130 (13.4)
Nausea	56 (7.6)	47 (6.3)	23 (18.1)	52 (23.5)	79 (9.1)	99 (10.2)
Diarrhoea	58 (7.8)	24 (3.2)	17 (13.4)	14 (6.3)	75 (8.6)	38 (3.9)
Vomiting	17 (2.3)	18 (2.4)	10 (7.9)	28 (12.7)	27 (3.1)	46 (4.7)
General disorders and administration site conditions	58 (7.8)	66 (8.8)	2 (1.6)	6 (2.7)	60 (6.9)	72 (7.4)
Infusion site extravasation	41 (5.5)	54 (7.2)	0	1 (0.5)	41 (4.7)	55 (5.7)
Pyrexia	17 (2.3)	17 (2.3)	2 (1.6)	5 (2.3)	19 (2.2)	22 (2.3)
Infections and infestations	44 (5.9)	38 (5.1)	1 (0.8)	2 (0.9)	45 (5.2)	40 (4.1)
Infection	44 (5.9)	38 (5.1)	1 (0.8)	2 (0.9)	45 (5.2)	40 (4.1)
Nervous system disorders	24 (3.2)	41 (5.5)	6 (4.7)	16 (7.2)	30 (3.5)	57 (5.9)
Headache	24 (3.2)	41 (5.5)	6 (4.7)	16 (7.2)	30 (3.5)	57 (5.9)
Skin and subcutaneous tissue disorders	11 (1.5)	38 (5.1)	6 (4.7)	31 (14.0)	17 (2.0)	69 (7.1)
Pruritus	7 (0.9)	20 (2.7)	6 (4.7)	28 (12.7)	13 (1.5)	48 (4.9)
Pruritus generalised	4 (0.5)	19 (2.5)	0	3 (1.4)	4 (0.5)	22 (2.3)

Phase I Safety Analysis Set

In the Phase I Safety Analysis Set, a total number of 340 TEAEs were reported for delafloxacin. Out of the 814 subjects included in the 20 studies in the Phase I Safety Analysis Set, no deaths or SAEs were reported. One subject had a severe TEAE (dysphagia) which was assessed as unrelated to the study treatment by the investigator. 42.5% of subjects experienced any TEAE and 30.6% of subjects

experienced a treatment-related TEAE which were all of mild or moderate severity. In 1.5% of cases, TEAEs lead to premature study drug discontinuation and 1.4% of cases were treatment-related.

By SOC, the most commonly reported TEAEs were related to SOC gastrointestinal tract, nervous system disorders and administration site conditions (IV formulation). By preferred term, the most commonly reported TEAEs (i.e., incidence of ≥ 5% in combined doses and regimens) were the following: diarrhoea (13.3%), nausea (10.2%), headache (9.3%), vomiting (4.4%), dizziness (3.9%) and infusion site pain (3.7%; IV formulation). The integrated data suggest a higher frequency of gastrointestinal and infusion-related (with IV dosing) TEAEs at higher doses. During the clinical development program, 10 oral formulations of delafloxacin have been studied, in part to mitigate gastrointestinal events, and 4 IV formulations have been studied. The incidence of diarrhoea (7.6%) and nausea (7.8%) and headache (3.2%) reported in pooled Phase III studies were reduced with the improved formulations.

TEAEs related to study drug

Phase II and III Safety Analysis Set

The table below presents TEAEs considered by the investigator to be related to study drug in pooled phase II and phase III studies and Phase II and III Safety Analysis Set, which occurred in ≥ 2% of patients in either treatment group.

Table 31: Treatment - Related Treatment-Emergent Adverse Events with Incidence of Preferred Term ≥ 2% in Either Treatment Arm of the Pooled Phase III Studies – Phase II and III Safety Analysis Set

System organ class Preferred Term	Pooled Phase 3 studies		Pooled Phase 2 studies		Phase II and III Safety Analysis Set	
	Delafloxacin (N = 741) n (%)	Vancomycin (Aztreonam) (N = 751) n (%)	Delafloxacin (N = 127) n (%)	Pooled Comparators (N = 221) n (%)	Delafloxacin (N = 868) n (%)	All Comparators (N = 972) n (%)
Total number of related TEAEs with incidence of preferred term ≥ 2%	103	85	47	87	150	172
Patients with at least one related TEAE with incidence of preferred term ≥ 2%	88 (11.9)	74 (9.9)	34 (26.8)	64 (29.0)	122 (14.1)	138 (14.2)
Gastrointestinal disorders	81 (10.9)	45 (6.0)	32 (25.2)	46 (20.8)	113 (13.0)	91 (9.4)
Nausea	45 (6.1)	32 (4.3)	23 (18.1)	44 (19.9)	68 (7.8)	76 (7.8)
Diarrhoea	45 (6.1)	15 (2.0)	15 (11.8)	9 (4.1)	60 (6.9)	24 (2.5)

System organ class Preferred Term	Pooled Phase 3 studies		Pooled Phase 2 studies		Phase II and III Safety Analysis Set	
	Delafloxacin (N = 741) n (%)	Vancomycin (Aztreonam) (N = 751) n (%)	Delafloxacin (N = 127) n (%)	Pooled Comparators (N = 221) n (%)	Delafloxacin (N = 868) n (%)	All Comparators (N = 972) n (%)
Skin and subcutaneous tissue disorders	7 (0.9)	35 (4.7)	5 (3.9)	25 (11.3)	12 (1.4)	60 (6.2)
Pruritus	3 (0.4)	17 (2.3)	5 (3.9)	23 (10.4)	8 (0.9)	40 (4.1)
Pruritus generalised	4 (0.5)	19 (2.5)	0	2 (0.9)	4 (0.5)	21 (2.2)

TEAEs by severity

Phase II and III Safety Analysis Set

The overall incidence of moderate TEAEs was 16.5% due to a higher incidence in the phase II studies (26.0%) compared to phase III studies (14.8%). Severe TEAEs were documented in < 4% of patients in either group. Most of severe TEAEs were also categorised as serious adverse events (SAEs). Patients with SAEs are discussed in section 4.4. Mostly, serious TEAEs were not related to delafloxacin treatment. The most common severe TEAEs in the delafloxacin group in Phase II and III Safety Analysis Set were infections and infestations (2.0%).

AEs of special interest (AESIs)

AESIs were selected based on medical issues of interest for the fluoroquinolone class of antibiotics such as follows: *C. difficile* diarrhoea, dysglycaemia, potential hepatic-related events, potential QT prolongation, potential seizures, potential myopathy, potential neuropathy, potential tendon disorder, potential phototoxicity and potential allergic reaction.

RX-3341-302

Table 32: RX-3341-302 - Treatment - Emergent Adverse Events of Special Interest by Special Interest Type and Preferred Term

Special Interest Type Preferred Term	Delafloxacin (N = 324)	Vancomycin + Aztreonam (N = 326)
Number of patients with at least one TEAE of special interest	38 (11.7)	64 (19.6)
Potential allergic reaction	**17 (5.2)**	**45 (13.8)**
Dermatitis	1 (0.3)	0
Dermatitis Allergic	0	2 (0.6)
Dermatitis Atopic	0	1 (0.3)
Dermatitis Contact	0	1 (0.3)
Drug Hypersensitivity	0	1 (0.3)
Eosinophilia	0	1 (0.3)
Eye Pruritus	0	1 (0.3)
Hypersensitivity	1 (0.3)	3 (0.9)
Pruritus	3 (0.9)	11 (3.4)

Pruritus Generalised	3 (0.9)	15 (4.6)
Rash	2 (0.6)	4 (1.2)
Rash Erythematous	0	1 (0.3)
Rash Generalised	0	2 (0.6)
Rash Macular	1 (0.3)	0
Rash Maculo-Papular	2 (0.6)	0
Urticaria	4 (1.2)	4 (1.2)
Potential hepatic-related	**13 (4.0)**	**12 (3.7)**
Acute Hepatitis C	1 (0.3)	0
Alanine Aminotransferase Increased	12 (3.7)	10 (3.1)
Aspartate Aminotransferase Increased	7 (2.2)	8 (2.5)
Hepatic Cirrhosis	0	1 (0.3)
Hepatitis C	1 (0.3)	0
Transaminases Increased	1 (0.3)	1 (0.3)
Potential myopathy	**6 (1.9)**	**7 (2.1)**
Blood Creatine Increased	0	1 (0.3)
Blood Creatine Phosphokinase Increased	5 (1.5)	5 (1.5)
Muscle Spasms	0	1 (0.3)
Myalgia	1 (0.3)	0
Dysglycaemia	**5 (1.5)**	**4 (1.2)**
Hypoglycaemia	2 (0.6)	3 (0.9)
Hypoglycaemia	2 (0.6)	3 (0.9)
Hyperglycaemia	3 (0.9)	1 (0.3)
Hyperglycaemia	2 (0.6)	1 (0.3)
Type 2 Diabetes Mellitus	1 (0.3)	0
Potential neuropathy	**2 (0.6)**	**2 (0.6)**
Cervical Radiculopathy	0	1 (0.3)
Hypoaesthesia	1 (0.3)	0
Neuropathy Peripheral	0	1 (0.3)
Paraesthesia	2 (0.6)	0
Potential seizures	**1 (0.3)**	**0**
Syncope	1 (0.3)	0

RX-3341-303

Table 33: RX-3341-303 - Treatment - Emergent Adverse Events of Special Interest by Special Interest Type and Preferred Term

MedDRA System Organ Class (SOC) and Adverse Event (Preferred Term [PT])	Delafloxacin (N = 417)	Vancomycin + Aztreonam (N = 425)
Total no. of TEAEs of special	50	72
Patients with any TEAE of special	39 (9.4)	58 (13.6)
Potential myopathy	**8 (1.9)**	**21 (4.9)**
Blood creatine phosphokinase	5 (1.2)	10 (2.4)
Renal failure acute	1 (0.2)	3 (0.7)
Musculoskeletal pain	1 (0.2)	2 (0.5)

