30 March 2023
EMA/CHMP/783414/2023
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Tenkasi

International non-proprietary name: oritavancin

Procedure No. EMEA/H/C/003785/II/0037

Marketing authorisation holder (MAH) Menarini International Operations Luxembourg S.A.

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List of abbreviations

ABSSSI	Acute Bacterial Skin and Skin Structure Infections
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Plasma Concentration-Time Curve
AUC_{0-72}	Area Under the Plasma Concentration-Time Curve, from Baseline to 72 Hours Post- dose
$AUC_{0-\infty}$	Area Under the Plasma Concentration-Time Curve, Total Drug Exposure Over Time
BID	Twice a Day
BMI	Body Mass Index
CFU	Colony Forming Unit
CHMP	Committee for Medicinal Products for Human Use
CL	Clearance
C_{max}	Maximum Concentration
CSR	Clinical Study Report
%CV	Coefficient of Variation
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
GCP	Good Clinical Practice
INR	International Normalized Ratio
IV	Intravenous
LC	Liquid Chromatography
MAH	Marketing Authorisation Holder
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimal Inhibitory Concentration
min	Minimum
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MS	Mass Spectrometry
PK	Pharmacokinetic

PIP	Paediatric Investigation Plan
PT	Prothrombin Time
PTA	Probability of Target Attainment
Q1	First Quartile
Q3	Third Quartile
RMP	Risk Management Plan
RSI	Request for Supplementary Information
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
t½	Half-Life
TEAE	Treatment-Emergent Adverse Event
tmax	Time of Maximum Concentration
ULN	Upper Limit of Normal
Vz	Volume of Distribution

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Menarini International Operations Luxembourg S.A. submitted to the European Medicines Agency on 26 August 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of paediatric population, aged between 3 months and less than 18 years for Tenkasi (oritavancin) 400 mg based on interim results from study TMC-ORI-11-01; this is a multicenter, open-label, dose-finding study of oritavancin single dose infusion in paediatric subjects less than 18 years of age with suspected or confirmed bacterial infections. The purpose of this Phase 1 study is to evaluate the safety, tolerability, and PK of oritavancin in paediatric subjects and determine the optimal dose for a Phase 2 trial in pediatric subjects with ABSSSI. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.0 of the RMP has also been submitted.
In addition, MAH is also taking this opportunity to update the contact details of the local representatives in the Package Leaflet.
Furthermore, the PI is brought in line with the latest QRD template version 10.2 rev 1.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) (P/0236/2022) on the agreement of a paediatric investigation plan (PIP).

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

Information relating to orphan market exclusivity

Not applicable.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH 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.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Janet Koenig

Timetable	**Actual dates**
Submission date	26 August 2022
Start of procedure:	17 September 2022
CHMP Rapporteur Assessment Report	11 November 2022
PRAC Rapporteur Assessment Report	17 November 2022
PRAC members comments	23 November 2022
Updated PRAC Rapporteur Assessment Report	24 November 2022
PRAC Outcome	1 December 2022
CHMP members comments	5 December 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	8 December 2022
Request for supplementary information (RSI)	15 December 2022
CHMP Rapporteur Assessment Report	28 February 2023
PRAC Rapporteur Assessment Report	3 March 2023
PRAC members comments	8 March 2023
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	16 March 2023
CHMP members comments	
Updated CHMP Rapporteur Assessment Report	
Opinion	30 March 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Tenkasi 400 mg powder for concentrate for solution for infusion is currently approved for treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults.

Epidemiology

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).

Aetiology and pathogenesis

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 15.5% in 2019, ranging from 1.1% in Norway to 46.7% in Romania (ECDC, Surveillance Report: Antimicrobial resistance in EU/EEA (EARS-Net), 2020).

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.

Management

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, several 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. 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.

Products specifically licensed for paediatric patients (varying age ranges) within the EU include tedizolid, vancomycin, teicoplanin, tigecycline, ceftaroline, and daptomycin.