Renal impairment	1 (0.2)	1 (0.2)
Blood creatinine increased	0	2 (0.5)
Myalgia	0	2 (0.5)
Renal failure	0	2 (0.5)
C. difficile diarrhoea	**1 (0.2)**	**0**
Clostridium difficile infection	1 (0.2)	0
Convulsions	**0**	**1 (0.2)**
Convulsion	0	1 (0.2)
Potential peripheral	**2 (0.5)**	**2 (0.5)**
Paraesthesia	2 (0.5)	1 (0.2)
Hypoaesthesia	0	1 (0.2)
Potential tendon disorder	**3 (0.7)**	**1 (0.2)**
Tendonitis	3 (0.7)	0
Trigger finger	0	1 (0.2)
Potential QT prolongation	**1 (0.2)**	**1 (0.2)**
Syncope	1 (0.2)	0
Loss of consciousness	0	1 (0.2)
Potential allergic reactions	**14 (3.4)**	**20 (4.7)**
Dermatitis contact	4 (1.0)	2 (0.5)
Dermatitis	2 (0.5)	1 (0.2)
Urticaria	2 (0.5)	5 (1.2)
Bronchospasm	1 (0.2)	0
Dermatitis allergic	1 (0.2)	0
Drug eruption	1 (0.2)	0
Hypersensitivity	1 (0.2)	1 (0.2)
Rash	1 (0.2)	7 (1.6)
Rash erythematous	1 (0.2)	0
Rash vesicular	1 (0.2)	0
Swelling face	1 (0.2)	0
Dermatitis atopic	0	1 (0.2)
Rash macular	0	1 (0.2)
Rash maculopapular	0	1 (0.2)
Rash pustular	0	1 (0.2)
Hyperglycaemia	**3 (0.7)**	**3 (0.7)**
Diabetes mellitus	3 (0.7)	1 (0.2)

Hyperglycaemia	0	1 (0.2)
Type 2 diabetes mellitus	0	1 (0.2)
Hepatic related events	**11 (2.6)**	**18 (4.2)**
AST increased	4 (1.0)	6 (1.4)
ALT increased	2 (0.5)	4 (0.9)
Hepatic enzyme increased	2 (0.5)	2 (0.5)
Hypertransaminasaemia	2 (0.5)	1 (0.2)
Transaminase increased	2 (0.5)	4 (0.9)
GGT increased	1 (0.2)	1 (0.2)
Liver function test abnormal	0	2 (0.5)

Phase I Safety Analysis Set

Generally, the incidence of AESIs regardless of causality in the Phase I studies was 7.4%. Potential allergic reactions occurred in 3.4% of subjects, potential myopathy in 2.0%, hepatic related events in 0.9%, potential peripheral neuropathy in 0.9%, potential QT prolongation in 0.4%, and *C. difficile* diarrhoea in 0.1%. Few subjects (2.7%) had AESI that were considered to be treatment-related by the investigator, i.e. potential allergic reactions (1.6%), hepatic related events (0.7%), *C. difficile* diarrhoea (0.1%), potential myopathy (0.1%) and potential QT prolongation (0.1%).

AESIs lasting longer than 30 days

In the Phase II and III Safety Analysis Set AESIs with longer than 30 days duration occurred in the categories hepatic events, dysglycaemia, potential peripheral neuropathy, potential myopathy, potential tendon disorder, potential allergic reactions and potential phototoxicity.

In the Phase I Safety Analysis Set, four subjects had an AESI lasting longer than 30 days: 2 with rash (potential allergic reaction), 1 with *C. difficile* colitis, and 1 with blood creatinine increased (potential myopathy).

Potential hepatic-related events

Phase II and III Safety Analysis Set

Table 34: Treatment-Emergent Hepatic Adverse Events – Phase II and III Safety Analysis Set

Special Interest Preferred Term	Pooled Phase III Skin		Pooled Phase II Skin		Phase II and III Safety Analysis Set	
	Delafloxacin (N = 741) n (%)	Vancomycin (Aztreonam) (N = 751) n (%)	Delafloxacin (N = 127) n (%)	Pooled Comparators (N = 221) n (%)	Delafloxacin (N = 868) n (%)	All Comparators (N = 972) n (%)

Hepatic events	23 (3.1)	30 (4.0)	5 (3.9)	3 (1.4)	28 (3.2)	33 (3.4)
Alanine aminotransferase increased	14 (1.9)	14 (1.9)	3 (2.4)	1 (0.5)	17 (2.0)	15 (1.5)
Aspartate aminotransferase increased	10 (1.3)	14 (1.9)	0	1 (0.5)	10 (1.2)	15 (1.5)
Transaminases increased	3 (0.4)	5 (0.7)	0	0	3 (0.3)	5 (0.5)
Hepatic enzyme increased	2 (0.3)	2 (0.3)	0	1 (0.5)	2 (0.2)	3 (0.3)
Liver function test abnormal	0	2 (0.3)	2 (1.6)	1 (0.5)	2 (0.2)	3 (0.3)
Hypertransaminasae mia	2 (0.3)	1 (0.1)	0	0	2 (0.2)	1 (0.1)
Gamma-glutamyltransferase increased	1 (0.1)	1 (0.1)	0	0	1 (0.1)	1 (0.1)
Hepatic cirrhosis	0	1 (0.1)	0	0	0	1 (0.1)

AESIs related to study drug

Table 35: Related Treatment-Emergent Hepatic Adverse Events – Phase II and III Safety Analysis Set

Special Interest Preferred Term	Pooled Phase III Skin		Pooled Phase II Skin		Phase II and III Safety Analysis Set	
	Delafloxacin (N = 741) n (%)	Vancomycin (Aztreonam) (N = 751) n (%)	Delafloxacin (N = 127) n (%)	Pooled Comparators (N = 221) n (%)	Delafloxacin (N = 868) n (%)	All Comparators (N = 972) n (%)
Hepatic related events	16 (2.2)	20 (2.7)	4 (3.1)	3 (1.4)	20 (2.3)	23 (2.4)
Alanine aminotransferase increased	10 (1.3)	10 (1.3)	2 (1.6)	1 (0.5)	12 (1.4)	11 (1.1)
Aspartate aminotransferase increased	6 (0.8)	10 (1.3)	0)	1 (0.5)	6 (0.7)	11 (1.1)
Transaminases increased	3 (0.4)	2 (0.3)	0	0	3 (0.3)	2 (0.2)
Hepatic enzyme increased	1 (0.1)	2 (0.3)	0	1 (0.5)	1 (0.1)	3 (0.3)
Liver function test abnormal	0	2 (0.3)	2 (1.6)	1 (0.5)	2 (0.2)	3 (0.3)
Hypertransaminasaemia	1 (0.1)	1 (0.1)	0	0	1 (0.1)	1 (0.1)

Dysglycaemia

Phase II and III Safety Analysis Set

Table 36: Treatment-Emergent Adverse Events of Dysglycaemia – Phase II and III Safety Analysis Set

Special Interest Preferred Term	Pooled Phase III Skin		Pooled Phase II Skin		Phase II and III Safety Analysis Set	
	Delafloxacin (N = 741) n (%)	Vancomycin (Aztreonam) (N = 751) n (%)	Delafloxacin (N = 127) n (%)	Pooled Comparators (N = 221) n (%)	Delafloxacin (N = 868) n (%)	All Comparators (N = 972) n (%)
Glucose related events						
Hyperglycaemia	6 (0.8)	4 (0.5)	3 (2.4)	6 (2.7)	9 (1.0)	10 (1.0)
Hyperglycaemia	2 (0.3)	2 (0.3)	2 (1.6)	3 (1.4)	4 (0.5)	5 (0.5)
Diabetes mellitus	3 (0.4)	1 (0.1)	0	0	3 (0.3)	1 (0.1)
Blood glucose increased	0	0	1 (0.8)	3 (1.4)	1 (0.1)	3 (0.3)
Type 2 diabetes mellitus	1 (0.1)	1 (0.1)	0	1 (0.5)	1 (0.1)	2 (0.2)
Hypoglycaemia	2 (0.3)	3 (0.4)	0	0	2 (0.2)	3 (0.3)
Hypoglycaemia	2 (0.3)	3 (0.4)	0	0	2 (0.2)	3 (0.3)

Phase II data

Study report of RX-3341-201 states that low serum glucose values were observed in 1 tigecycline treated patient and 11 delafloxacin-treated patients (9 patients in the 450 mg delafloxacin group and 3 patients in the 300 mg delafloxacin group). Only 1 patient in the 450 mg group reported an AE of true hypoglycaemia. Since the 450mg IV delafloxacin treatment arm was excluded from phase II and II integrated data set, this event is not listed in the phase II data pool table.

AESIs related to study drug

Rates of treatment-related hyperglycaemia (0.3% and 0.4%) and hypoglycaemia (0.1% and 0.2%) were similar between patients in the delafloxacin and comparator groups, respectively. No major differences in the incidence of dysglycaemia-related preferred terms were detected.

Potential neuromuscular and convulsion events

Potential myopathy

Rates of events for potential myopathy were lower in patients in the delafloxacin group versus comparator group (2.1% and 3.9%, respectively). The term potential myopathy included renal failure, which contributed to the higher rate in the comparator group due to vancomycin nephrotoxicity. Rates of potential myopathy lasting longer than 30 days were lower in patients in the delafloxacin group versus comparator group (0.6% and 1.2%, respectively [data not shown]). These events were mild or moderate in severity and non-serious. No treatment discontinuations or SAEs were attributed to myopathy in patients treated with delafloxacin

Potential neuropathy

Rates of events for potential peripheral neuropathy were similar between patients in the delafloxacin and comparator groups (0.6% and 0.7%, respectively). Rates of potential peripheral neuropathy lasting longer than 30 days were similar between patients in the delafloxacin and comparator groups (0.1% and

0.3%, respectively [data not shown]). These events were mild or moderate in severity and non-serious. No treatment discontinuations or SAEs were attributed to peripheral neuropathy in patients treated with delafloxacin.

Potential tendon disorder

Rates of potential tendon disorder were similar between the delafloxacin and comparator groups (0.3% and 0.1%, respectively). No cases of tendon rupture were reported. Rates of potential tendon disorder lasting longer than 30 days were similar between the delafloxacin and comparator groups (0.2% and 0.1%, respectively). These events were mild or moderate in severity and non-serious. No treatment discontinuations or SAEs were attributed to tendon disorders in patients treated with delafloxacin.

Potential seizures

Rates of convulsions were the same between patients in the delafloxacin and comparator groups (0.1% in both treatment groups). No patients in either treatment group had convulsions lasting longer than 30 days (data not shown). There were no premature discontinuations from delafloxacin due to an event of convulsions. Case narratives with comprehensive causality assessment of patients experiencing convulsions and potential seizure events including syncope were provided for the three patients included in Phase II studies who experienced events of convulsion/potential seizure or syncope, two of them possibly related to delafloxacin use.

AESIs related to study drug

Rates of treatment-related potential myopathy were lower in patients in the delafloxacin group versus comparator group (1.0% and 2.4%, respectively). Rates of treatment-related potential peripheral neuropathy were similar between patients in the delafloxacin and comparator groups (0.2% and 0.3%, respectively). No patients in either treatment group had treatment-related potential tendon disorder. One patient in the comparator group had treatment-related convulsions compared with no patients in the delafloxacin group.

Potential allergic reaction

Phase II and III Safety Analysis Set

Table 37: Treatment-Emergent Adverse Events of Potential Allergic Reactions– Phase II and III Safety Analysis Set

Special Interest Preferred Term	Pooled Phase III Skin		Pooled Phase II Skin		Phase II and III Safety Analysis Set	
	Delafloxacin (N = 741) n (%)	Vancomycin (Aztreonam) (N = 751) n (%)	Delafloxacin (N = 127) n (%)	Pooled Comparators (N = 221) n (%)	Delafloxacin (N = 868) n (%)	All Comparators (N = 972) n (%)
Potential allergic reactions	27 (3.6)	39 (5.2)	8 (6.3)	25 (11.3)	35 (4.0)	64 (6.6)
Dermatitis contact	4 (0.5)	3 (0.4)	3 (2.4)	3 (1.4)	7 (0.8)	6 (0.6)
Urticaria	6 (0.8)	9 (1.2)	0	2 (0.9)	6 (0.7)	11 (1.1)
Rash	3 (0.4)	11 (1.5)	2 (1.6)	10 (4.5)	5 (0.6)	21 (2.2)
Rash pustular	2 (0.3)	1 (0.1)	2 (1.6)	2 (0.9)	4 (0.5)	3 (0.3)
Dermatitis	3 (0.4)	1 (0.1)	0	0	3 (0.3)	1 (0.1)
Hypersensitivity	2 (0.3)	4 (0.5)	0	2 (0.9)	2 (0.2)	6 (0.6)

Dermatitis allergic	1 (0.1)	2 (0.3)	1 (0.8)	2 (0.9)	2 (0.2)	4 (0.4)
Rash maculopapular	2 (0.3)	1 (0.1)	0	1 (0.5)	2 (0.2)	2 (0.2)
Bronchospasm	1 (0.1)	0	0	1 (0.5)	1 (0.1)	1 (0.1)
Rash erythematous	1 (0.1)	1 (0.1)	0	0	1 (0.1)	1 (0.1)
Rash macular	1 (0.1)	1 (0.1)	0	0	1 (0.1)	1 (0.1)
Drug eruption	1 (0.1)	0	0	0	1 (0.1)	0
Rash vesicular	1 (0.1)	0	0	0	1 (0.1)	0
Swelling face	1 (0.1)	0	0	0	1 (0.1)	0
Rash generalised	0	2 (0.3)	0	2 (0.9)	0	4 (0.4)
Dermatitis atopic	0	2 (0.3)	0	0	0	2 (0.2)
Drug hypersensitivity	0	1 (0.1)	0	0	0	1 (0.1)
Lip swelling	0	0	0	1 (0.5)	0	1 (0.1)
Rhinitis allergic	0	0	0	1 (0.5)	0	1 (0.1)

AESIs related to study drug

Rates of treatment-related potential allergic reactions were lower in patients in the delafloxacin group versus comparator group (1.3% and 3.5%, respectively). The incidence of urticaria, dermatitis, and hypersensitivity was higher in pooled phase III compared to pooled phase II. In contrast, in pooled phase II the incidences of pustular rash and rash were higher than in pooled phase III.

Potential QT prolongation

Phase II and III Safety Analysis Set

Three patients (0.3%) in the delafloxacin group had events for potential QT prolongation (preferred term: syncope) compared with 1 patient (0.1%) in the comparator group (preferred term: loss of consciousness). No patients in either treatment group had an event lasting longer than 30 days. No treatment discontinuations or SAEs were attributed to potential QT prolongation in patients treated with delafloxacin. Baseline electrocardiograms (ECGs) were collected and only repeated as clinically necessary. No follow-up ECGs were performed for cause.

AESIs related to study drug

The events in the delafloxacin group were considered unrelated to treatment, while the event in the comparator group was considered related to treatment. The individual case reports for all events of potential QT prolongation in the delafloxacin group were provided and critically discussed in terms of underlying concomitant disease, concomitant drug medications and potential relation to delafloxacin treatment. Three cases of syncope were classified as 'potential QT prolongation based on the Standardised MedDRA Queries (SMQs). The investigator did not consider them as due to QT prolongation and as such did not consider ECGs necessary. Patient narratives were provided with plausible causality assessment and the events of syncope were considered unrelated to delafloxacin.

Phase I Cardiac Safety Studies M01-365 and RX-3341-111

As part of the ongoing cardiovascular assessment, 2 detailed evaluations of the effect of delafloxacin on the QT interval have been conducted: M01-365 and RX-3341-111. Delafloxacin did not have an effect on

the QTcF interval, nor was there any evidence of a significant effect on atrioventricular conduction or cardiac depolarisation as measured by the PR and QRS interval durations.

C. difficile diarrhoea

Phase II and III Safety Analysis Set

Two patients (0.2%) in the delafloxacin group had *C. difficile* diarrhoea compared with none in the comparator group, i.e. patient 840 363 3931 and patient 203 0030 from RX 3341-303 and RX-3341-201, respectively). Patient 840-363-3931 entered the study as a prior treatment failure with previous treatment with Bactrim (sulfamethoxazole / trimethoprim) and clindamycin. Neither patient had *C. difficile* diarrhoea lasting longer than 30 days (data not shown). In both patients, the events of diarrhoea were considered related to treatment and of mild severity. No treatment discontinuations or SAEs were attributed to *C. difficile* diarrhoea in patients treated with delafloxacin.

AESIs related to study drug

Both events of *C. difficile* diarrhoea in RX-3341-303 and RX-3341-201 were considered at least possibly related to delafloxacin treatment. Case narratives were provided for both patients.

Potential phototoxicity

Phase II and III Safety Analysis Set

One patient (0.1%) in the 300 mg delafloxacin group experienced an event of potential phototoxicity (RX-3341-201, Patient 201-215-0005) compared with none in the comparator group. The event lasted longer than 30 days (data not shown). Because this event onset was 11 days after the end of treatment in a patient who worked outdoors in construction, the investigator considered it unrelated to treatment. No treatment discontinuations or SAEs were attributed to phototoxicity events in patients treated with delafloxacin.

Phase I Phototoxicity Study M01-284

Delafloxacin's potential for photosensitivity was evaluated in **M01-284**. Delafloxacin failed to demonstrate a significant phototoxic effect at clinically relevant plasma concentrations. In particular, the classical pattern of fluoroquinolone phototoxicity as detected in previous phototoxicity studies (i.e., an ultraviolet A (UVA) phenomenon maximal at 24 h) was not seen.

AESIs related to study drug

In RX-3341-201, the one case report of potential phototoxicity in patient 201-215-0005 was considered unrelated to delafloxacin-treatment.

Serious adverse event and deaths

Deaths

Phase II and III Safety Analysis Set

There were a total of 4 TEAEs leading to death, 1 in the delafloxacin group (septic shock [RX-3341-302]) and 3 in the comparator group (myocardial infarction [RX-3341-303]; intestinal ischemia [RX-3341-303]; and pulmonary embolism [RX-3341-302], all of which were unrelated to treatment.

In RX-3341-302, Patient #376 081 0724, an 89-year old male was treated with delafloxacin for 14 days for cellulitis of the left leg; a causative pathogen was not identified. The patient had a complicated medical history including diabetes mellitus, atrial fibrillation, placement of a cardiac assist device, cerebrovascular accident, chronic obstructive pulmonary disease, chronic renal failure, congestive heart failure, and

myocardial ischemia. He had signs of systemic infection at baseline. The patient was discharged to a rehabilitation institute after 14 days of treatment with delafloxacin and assessed as failure. There is no record of any discharge antibiotics given after end of study treatment. The patient returned to the hospital 5 days after the last dose of delafloxacin. The patient died on the same day following cellulitis and sepsis leading to septic shock and cardiopulmonary arrest in the setting of ischemic heart disease and atrial fibrillation assessed as unrelated to study treatment by the investigator.

Pooled Phase 1 studies and non-integrated studies

No deaths were reported in the pooled Phase 1 studies or in the non-integrated studies.

Serious adverse events

Phase II and III Safety Analysis Set

The incidence of SAEs was similar between treatment groups (3.7% with delafloxacin and 3.8% with comparators). The most common system organ class of events was infections / infestations (2.2%) followed by respiratory, thoracic and mediastinal disorders (0.5%), injury poisoning and procedural complications (0.3%), psychiatric disorders (0.2%) and skin and subcutaneous tissue disorders (0.2%). Events of more than 1 report in the delafloxacin group include cellulitis (4 patients), skin infection (4 patients), infection (2 patients), and pulmonary embolism (2 events). The majority of events were considered unrelated to treatment. Six patients were assessed as having SAEs related to treatment, 2 delafloxacin patients (1 patient with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased and 1 patient with urticaria), and 4 comparator treated patients (2 patients with renal failure, 1 patient with acute renal failure, and 1 patient with rash).

Phase I Safety Analysis Set

No serious treatment - emergent adverse events were reported in the pooled Phase 1 studies.

Laboratory findings

Phase II and III Safety Analysis Set

Table 38: Clinically Notable Abnormal Laboratory Results at End of Treatment - Phase II and III Safety Analysis Set

Parameter Criterion	n / N (%) of Subjects	
	Delafloxacin (N = 868)	All Comparators (N = 972)
ALT (U/L)		
> 2 x ULN	31 / 832 (3.7)	39 / 927 (4.2)
> 3 x ULN	10 / 832 (1.2)	12 / 927 (1.3)
> 5 x ULN	2 / 832 (0.2)	5 / 927 (0.5)
AST (U/L)		
> 2 x ULN	26 / 834 (3.1)	26 / 942 (2.8)
> 3 x ULN	8 / 834 (1.0)	8 / 942 (0.8)
> 5 x ULN	2 / 834 (0.2)	1 / 942 (0.1)
Total Bilirubin (µmol/L)		
> 2 x ULN	0 / 858	0 / 963
Serum Creatinine (µmol/L)		
> 2 x ULN	0 / 862	4 / 969 (0.4)
> 3 x ULN	0 / 862	2 / 969 (0.2)
Glucose (mmol/L)		
< 22.2	2 / 542 (0.4)	2 / 641 (0.3)

TEAE tables by System Organ Class and Preferred Term for Pool Phase II Pool, Pool Phase III and Pool Phase II and III Pool were provided for each intrinsic factor (age, gender, race, ethnicity, BMI (< 30 kg/m2 or ≥ 30 kg/m2), diabetic/not diabetic, renal function, history of hepatitis). Regarding intrinsic factors, no major safety signals were obvious regarding age, gender, race, ethnicity, BMI, having diabetes, or a history of hepatitis (as assessed by the SOC and preferred terms of TEAE regardless of the treatment causality).