2.1.2. About the product

The active substance of Tenkasi 400 mg powder for concentrate for solution for infusion is oritavancin. Oritavancin is a semi-synthetic lipoglycopeptide antibiotic active against Gram-positive bacteria. Its antibacterial activity is based on three principal mechanisms of action: 1) inhibition of the transglycosylation (polymerisation) step of cell wall biosynthesis by binding to the stem peptide of peptidoglycan precursors; 2) inhibition of the transpeptidation (crosslinking) step of cell wall biosynthesis by binding to the peptide bridging segments of the cell wall; and 3) disruption of bacterial membrane integrity, leading to depolarisation, permeabilisation, and rapid cell death. Oritavancin exhibits rapid, extensive tissue distribution and a long terminal half-life (245 hours) and is not metabolised.

Oritavancin was approved in the EU on 18th March 2015 (EMEA/H/C/003785) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults and the recommended dose is a single 1200 mg intravenous (IV) infusion over 3 hours. In adults, no dose adjustment is needed in patients with mild/moderate renal or hepatic impairment.

This application concerns the extension of indication to the paediatric population aged 3 months to less than 18 years based on the interim report of study TMC-ORI-11-01. The proposed dose is 15 mg/kg as a single dose infused over 3 hours.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Study TMC-ORI-11-01 is part of the Paediatric Investigation Plan (PIP) for oritavancin (EMEA-001270-PIP01-12; see table below). Study 3 is ongoing and planned to be completed by July 2023.

Area	Description
Quality- related studies	**Study 1** Age-appropriate dosage form for parenteral use for the paediatric population from birth to less than 3 months of age.
Non-clinical studies	Not applicable
Clinical studies	**Study 2** Open-label, dose-finding trial to evaluate PK, safety and tolerability of oritavancin single dose infusion in children from birth to less than 18 years of age with confirmed or suspected bacterial infections receiving antibiotic therapy (TMC-ORI-11-01) **Study 3** Open label trial to evaluate PK, safety and tolerability of oritavancin in children from birth to less than 3 months of age with confirmed or suspected bacterial infections receiving antibiotic therapy .
Extrapolation, modelling and simulation studies	**Study 4** Pop PK and pop PK/PD modelling and simulation study in paediatric patients from birth to less than 18 years of age to inform dosing recommendation of oritavancin in paediatric subjects from birth to less than 18 years.

2.1.4. General comments on compliance with GCP

The MAH has provided a statement that study TMC-ORI-11-01 was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline. The study was conducted at 8 sites in the US.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Summary of the ERA

Subject of the extension is the inclusion of paediatric patients 3 months and older in the SmPC.

The maximum daily dose and the predicted environmental concentration remain unchanged compared with the initial environmental risk assessment.

The MAH is of the opinion that the ERA performed for the previous application will be still valid for the current variation. Therefore, no new ERA data have been provided by the MAH.

CHMP agreed that the present application for extension to include paediatric patients from 3 months of age in the SmPC without changing the maximum recommended daily dose of 1200 mg will not lead to an increased predicted environmental concentration compared to the initial environmental risk

assessment. Hence, the initial environmental risk assessment is still valid and an update is considered not necessary.

2.2.2. Discussion on non-clinical aspects

No new non-clinical studies have been performed to support this change in indication.

It is expected that Tenkasi will not pose a risk to the environment if it will be used in accordance with the SmPC. The environmental risk assessment is finalised.

2.2.3. Conclusion on the non-clinical aspects

Considering the above data, oritavancin is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The MAH 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 number in PIP / study code	**Study design**	**Subjects**	**Dosing Regimen**	**Total number of subjects enrolled/completed**
Study 2 TMC-ORI-11-01	ongoing, open-label, multicentre study to evaluate the PK, safety and tolerability of oritavancin	Paediatric subjects <18 years of age with suspected or confirmed bacterial infections	Single IV dose of oritavancin 15 mg/kg or 20 mg/kg marketed formulation	48 subjects enrolled (Cohorts 1 to 4) 35 subjects completed

2.3.2. Pharmacokinetics

This application regarding the extension of indication to paediatric patients aged 3 months to <18 years relies on the concept of extrapolation of efficacy based on comparable oritavancin plasma exposures in children and adults.