Age

The majority of patients in the analysis set were ≤ 65 years (N=759 in the delafloxacin group). In the pooled Phase II and Phase III studies, 26.7% (203 / 759) of patients ≤ 65 years of age experienced TEAEs that were considered to be delafloxacin-related compared to 17.4% (19 / 109) of patients treated with delafloxacin who were > 65 years of age. The majority of TEAEs recorded were mild in intensity. The incidence of moderate and severe TEAEs was rather comparable between patients ≤ and > 65 years of age. In the group of subjects ≤ 65 years, 28 patients (3.7%) experienced a serious TEAEs out of which 1 was considered related to delafloxacin treatment. Similarly, 4 patients (3.7%) and 1 treatment-related case were reported in subjects > 65 years. The incidence of TEAEs leading to study drug discontinuation was similar in both age groups (1.6% versus 1.8%) whereas the incidence of related TEAEs was slightly lower in subjects ≤ 65 years (N= 4; 0.5%) compared to subjects >65 years (N=2; 1.8%). AESIs were equally reported in both age groups (11.1% versus 11.0%, respectively).

Gender

In the pooled Phase II and Phase III studies, 23.5% (126 / 536) of male patients and 28.9% (96 / 332) of female patients treated with delafloxacin reported TEAEs that were considered to be drug related. TEAEs presented by maximum intensity were mostly mild and equally distributed between both genders. Similarly, for both genders 1 case of serious TEAE was reported. The incidences of TEAEs leading to study drug discontinuation, related TEAE leading to premature study drug discontinuation and AESIs were low and comparable between both genders.

Race

The majority of patients in the analysis set were White (N = 736 patients in the delafloxacin group) followed by Black or African American, (N = 54 patients). Of these White patients, 26.2% (193 patients) reported treatment-related AEs. Black or African American patients treated with vancomycin experienced treatment-related TEAEs at a higher rate (41.9% (31 / 74 patients)) compared to those in the same subgroup treated with delafloxacin (24.1% (13 / 54 patients)). The incidences of related serious TEAEs, TEAEs leading to study drug discontinuation, related TEAE leading to premature study drug discontinuation and AESIs were low and comparable between races. The numbers of patients in the other race subgroups (American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islander, or "Other") were insufficient to provide meaningful comparisons between the delafloxacin and comparator arms.

Body mass index category

Phase II and III Safety Analysis Set

In the pooled Phase II and Phase III studies, 125 / 497 (25.2%) of patients with BMI < 30 kg/m^2 reported treatment - related TEAEs compared to 97 / 371 (26.1%) of patients with BMI ≥ 30 kg/m^2 treated with delafloxacin. About 40% of patients in the treated population in the Phase III ABSSSI studies were obese (BMI ≥ 30 kg/m^2). Two subjects (0.5%) with BMI ≥ 30 kg/m^2 experienced a delafloxacin-related serious TEAE whereas no patients with BMI < 30 kg/m^2. The TEAEs leading to study drug discontinuation, related TEAE leading to premature study drug discontinuation and AESIs were low and comparable between both groups. One patient with BMI < 30 kg/m^2 died in the delafloxacin group. Assessment of this single case is provided in section 4.4.1.

RX-3341-302

For patients with BMI <30 kg/m^2 and BMI ≥30 kg/m^2, lower percentages of patients experienced TEAEs in the delafloxacin treatment group than in the vancomycin + aztreonam treatment group. For the delafloxacin treatment group, the incidences of TEAEs were similar between patients with BMI <30 kg/m^2 (45.6% [94 of 206]) and patients with BMI ≥30 kg/m^2 (50.8% [60 of 118]). For the vancomycin + aztreonam treatment group, the incidences of TEAEs were similar between patients with BMI <30 kg/m^2 (58.8% [137 of 233]) and patients with BMI ≥30 kg/m^2 (60.2% [56 of 93]).

Additionally, in obese subjects, a lower percentage of subjects in the delafloxacin group compared with the vancomycin + aztreonam group experienced TEAEs related to study drug (27.1% vs 32.3%), TEAEs of special interest (11.0% vs 21.5%), TEAEs leading to premature study drug discontinuation (0 vs 3.2%), and TEAEs related to study drug and leading to premature study drug discontinuation (0 vs 2.2%). A slightly higher percentage of subjects in the delafloxacin group than in the vancomycin + aztreonam group experienced TEAEs assessed as moderate or severe in intensity (21.2% vs 19.4%). In obese subjects, 1 subject (in the vancomycin + aztreonam group) had an SAE leading to death.

There were no clear differences in haematology or chemistry outcomes between delafloxacin and vancomycin and no evidence of major dysglycaemias with either drug.

RX-3341-303

No comprehensive safety evaluation for delafloxacin in patients with BMI <30 kg/m^2 and BMI ≥30 kg/m^2 was provided.

Diabetes

In the pooled Phase II and Phase III studies, 15 / 93 (16.1%) patients with diabetes reported treatment - related TEAEs compared to 207/775 (26.7%) of non - diabetic patients treated with delafloxacin. For the subgroup of patients with diabetes, treatment - related TEAEs were more common in the comparator

group versus the delafloxacin group. Two (0.3%) non-diabetic patients experienced a delafloxacin-related serious TEAE whereas no patients in the diabetic group. Similarly, no diabetic patient experienced TEAEs leading to study drug discontinuation and related TEAE leading to premature study drug discontinuation compared to 14 (1.8%) and 6 (0.8%) respectively of non-diabetic patients.

Renal impairment

Phase II and III Safety Analysis Set

Patients with mild to moderate renal impairment were eligible for inclusion in RX-3341-201, RX-3341-202 and RX-3341-302, and patients with mild, moderate or severe renal impairment were eligible for inclusion in RX-3341-303.

A total of 139 (16%) patients treated with delafloxacin had creatinine clearance < 90 mL/min at baseline. In the pooled Phase II and Phase III studies, 32 (23.0%) patients with creatinine clearance < 90 mL/min treated with delafloxacin reported treatment - related TEAEs. No serious treatment-related TEAEs were reported for renal impaired patients. The incidences of TEAEs leading to study drug discontinuation and related TEAE leading to premature study drug discontinuation were low (3 [2.2%] and 1 [0.7%] respectively.

Phase I Study RX-3341-110: Effect of Renal Impairment on the Safety of Oral and IV Delafloxacin, IV Captisol, and IV Placebo

RX-3341-110 was an open-label, placebo-controlled single daily oral and IV dose study designed to assess the pharmacokinetics of delafloxacin in normal healthy subjects and in subjects with mild, moderate, and severe renal disease. In a crossover study design, subjects received single oral doses of 400 mg, single 300 mg IV infusions formulated in Captisol, as well as a single 1 h IV infusion of Captisol placebo. An additional treatment group included subjects with end-stage renal disease (ESRD) who received a 300 mg delafloxacin IV infusion approximately 1 h prior to initiation of dialysis and, on a subsequent haemodialysis session, a 300 mg delafloxacin infusion approximately 1 h after the completion of dialysis.

A total of 44 subjects were assessed for safety. Overall, 28 of 44 (63.6%) reported 1 or more TEAEs. The most common TEAEs reported included diarrhoea, nausea, vomiting, fatigue, headache, dizziness, hypoglycaemia, and pruritus. Treatment-emergent AEs were reported by 2 of 9 subjects (22.2%) in the healthy group, 5 of 8 subjects (62.5%) in the mild renal impairment group, 3 of 8 subjects (37.5%) in the moderate renal impairment group, and 5 of 9 subjects (55.6%) in the severe renal impairment group after the 300-mg delafloxacin/Captisol IV infusion. For the ESRD group, TEAEs were reported by 8 of 10 subjects (80.0%) when the 300-mg delafloxacin/Captisol IV infusion was administered 1 hour before haemodialysis and by 7 of 10 subjects (70.0%) when administered 1 hour after haemodialysis. In subjects who reported treatment-related TEAEs, the majority had TEAEs that were considered possibly (22.7%) or probably (15.9%) related to study drug. With the exception of 31 moderate TEAEs and 1 severe TEAE, all TEAEs were of mild severity. Two subjects (4.5%) were discontinued due to TEAEs. Subject 0001102 (healthy group) was discontinued due to a severe, unrelated TEAE of *Clostridium difficile* colitis and Subject 0001406 (severe renal impairment group) was discontinued due to a moderate, unrelated TEAE of musculoskeletal pain in the left shoulder. There were no deaths, SAEs, or other AEs leading to study discontinuation. Overall, there were no apparent treatment-related trends observed in the clinical laboratory assessments, vital sign measurements, ECG results, or physical examination findings.

Hepatic impairment

Phase II and III Safety Analysis Set

A total of 233 (27%) patients treated with delafloxacin had a history of infectious hepatitis. In the pooled Phase II and Phase III studies, 68 (29.2%) patients with hepatitis B or C in the delafloxacin group reported treatment - related TEAEs. Three subjects (1.3%) experienced TEAEs leading to study drug discontinuation. No cases of related serious TEAEs, related TEAE leading to premature study drug discontinuation and death were reported for patients with history of infectious hepatitis.

Phase I Study ML-3341-112: Effect of Hepatic Impairment on the Safety of IV Delafloxacin

ML-3341-112 was a Phase I, multi-centre, open-label, single-dose, pharmacokinetic study. A total of 40 subjects were stratified into groups based on hepatic function as defined by the Child Pugh classification system. All subjects received a single 1 h IV infusion of 300 mg delafloxacin.

A total of 39 subjects were assessed for safety. Overall, 11 TEAEs were reported and 10 of 39 subjects (25.6%) reported at least 1 TEAE. Treatment-emergent AEs were reported by 1 of 7 subjects (14.3%) in the mild hepatic impairment group, no subjects in the moderate hepatic impairment group, 2 of 6 subjects (33.3%) in the severe hepatic impairment group, and 7 of 20 subjects (35.0%) overall in the healthy subjects group (3 of 7 subjects [42.9%] in the mild hepatic impairment match group, 3 of 7 subjects [42.9%] in the moderate hepatic impairment match group, and 1 of 6 subjects [16.7%] in the severe hepatic impairment match group). In subjects who reported treatment-related TEAEs, the majority reported TEAEs that were considered probably (7.7%) to study drug or possibly (5.1%) related to study drug. With the exception of 2 moderate TEAEs, all TEAEs were of mild severity. Moderate TEAEs reported included headache and drug hypersensitivity. Three subjects (7.7%) were discontinued due to TEAEs. Subject 1101 (mild hepatic impairment group) was discontinued due to a mild, probably related TEAE of drug hypersensitivity, Subject 1113 (healthy subject, mild hepatic impairment match group) was discontinued due to a mild, possibly related TEAE of presyncope, and Subject 2211 (healthy subject, moderate hepatic impairment match group) was discontinued due to a moderate, probably related TEAE of drug hypersensitivity. All TEAEs resolved by the end of the study.

No deaths or SAEs were reported in this study. There were no apparent treatment-related trends or clinically significant findings observed in the clinical laboratory assessments, vital sign measurements, ECG results, or physical examination findings.

Immunological events

Potential allergic reaction was considered an adverse event of special interest and 3 premature discontinuations from delafloxacin were reported (2 patients with urticaria, 1 patient with allergic dermatitis). One patient in the delafloxacin group experienced a treatment-related SAE of urticaria.

Safety related to drug-drug interactions and other interactions

Phase I Study ML-3341-118: Effect of Repeated Oral Doses of Delafloxacin Co-administered with a Single Oral Dose of Midazolam on Safety in Healthy Subjects

ML-3341-118 was a Phase I, non-randomized, open-label study designed to evaluate the effect of repeated oral doses of delafloxacin on the PK profile of a single oral dose of midazolam in healthy subjects. Twenty-two male and female subjects received a single 5 mg oral dose of midazolam on Day 1, oral delafloxacin (450 mg) twice-daily (Q12h) doses on Days 3 to 8, and co administered a single 5 mg oral dose of midazolam in the morning on Day 8.

A total of 22 subjects were assessed for safety. A total of 5 subjects (22.7%) reported at least 1 TEAE; 1 subject (4.5%) after receiving midazolam alone, 4 subjects (18.2%) after receiving delafloxacin alone, and no subjects after receiving midazolam co administered with delafloxacin. In subjects who reported

TEAEs, the majority had TEAEs that were considered probably related to study drug (3 subjects, 13.6%), which were reported after administration of delafloxacin alone. All TEAEs were mild in severity. The most frequently reported TEAE overall was diarrhoea (3 subjects, 13.6%). All events of diarrhoea were reported after administration of delafloxacin alone, were mild, and did not lead to treatment discontinuation. The single TEAE reported after administration of midazolam alone was headache, which was considered not related to study drug by the investigator. There were no deaths, serious AEs, or TEAEs leading to study discontinuation. All TEAEs resolved by the end of the study. With the exception of increased blood creatinine in 1 subject, there were no clinically significant findings noted or TEAEs reported resulting from clinical laboratory assessments, vital sign measurements, physical examination findings, or ECG results.

Discontinuation due to adverse events

Phase II and III Safety Analysis Set

Fewer patients had TEAEs leading to premature study drug discontinuation in the delafloxacin group versus the comparator group (1.6% and 3.8%, respectively). Most of study drug discontinuations were reported in phase III studies (13 [1.8%]) compared to phase II studies (1 [0.8%]). Events of more than 1 report in the delafloxacin group include urticaria (2 patients) and hypersensitivity (2 patients). Fewer patients had treatment - related TEAEs leading to premature study drug discontinuation in the delafloxacin group versus the comparator group (6 (0.7%) and 23 (2.4%) patients, respectively). In the delafloxacin group treatment-related TEAEs leading to premature study drug discontinuation were urticaria (2 [0.2%]), hypersensitivity (2 [0.2%]), dermatitis allergic (1 [0.1%]) and vomiting (1 [0.1%]). In the phase II studies only one case of bacteraemia and one of pyrexia occurred whereas all other treatment discontinuations were counted in phase III studies.

2.6.1. Discussion on clinical safety

Safety Database

Delafloxacin has been evaluated in 30 completed Phase I to Phase III clinical studies comprising a total of 2658 delafloxacin-treated subjects. The Phase I Safety analysis set included 814 subjects who received at least 1 dose of IV or oral delafloxacin in 20 completed Phase I single or multiple dose regimen studies with different formulations. The Phase II and III Safety Analysis set included 1840 subjects with ABSSSI who received delafloxacin or comparator, 868 of whom received multiple doses of delafloxacin in the 300 mg IV / 450 mg oral delafloxacin Q12h treatment arms in 4 controlled Phase II and III studies (RX-3341-201, RX-3341-202, RX-3341-302 and RX-3341-303). Moreover, additional safety data was provided from Non-integrated studies (3 Phase I, 2 Phase II and 1 Phase III) and six phase I studies performed in special populations. The mean duration of exposure in the integrated studies as well as in the single pivotal studies ranged from 4.6 days to 7.3 days. Overall, the size of safety database can be regarded as sufficient to evaluate the safety of delafloxacin in patients with ABSSSI.

Adverse events

The CHMP noted that for other fluoroquinolones, the indication cSSTI/ABSSSI is restricted to second/last line indication based on evaluated risks. In order to evaluate the first line indication initially claimed by the applicant, the CHMP reviewed the safety profile of delafloxacin based on the data submitted by the applicant, literature data and the product information of other fluoroquinolones, in the absence of direct in vivo comparisons between delafloxacin and other fluoroquinolones.

Common adverse events

In the Phase II and III Safety Analysis Set a total number of 868 subjects were treated with delafloxacin and experienced an absolute number of 1008 TEAEs. The most common TEAEs in the delafloxacin group were nausea (9.1%), diarrhoea (8.6%), infection (5.2%), infusion site extravasation (4.7%), and headache (3.5%). Notably, the incidence of diarrhoea was higher in the delafloxacin group (8.6%) compared to the comparator (3.9%) whereas the other SOCs were rather comparable between both groups. Overall, the incidence of gastrointestinal disorders for delafloxacin was higher in the Phase II and III Safety Analysis Set (16.5%) compared to the pooled phase III study data (14.4%) due to higher rates in Phase II studies. A higher frequency of GI disorders appears to occur at higher doses of delafloxacin. Use of a suboptimal formulation and higher than the selected ready-to-market dose of delafloxacin in Phase II studies was the likely cause for the higher frequency of gastrointestinal disorders observed in Phase II studies. The incidences of gastrointestinal disorders were comparable between the two pivotal studies. Additional data were provided for TEAEs and ADRs with incidence ≤ 2% or 5% in phase II and III Safety Analysis Set and both pivotal studies and showed no major discrepancies.

Relationship, Severity and Time to Onset of TEAEs

The TEAEs considered by the investigator to be related to study drug in the Phase II and III Safety Analysis Set were largely in concordance with the overall reported TEAEs. As expected, gastrointestinal TEAEs dominated. The most common severe TEAEs in the delafloxacin group in Phase II and III Safety Analysis Set were infections and infestations (2.0%). Additional data were provided for treatment-related TEAEs with incidence ≤ 2% or 5% in phase II and III Safety Analysis Set and both pivotal studies. Onset of nausea, vomiting, and diarrhoea within the first 5 days was similar for delafloxacin and comparators in the pooled analysis. Individual data for the onset of these gastrointestinal events in study RX-3341-303 with respect to switch from intravenous to oral therapy as well as time to onset data for both Phase III studies were provided. The increase in the incidence in overall GI events was mostly due to an increase in the incidence in diarrhoea which might be caused by switching from IV formulation to oral but also by the cumulative dose administered.

Adverse events of special interest

In general, some rare or very rare adverse events know to be associated with the class of fluoroquinolones such as psychiatric disorders. All TEAEs and ADRs that were reported for delafloxacin and comparator arms were provided for the individual Phase III studies and the Phase II and III safety pool. Based on the limited size of the safety database, it is not possible to detect rare and very rare events. Therefore, the possibility of these class effects cannot be excluded for delafloxacin.

Different headings were used to count events of potential seizure including syncope which may also be used to evaluate cardiovascular events. The respective term was re-evaluated in the context of system organ class. The applicant specified the preferred term syncope based on underlying cause and adjusted tabular calculations for potential QT prolongation and potential seizures. Case narratives for patients experiencing syncope were provided and supported the re-categorisation all three of these events under 'potential QT prolongation'. No event was considered as 'potential for seizure'.

The CHMP noted that for other fluoroquinolones, the indication cSSTI/ABSSSI is restricted to second/last line indication based on evaluated risks. In order to evaluate the first line indication initially claimed by the applicant, the CHMP reviewed the safety profile of delafloxacin based on the data submitted by the applicant, literature data and the product information of other fluoroquinolones, in the absence of direct in vivo comparisons between delafloxacin and other fluoroquinolones.

Based on preclinical data, a potentially favourable safety profile of delafloxacin was anticipated regarding cardiac effects (including QT prolongation), hepatotoxicity, CNS effects, and based on Phase I data phototoxicity. Some data suggest a possible safety benefit of delafloxacin compared to other fluoroquinolones, in particular for QT prolongation phototoxicity. Some favourable trends were observed

also for nervous system disorders, psychiatric effects, and potentially blood and lymphatic system disorders. However, for other ADRs, delafloxacin showed a trend to a less favourable safety profile, e.g. in the gastrointestinal disorder SOC.

Rates of treatment - related hepatic events were similar between patients in the delafloxacin and comparator groups. The incidence of hepatic-related TEAEs for delafloxacin was comparable to those of moxifloxacin and levofloxacin as reported in the originator SmPC's. In addition, the applicant has provided published data for moxifloxacin and compared those to delafloxacin and vancomycin + aztreonam, respectively. A comparison regarding hepatitis as well as acute and severe liver injury remains difficult given that these events are rare and very rare for moxifloxacin and levofloxacin. As such, the comparison is based mostly on transaminase elevations and increases in hepatic enzymes which seem to occur with similar frequency for moxifloxacin and levofloxacin. Since the occurrence of increased liver parameters as well as infectious hepatitis is common in this patient group, the assessment of the impact of delafloxacin itself on the liver is hampered. This concern also applies to the comparator group, since hepatobiliary disorders are not listed in section 4.8 for vancomycin following latest Article 31 referral. The applicant presented an overview on patient demographic with history of drug and/or alcohol abuse and analysed the occurrence of hepatic-related TEAEs in the delafloxacin group and vancomycin + aztreonam group, respectively. Considering the high number of drug and alcohol abusive patients included in the Phase III studies, confounding of hepatic-related ADRs remains a possibility. However, no significant safety signals in drug/alcohol abusive patients compared to non-abusers were apparent in the Phase II and III Pool. Upon assessment of an additional comparison of ADR frequencies in patients with and without hepatic impairment in the Phase II and III safety pool and between individual Phase III studies in order to evaluate hepatic effects of delafloxacin, the CHMP considered that overall, the safety of delafloxacin in patients with hepatic impairment compared to patients without hepatic impairment appears to be comparable, without need for dose adjustment.

Rates of treatment-related hyperglycaemia and hypoglycaemia were similar between patients in the delafloxacin and comparator groups. Compared to other approved fluoroquinolones and given the limited size of the delafloxacin safety database, it cannot be ruled out that delafloxacin can favour dysglycaemias. Regarding diabetic patients, the safety profile of delafloxacin appears to be similar in diabetic and not diabetic patients. The case narrative of one diabetic patient who experienced an event of borderline hypoglycaemia was provided and considered unrelated to delafloxacin.

Rates of treatment-related potential myopathy were lower in patients in the delafloxacin group versus comparator group (1.0% and 2.4%, respectively). Overall, the incidences of myopathy-related preferred terms were lower for delafloxacin compared to comparators. Rates of treatment-related potential peripheral neuropathy were similar between patients in the delafloxacin and comparator groups. The total number and incidence of delafloxacin-related paraesthesia was higher in pooled Phase III than in pooled phase II studies and the comparator groups. Case narratives for patients experiencing paraesthesia were provided. Overall, the potential of delafloxacin to induce peripheral neuropathy cannot be excluded.

Three cases of potential tendinopathy were reported in the RX-3341-303 study, but no patients in either treatment group were considered to have treatment-related potential tendon disorder.

One patient in study RX-3341-302 had a possibly treatment-related event of convulsions compared with no and one in study RX-3341-201. Case narratives were provided. Based on the available data it cannot be fully excluded that delafloxacin may have lowered the seizure threshold in these patients further.

The incidence of treatment-related renal impairment was higher for delafloxacin than for the comparator and few cases of renal failure were reported. The applicant clarified that none of the cases of treatment-related "CPK increase" were reported together with renal impairment / failure. Case narratives of patients with treatment-related CPK increase and of patients with renal impairment/renal failure were provided.

Rates of treatment-related potential allergic reactions were lower in patients in the delafloxacin group versus comparator group. The incidence of urticaria, dermatitis, and hypersensitivity was higher in pooled phase III compared to pooled phase II. In contrast, in pooled phase II the incidences of pustular rash and rash were higher than in pooled phase III. There were three premature discontinuations from delafloxacin due to an event of potential allergic reaction (2 patients with urticaria, 1 patient with allergic dermatitis). One delafloxacin-treated patient experienced the SAE of urticaria which was considered treatment-related. Compared to other approved fluoroquinolones, it cannot be ruled out that delafloxacin can favour urticarial, rash, dermatitis and hypersensitivity. Additional data for pruritus, rash and urticarial were provided. The number of patients with overall pruritus, rash and urticaria was higher in RX-3341-302 study than in RX-3341-303 study (7.8% vs 4.3%, respectively), this was also the case considering each term separately. When considered separately, pruritus, rash and urticaria incidences in the delafloxacin group remained below 2% in both studies. This was not the case in the vancomycin + aztreonam group in which pruritus and rash incidences were higher than 2% in both trials. The driver of the study difference appears to be the high incidence of pruritus for the vancomycin + aztreonam arm in the RX-3341-302 study vs RX-3341-303.

Three patients in the delafloxacin group had events for potential QT prolongation (syncope) compared with 1 patient in the comparator group (loss of consciousness). No patients in either treatment group had an event lasting longer than 30 days. No treatment discontinuations or SAEs were attributed to potential QT prolongation in patients treated with delafloxacin. The events in the delafloxacin group were considered unrelated to treatment, while the event in the comparator group was considered related to treatment. No cardiac safety signal was identified for delafloxacin investigated in phase I studies M01-365 and RX-3341-111. The individual case reports for all events of potential QT prolongation in the delafloxacin group were provided. Three cases of syncope were classified as 'potential QT prolongation' based on the Standardised MedDRA Queries (SMQs). The investigator did not consider them as due to QT prolongation and as such did not consider ECGs necessary. Patient narratives were provided with plausible causality assessment and the events of syncope were considered unrelated to delafloxacin.

For Cardiac Safety Study RX-3341-111 clarification on 3 subjects who had a change in QT/ QTc interval from baseline > 60 msec was provided. Given that none of the patients experienced an event of arrhythmia and QT prolongations were still below 500ms, no clinically significant QT prolongations seems to be apparent.

With regard to *C. difficile* diarrhoea no relevant signal could be identified for delafloxacin based on pooled and individual study data. The missing case narrative of the one case of *C. difficile* diarrhoea case in study RX-3341-201 was provided. Based on the available data, a statement was added to the product information that *Clostridioides difficile*-associated disease has been reported in users of nearly all systemic antibacterial medicinal products, with severity ranging from mild diarrhoea to fatal colitis.

In RX-3341-201, the one case of potential phototoxicity in patient 201-215-0005 was reported and considered unrelated to delafloxacin-treatment. Phase I Study M01-284 was designed to investigate the photosensitizing potential of oral delafloxacin at 200 mg and 400 mg doses. No safety signal for potential phototoxicity was identified for delafloxacin based on pooled and individual study data.

Serious AEs and deaths

Deaths

There were a total of 4 TEAEs leading to death, 1 in the delafloxacin group (septic shock [RX-3341-302]) and 3 in the comparator group (myocardial infarction [RX-3341-303]; intestinal ischemia [RX-3341-303]; and pulmonary embolism [RX-3341-302]). All of these events were considered unrelated to treatment.

Serious adverse events

In Phase II and III safety analysis set, six patients were assessed as having SAEs related to treatment, 2 delafloxacin patients (1 patient with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased and 1 patient with urticaria), and 4 comparator treated patients (2 patients with renal failure, 1 patient with acute renal failure, and 1 patient with rash). The overall incidence of SAEs in the Phase II and III safety analysis was similar between the delafloxacin treatment group and the comparator group (3.7% vs. 3.8%, respectively). There were no differences in the overall incidence of SAEs as well as incidences for any SOCs reported except for cellulitis, skin infection, infection and pulmonary embolism which were slightly higher in pooled phase III studies compared to phase II studies. In RX-3341-302 and RX-3341-303 the most frequent SAE for delafloxacin was cellulitis and skin infection, respectively. One AESI of urticaria occurred in one patient that was probably related to delafloxacin treatment. The applicant sufficiently provided a case narrative for this subject. No differences in the incidence of SAE could be observed between oral and intravenous formulations of delafloxacin. Cases of pulmonary embolism were described in more detail. No further cases of VTE occurred in the delafloxacin arm in addition to the two cases which have already been reported in the RX-3341-303 trial. Details on the cases of pulmonary embolism were provided. VTE and pulmonary embolism were not related to delafloxacin.

Pregnancies

There has been one pregnancy reported in RX-3341-302 which resulted in an SAE when the patient experienced a spontaneous abortion. The event was considered unrelated to study drug. However, based on the available data, the CHMP considered that the use of delafloxacin should be contraindicated in pregnancy, in women of childbearing potential not using contraception and in breast-feeding.

Laboratory findings

The most common reported laboratory-related TEAEs in the Phase II and III Safety Analysis Set were increases in ALT, AST, serum creatinine and decrease in blood glucose concentration. In general, the incidences of laboratory-related TEAEs were comparable between both groups except for increase in serum creatinine which was slightly higher in the comparator group then in the delafloxacin group. Based on data provided in the Phase II and III Safety Analysis Set no laboratory-related safety signal was identified for delafloxacin. Of note, both pivotal studies enrolled a considerable number of patients with documented history of drug and/or alcohol abuse and known hepatitis C infection. No major safety signals were apparent in patients with and without a documented history of drug and/or alcohol abuse and known hepatitis C infection.

Safety in special populations

In the pooled Phase II and Phase III studies, no clinically relevant differences in the safety profile of oral and intravenous delafloxacin for the intrinsic factors age, gender, race, ethnicity, BMI category, diabetes and the extrinsic factor geographic region was identified. Data on geriatric patients as well as a comprehensive overview on preferred terms and SOC's for each intrinsic factor were provided and showed no major safety signal.

For patients with renal impairment a comparative description of absolute and relative numbers of TEAEs observed in patients with creatinine clearance < and > 90 mL/min stratified by grade of renal impairment was provided. Separate tables with TEAEs and ADRs (>0.4%) by SOC and PT in patients with renal impairment and stratified by degree of renal impairment (mild, moderate, severe) were presented. No safety signal was identified for the different formulations and methods of administration of delafloxacin investigated in patients mild to moderate renal impairment. The patients with severe renal impairment treated with delafloxacin were too limited to conclude on safety in this population.

Adverse events of delafloxacin in hepatic impaired patients were assessed under the term "History of infectious hepatitis". However, this term does not capture all possible causes for hepatic impairment. In addition, patients with Child-Pugh Class B or C liver disease and alanine aminotransferase (ALT) >3 × ULN where excluded from the two pivotal studies. An overview on safety data in patients with hepatic impairment included in studies RX-3341-302 and RX-3341-303 with or without history of hepatitis was provided. A comparison of ADR frequencies by SOC and PT in patients with and without hepatic impairment in the Phase II and III safety pool and between individual Phase III studies did not reveal a safety signal in patients with hepatic impairment.

Safety related to drug-drug interactions and other interactions

Results of safety analysis in study ML-3341-118 revealed that the most commonly treatment-related TEAE observed only with oral delafloxacin was diarrhoea which was reported by 3 subjects (13.6%). No safety signal was identified for delafloxacin after concomitant administration with midazolam in study ML-3341-118.

Discontinuation due to AEs

Summary of phase II and phase III analysis set as well as single reports from the pivotal studies revealed that most TEAEs leading to study drug discontinuation related to delafloxacin treatment were categorised as hypersensitivity reactions such as urticaria. In both pivotal studies only AESIs related to potential allergic reaction occurred that led to discontinuation of delafloxacin. All cases reported were considered related to delafloxacin treatment. Two (0.6%) SAEs in the delafloxacin group led to discontinuation of study drug in RX-3341-302 which were as follows: cellulitis (unrelated) and pyoderma gangrenosum (unrelated). In RX-3341-303, 5 (1.2%) patients in the delafloxacin group experienced a SAE that led to study drug discontinuation which were as follows: acute respiratory failure (unrelated), urticaria (probable related), subdural haematoma (unrelated), pulmonary embolism (unrelated), hypersensitivity (probable related) and skin infection (unrelated).

2.6.2. Conclusions on the clinical safety

Overall, delafloxacin was well tolerated during the clinical studies. By SOC, gastrointestinal disorders namely nausea and diarrhoea dominated in the delafloxacin group.

Overall, the safety profile of delafloxacin appears to be comparable to that of other fluoroquinolones. It is acknowledged that the data provided for delafloxacin so far are too limited to conclude on the risk of serious ADRs with frequency rare (e.g. tendon rupture) and no comprehensive conclusions on such ADRs can be drawn. Nevertheless, an improved safety profile compared to those of other fluoroquinolones could not be demonstrated for delafloxacin. Therefore, a restricted indication (similar to the wording of the indication of moxifloxacin) is recommended, which was agreed by the applicant.

2.7. Risk Management Plan

Safety concerns

Summary of Safety Concerns	
Important Identified Risks	• Tendinopathy • Peripheral Neuropathy
Important Potential Risks	• Long-lasting and / or potentially irreversible severe adverse reactions • Aortic aneurysm and dissection • Renal damage secondary to sulfobutylether-β-cyclodextrin

	(SBECD) accumulation in patients with severe renal impairment [IV formulation]
Missing Information	• None

Pharmacovigilance plan

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction for the Important potential risk "Long-lasting and / or potentially irreversible severe adverse reactions".

No additional pharmacovigilance activities are planned for the product.

Risk minimisation measures

Safety concern	Risk minimisation measures

Important identified risk: Tendinopathy	Routine risk minimisation measures:
	 - SmPC section 4.2 Posology and method of administration
	 - SmPC section 4.3 Contraindications
	 - SmPC section 4.4 Special warnings and precautions for use
	 - SmPC section 4.8 Undesirable effects
	
	 - PL section 2 What you need to know before you are given/take delafloxacin
	   You must not be given/Do not take delafloxacin
	   Warning and precautions
	 - PL section 4 Possible side effects
	
	 Legal status: prescription only medicine
	
	 Additional risk minimisation measures:
	 No additional risk minimisation measures

Important identified risk: Peripheral Neuropathy	Routine risk minimisation measures: - SmPC section 4.4 Special warnings and precautions for use - SmPC section 4.8 Undesirable effects - PL section 2 What you need to know before you are given/take delafloxacin Warning and precautions Legal status: prescription only medicine Additional risk minimisation measures: No additional risk minimisation measures
Important potential risk: Long-lasting and / or potentially irreversible severe adverse reactions	Routine risk minimisation measures: - SmPC section 4.4 Special warnings and precautions for use - SmPC section 4.8 Undesirable effects - PL section 2 What you need to know before you are given/take delafloxacin Warning and precautions - PL section 4 Possible side effects Legal status: prescription only medicine Additional risk minimisation measures: No additional risk minimisation measures

Safety concern	Risk minimisation measures
Important potential risk: Aortic aneurysm and dissection	Routine risk minimisation measures: - SmPC section 4.4 Special warnings and precautions for use - PL section 2 What you need to know before you are given/take delafloxacin Warning and precautions Legal status: prescription only medicine Additional risk minimisation measures: No additional risk minimisation measures
Important potential risk: Renal damage secondary to sulfobutylether-β-cyclodextrin (SBECD) accumulation in patients with severe renal impairment [IV formulation]	Routine risk minimisation measures: - SmPC section 4.2 Posology and method of administration - SmPC section 4.4 Special warnings and precautions for use - PL section 2 What you need to know before you are given/take delafloxacin Warning and precautions - PL section 3 How to use delafloxacin Legal status: prescription only medicine Additional risk minimisation measures: No additional risk minimisation measures

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of delafloxacin with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers delafloxacin to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. 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.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Quofenix (delafloxacin) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Skin and soft tissue infections are among the most common infections in both hospitals and community settings and remain a significant source of morbidity and mortality. Acute Bacterial Skin and Skin Structure Infections (ABSSSI) are more serious than uncomplicated skin infections and include cellulitis, erysipelas, wound infections and major abscesses which may require significant surgical intervention and parenteral antibiotic therapy.

The most common bacteria identified in ABSSSI are Gram-positive pathogens, including streptococci and staphylococci. The most frequently isolated Gram-positive ABSSSI pathogens are *S. aureus* (including methicillin-resistant *S. aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA)), followed by β-haemolytic streptococci. However, in approximately 14% of ABSSSI, Gram-negative pathogens are detectable.

3.1.2. Available therapies and unmet medical need

A number of antimicrobial agents are available for the treatment of ABSSSI and the benefit of systemic antimicrobial therapy, accompanied by surgical intervention as necessary, is clearly established. According to the clinical presentation and including other patient co-morbidities, treatment strategies in ABSSSI 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.

Currently, the only approved agents for the first line treatment of ABSSSI with adequate efficacy against MRSA allowing an IV-to-oral switch treatment scheme without necessitating a change in antibiotic and/or dose are linezolid and tedizolid phosphate. In particular, linezolid is increasingly utilised in the treatment

of ABSSSI, particularly if MRSA is considered a likely pathogen. However, its use may be associated with myelosuppression, peripheral and optic neuropathies, and lactic acidosis, particularly with therapy longer than typical for the treatment of ABSSSI. 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. Furthermore, resistance to currently available MRSA drugs has increased. 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.

Most approved agents for treatment of ABSSSI are only susceptible against Gram-positive pathogens. However, since Gram-negative pathogens may be the causing pathogens in ABSSSI as well, a new antibiotic covering both Gram-negative and Gram-positive bacteria may be of significant benefit.

Several fluoroquinolones (moxifloxacin, levofloxacin, ofloxacin) are approved for the indication cSSTI/ABSSSI as second/last line indication. For moxifloxacin and levofloxacin, the indication cSSTI was restricted to second line indication during referral procedures in 2008 and 2012 due to safety concerns. During national variation procedures, the SmPC of ofloxacin (originator) was adapted to be in line with the outcome of the referral procedure of levofloxacin and accordingly the indication cSSTI was restricted to last line indication as well.

Overall, new antibacterial drugs, especially those available as an oral formulation, are needed to treat infections due to Gram-positive and Gram-negative bacteria in both hospital and community settings.

3.1.3. Main clinical studies

Study RX-3341-302: A randomized, double-blind, multi-center Phase III study investigated the efficacy of IV delafloxacin vs vancomycin plus aztreonam in the treatment of patients with ABSSSI for 5 to 14 days (n= 660).

Study RX-3341-303: A randomized, double-blind, double-dummy, multi-center Phase III study investigated the efficacy of IV (3 days) followed by oral delafloxacin vs vancomycin plus aztreonam in the treatment of patients with ABSSSI for overall 5 to 14 days (n= 850).

3.2. Favourable effects

IV treatment - Study RX-3341-302:

Non-inferiority of IV delafloxacin to vancomycin + aztreonam was demonstrated for the co-primary analysis populations: ITT and CE. Clinical cure in the ITT population at FU visit was 172/331 (52.0%) in the delafloxacin group vs. 166/329 (50.5%) in the vancomycin + aztreonam group, and clinical cure in the CE population at FU visit 142/240 (59.2%) in the delafloxacin group vs. 142/244 (58.2%) in the vancomycin + aztreonam group. The lower limits of the 95% CIs for both co-primary endpoints were within -10% (i.e. 1.5% [-6.1, 9.1] for the ITT population and 1.0% [-7.8, 9.7] for the CE population). These results were supported by the sensitivity analyses of the primary efficacy outcomes.

Overall, the cure rates were relatively low compared to other studies in ABSSSI. However, this could be explained by early time point of the FU visit and strict definition of clinical cure (complete resolution of all baseline signs and symptoms of ABSSSI at FU) in line with the recommendation of the antibacterial guideline and its Addendum. It should be considered that in other studies in the indication ABSSSI a broader definition for treatment success was chosen (e.g. clinical success defined as improved so far that

no further antibiotic treatment is necessary). In study RX-3341-302, in the ITT population, success (cure + improved) at FU visit was detectable in 270/331 (81.6%) in the delafloxacin group vs. 274/329 (83.3%) in the vancomycin + aztreonam group. Success (cure + improved) in the CE population at FU visit was detectable in 233/240 (97.1%) in the delafloxacin group vs. 238/244 (97.5%) in the vancomycin + aztreonam group.

<u>IV (3 days) followed by oral treatment - Study RX-3341-303:</u>

For the primary endpoint of clinical cure, non-inferiority of IV followed by oral delafloxacin to vancomycin + aztreonam was not demonstrated for both co-primary populations. Clinical cure in the ITT population at FU visit was 244/423 (57.7%) in the delafloxacin group vs. 255/427 (59.7%) in the vancomycin + aztreonam group, and clinical cure in the CE population at FU visit 220/353 (62.3%) in the delafloxacin group vs. 224/329 (68.1%) in the vancomycin + aztreonam group. The lower limits of 95% CIs were within -10% (-2.0% [-8.6, 4.6]) for the ITT population, but not greater than -10% (-5.8% [-12.9, 1.4]) in the CE population.

As stated for study RX-3341-302, the cure rates were relatively low compared to other studies in ABSSSI. However, this could be explained by the early time point of the FU visit and strict definition of clinical cure (complete resolution of all baseline signs and symptoms of ABSSSI at FU) in line with the recommendation of the antibacterial guideline and its Addendum. It should be considered that in other studies in the indication ABSSSI a broader definition for treatment success was chosen (e.g. clinical success defined as improved so far that no further antibiotic treatment is necessary). The success rates (cure + improved where the investigator felt that no further antibiotics were needed in the respective populations) in the ITT population at FU were 87.2% in the delafloxacin group an 84.8% in the vancomycin + aztreonam group (95% CI −2.2, 7.2). In the CE-Population the success rates were 96.3% in the delafloxacin group and 97.0% in the vancomycin + aztreonam group (95% CI -3.5, 2.2). Accordingly, for the endpoint success at FU visit, non-inferiority of delafloxacin towards vancomycin + aztreonam has been demonstrated for both the ITT and CE population. Furthermore, the applicant provided two additional analyses showing that for study -303 non-inferiority could be concluded in a range of scenarios in the sensitivity analysis and that results are closer to the non-inferiority margin with imputed observations compared to the original "per protocol" analysis (although based on the missing at random assumption).

3.3. Uncertainties and limitations about favourable effects

In study RX-3341-302, non-inferiority of IV delafloxacin has been demonstrated in the ITT and CE populations (which was further supported by results of phase 2 study RX-3341-202). However, in study RX 3341-303, for the primary endpoint of clinical cure, non-inferiority of delafloxacin to vancomycin + aztreonam has only been demonstrated in the ITT population. The CHMP considered it acceptable to consider the single primary population ITT (all randomised patients) for primary analysis and to regard the CE population as secondary.

In the pivotal studies, the TOC visit was timed 14 + 1 days from randomisation (recommended TOC visit in the Addendum 7-14 days after last day of treatment). Taking the treatment duration of 5 to 14 days into account, the TOC visit was performed between day 0 and day 9 after the last day of treatment. The applicant addressed this issue and defined several additional analyses as sensitivity analysis. A new definition of investigator assessment at PTE was introduced within a window of 7 - 14 and 6 - 15 days after EOT (PTE7-14 - PTE6-15); all the assessments outside of that window were considered missing, and therefore counted as failure. If, instead, both the assessments are within the defined window after EOT, the earliest one (i.e., FU visit) was taken. Overall, the used time point of TOC visit was not optimal. However, additional analyses supported that the FU assessment performed earlier than the window of 7

- 14 days after the EOT had a negligible effect on the evaluation of the primary end-point in both pivotal studies.

In study RX-3341-302, the cure rates in the ITT and CE population at PTE, PTE7-14 and PTE6-15 were comparable between delafloxacin and vancomycin + aztreonam groups and the results of these sensitivity analyses supported the results of the primary analysis.

In study RX-3341-303, in the ITT population the cure rates at PTE, PTE7-14 and PTE6-15 were comparable between delafloxacin and vancomycin + aztreonam groups. However, in the CE population the cure rates at PTE, PTE7-14 and PTE6-15 tended to be in disfavour of delafloxacin (the lower limits of 95% CIs were below -10%). Overall, the sensitivity analyses supported the results of the primary analysis of clinical cure where for the CE population the lower limit of 95% CI was below -10%.

In study RX-3341-303, the success rates (cure + improved where the investigator felt that no further antibiotics were needed in the respective populations) at FU visit were comparable between treatment groups in both the ITT and CE population. Furthermore, non-inferiority of delafloxacin towards vancomycin + aztreonam for the endpoint success at FU visit has been demonstrated in both the ITT and CE population.

Furthermore, the applicant provided two additional analyses where results showed that for study -303 non-inferiority could be concluded in a range of scenarios in the sensitivity analysis and that results are closer to the non-inferiority margin with imputed observations compared to the original "per protocol" analysis (although based on the missing at random assumption).

In addition, no relevant differences of the predicted plasma exposures (measured on day 1 and day 3 after IV delafloxacin) in those who did and did not fail between studies RX-3341-302 and RX-3341-303 were detectable which supports the conclusion of non-inferiority.

Overall, non-inferiority of IV as well as IV followed by oral delafloxacin is concluded.

In both pivotal studies, cure rates were considerably higher at FU visit in patients in Europe (study RX-3341-302: delafloxacin 85.7%, vancomycin + aztreonam 70.9%, n=118; study RX-3341-303: delafloxacin 67.9%, vancomycin + aztreonam 69.9%; n=338) compared to North America (study RX 3341-302: delafloxacin 44.0%, vancomycin + aztreonam 46.4%, n=542; study RX 3341-303: delafloxacin 46.5%, vancomycin + aztreonam 49.5%; n=398).

Cure rates at FU visit in patients with cellulitis/erysipelas were higher in delafloxacin group compared to comparator group in study RX 3341-302 (delafloxacin: 67.2% n=128; vancomycin + aztreonam: 60.9% n=128), whereas in study RX 3341-303 cure rates at FU visit were slightly lower in delafloxacin group compared to comparator group (delafloxacin 59.9% n=202 vs. vancomycin + aztreonam 63.1% n=202).

In patients with major abscess cure rates at FU visit were higher in delafloxacin group compared to vancomycin + aztreonam group in both pivotal studies (study RX 3341-302: delafloxacin 52.4% n=84; vancomycin + aztreonam 48.2% n=83; study RX 3341-303: delafloxacin 64.2% n=106; vancomycin + aztreonam 57.5% n=106).

In contrast, in case of wound infection cure rates were considerably lower in the delafloxacin group compared to the comparator group in both pivotal studies ((study RX 3341-302: delafloxacin 33.6% n=116; vancomycin + aztreonam 41.4% n=116; study RX 3341-303: delafloxacin 46.8% n=111; vancomycin + aztreonam 54.5% n=112). However, further analysis indicated that a different treatment effect for the cure rate in patients with wound infection could not be statistically claimed. Furthermore, it was highlighted that in terms of success rate (cured or improved) the differences at FU between treatment arms in patients with wound infection were negligible in the RX-3341-302 study and the rate of success was even higher in patients treated with delafloxacin in the RX-3341-303 study. In addition, the

cure rates in patients treated with delafloxacin were also similar to those in patients treated with vancomycin + aztreonam when the analysis considered the assessment at the LFU.

3.4. Unfavourable effects

Overall, delafloxacin was well tolerated during clinical studies in the applied IV and oral dosages. The size of the presented safety database can be regarded as appropriate to characterize the safety profile of delafloxacin. The overview of the safety data suggested comparable profiles for delafloxacin and comparator vancomycin + aztreonam. The most common TEAEs after administration of delafloxacin were nausea (9.1%), diarrhoea (8.6%), infection (5.2%), infusion site extravasation (4.7%), and headache (3.5%). In the SOC gastrointestinal disorders more TEAEs related to study drugs were reported for delafloxacin compared to comparator in Phase 3 studies (10.9 vs. 6.0%) and in Phase 2 studies (25.2 vs.20.8%). In particular, diarrhoea was regarded as related to study drug more frequently in delafloxacin groups (Phase II and III safety analysis set: delafloxacin 6.9% vs. comparator 2.5%). However, most cases of diarrhoea were mild in intensity and did not result in a discontinuation of therapy. When comparing both pivotal studies RX-3341-302 and RX-3341-303 no significant differences in safety profile could be identified. In general, study RX-3341-303, which investigated intravenous followed by oral delafloxacin, tended to have a slightly better safety profile which would be in accordance with the lower C_{max} observed after a single 450 mg oral dose of delafloxacin compared to 300 mg intravenous delafloxacin in BE study RX-3341-115.

3.5. Uncertainties and limitations about unfavourable effects

Overall, the safety profile of delafloxacin appears to be comparable to that of other fluoroquinolones. The limitations of direct comparisons of clinical trial results to published meta-analyses across different and older studies are acknowledged. It is acknowledged that the data provided for delafloxacin are too limited to conclude on the risk of serious ADRs with frequency rare and very rare and no comprehensive conclusions on such ADRs can be drawn.

No significant safety advantage over the other fluoroquinolones is obvious that would justify an unrestricted indication in ABSSSI. Therefore, a restricted indication (in line with the wording of the indication of moxifloxacin) is recommended, which was agreed by the applicant.

3.6. Effects Table

Table 39: Effects Table for delafloxacin/Quofenix in ABSSSI

Effect	Short description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Non-inferiority	**RX-3341-302** ABSSSI Phase 3 study of IV delafloxacin (300 mg Q12h) vs. vancomycin (15 mg/kg IV Q12h) plus aztreonam (2 g IV Q12h until baseline culture confirmed negative for gram-negative) for 5 to 14 days	%	ITT clinical cure at FU visit: 52.0 CE clinical cure at FU visit: 59.2 ITT clinical success at FU visit: 81.6 CE clinical success at FU visit: 97.1	50.5 58.2 83.3 97.5	Non-inferiority margin (-10%) was met in ITT and CE populations (-6.1, 9.1) (-7.8, 9.7) (-7.6, 4.1) (-3.7, 2.7) There was fairly consistent numerical inferiority for IV delafloxacin vs. vancomycin + aztreonam	Study-Report
Non-inferiority	**RX-3341-303** ABSSSI Phase 3 study of IV delafloxacin (300 mg Q12h for 3 days/6 doses) followed by oral delafloxacin (450 mg Q12h) vs. vancomycin (15 mg/kg IV Q12h) plus aztreonam (2 g IV Q12h until baseline culture confirmed negative for gram-negative) for 5 to 14 days	%	ITT clinical cure at FU visit: 57.7 CE clinical cure at FU visit: 62.3 ITT clinical success at FU visit: 87.2 CE clinical success at FU visit: 96.3	59.7 68.1 84.8 97.0	Non-inferiority margin (-10%) for the primary EP clinical cure was only met in the ITT population (-8.6, 4.6) (-12.9, 1.4) (-2.2, 7.2) (-3.5, 2.2) Sensitivity analysis supported results of the primary analysis	Study-Report

Effect	Short description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Descriptive	**RX-3341-202** ABSSSI Phase 2 study of IV delafloxacin (300 mg Q12h) vs IV linezolid (600 mg Q12h) vs IV vancomycin (15 mg/kg Q12h); aztreonam added if gram-negative confirmed	%	ITT clinical cure at FU visit: 70.4	linezolid: 64.9 vancomycin: 54.1	only one systemic sign of infection was necessary to be enrolled; however, demonstrated that sufficiently ill population was investigated. overall supportive for IV delafloxacin in ABSSSI	Study-Report

Unfavourable Effects

Effect	Short description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Diarrhoea	Phase II and III Safety analysis Set	%	6.9	2.5	More gastrointestinal ADRs after delafloxacin compared to comparators, most cases of diarrhoea mild in intensity	Summary of safety
FQ class effect: Hyperglycaemia	Phase II and III Safety analysis Set	%	1.0	1.0	Frequency category of dysglycaemia comparable to other FQ	Summary of safety
FQ class effect: ADR Hypoglycaemia	Phase II and III Safety analysis Set	%	0.2	0.3	Frequency category of dysglycaemia comparable to other FQ	Summary of safety
FQ class effect: ADR Hepatotoxicity	Phase II and III Safety analysis Set: Alanine aminotransferase increased Aspartate aminotransferase increased	% %	1.4 0.7	1.1 1.1	Frequency category comparable to other FQ	Summary of safety
Other FQ class effects/ ADRs	Phase II and III Safety analysis Set				Frequency category comparable to other FQ	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

While for the primary endpoint of clinical cure in study RX-3341-302 non-inferiority of IV delafloxacin has been shown in the ITT and CE population, in study RX 3341-303 non-inferiority of IV followed by oral delafloxacin towards vancomycin + aztreonam was only demonstrated in the CE population.

Nevertheless, when considering the endpoint clinical success at FU visit as accepted in other procedures and taking into account the additional analyses provided by the applicant, non-inferiority of IV followed by oral delafloxacin towards vancomycin + aztreonam can be concluded as well.

Overall, the safety profile of delafloxacin appears to be comparable to that of other fluoroquinolones.

No significant safety advantage over the other fluoroquinolones is obvious that would justify an unrestricted indication in ABSSSI. Therefore, a restricted indication (in line with the wording of the indication of moxifloxacin) is recommended, which was agreed by the applicant.

3.7.2. Balance of benefits and risks

Based on the CHMP assessment of the available data, the applicant agreed to restrict the indication. The CHMP considered that the benefit-risk balance for *acute bacterial skin and skin structure infections (ABSSSI) in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections* is positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall benefit-risk of Quofenix is considered positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Quofenix is favourable in the following indication:

Quofenix is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections (see sections 4.4 and 5.1).

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

The CHMP 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.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out

in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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.

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 the available data, the CHMP considers that delafloxacin is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.