Study TMC-ORI-11-01 (ORKIDS)

This is an ongoing Phase 1, open-label, multicentre, sequential study to evaluate the PK, safety and tolerability of single-dose oritavancin in paediatric patients aged less than 18 years. The study is part of the Paediatric Investigation Plan (PIP) for oritavancin (EMEA-001270-PIP01-12).

Method

- **Bioanalytical method**

Oritavancin plasma concentrations were quantified using a validated LC-MS/MS method.

The MAH submitted the validation report of method for the determination of oritavancin inhuman plasma which was already assessed during the initial marketing authorisation procedure (EMEA/H/C/003785). The bioanalytical sample report has not been finalised since study TMC-ORI-11-01 (ORKIDS) is still ongoing.

Study participants

Main Inclusion criteria

- Males and females <18 years of age.
- Written informed consent provided before initiation of any study-related procedures; parent or legal guardian gave informed consent, as appropriate; and pediatric subject gave verbal assent where appropriate.
- Suspected or diagnosed Gram-positive bacterial infection for which the subject was receiving standard antibiotic therapy or subjects requiring perioperative prophylactic use of antibiotics.
- IV access to administer study drug.
- The subject would be observed in the ER or hospital for at least 1 hour after the study drug infusion was completed.

Main exclusion criteria

- Septic shock or acute hemodynamic instability.
- History of immune-related hypersensitivity reaction to glycopeptides (such as vancomycin, telavancin, or teicoplanin) or any of their excipients.
- Subjects who had taken vancomycin or other glycopeptides within 24 hours of screening or who were anticipated to need vancomycin, telavancin, teicoplanin or other glycopeptides within 48 hours after administration of study drug. Subjects who took dalbavancin were excluded if dalbavancin was taken within the previous 2 weeks or if subjects were anticipated to need dalbavancin within 48 hours after administration of study drug.
- Treatment with investigational medicinal product or investigational device within 30 days (or 5 times the t½ of the investigational medicine, whichever was longer) before enrolment and for the duration of the study.
- Subjects who were taking heparin or warfarin and/or required anticoagulant monitoring (activated partial thromboplastin time [aPTT], prothrombin time [PT], international normalized ratio [INR]).
- Subjects who required anticoagulant monitoring with an aPTT.
- Subjects with an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 × the upper limit of normal (ULN) or total bilirubin ≥2 × ULN.
- Neutropenia with absolute neutrophil count (ANC) <500 cells/mm^3.

- Active exposure to cytotoxic chemotherapy or immunosuppressive therapy with tacrolimus or cyclosporine.
- Subjects who received immunosuppressive treatment/chemotherapy within the 2 weeks prior to screening.
- Any chronic systemic immunosuppressive therapy equivalent to a prednisone dose higher than 15 mg/day.

Main Withdrawal criteria:

- Positive result for the urine or serum human chorionic gonadotropin (hCG) test administered at screening (females with child bearing potential)
- Adverse event(s)
- Death
- Subject withdrew consent

Treatments

The starting dose was chosen by adjusting the adult dose based on weight. In the two pivotal Phase 3 studies (SOLO I and SOLO II), a single dose of 1200 mg oritavancin was shown to be effective and safe in adults for the treatment of ABSSSI caused by Gram-positive pathogens. The average adult weight of 80 kg in the SOLO studies and the 1200 mg dose, gave a weight-based dose of 15 mg/kg. Oritavancin was administered as a single IV infusion over approximately 3 hours and the dose did not exceed 1200 mg.

Patients were enrolled in a stepwise approach, starting with the oldest age cohort and then progressing down the age range after PK and safety analyses had been performed (with the exception of Cohorts 3b and 4 which were enrolled concurrently):

- **Cohort 1** (age 12 to <18 years): a single oritavancin dose of 15 mg/kg.
- **Cohort 2** (6 to <12 years): a single oritavancin dose of 15 mg/kg.
- **Cohort 3** (age 2 to <6 years): a single oritavancin dose of 15 mg/kg.
    - **Cohort 3b** (age 2 to <6 years): a single oritavancin dose of 20 mg/kg.
- **Cohort 4** (age 3 months to <2 years): a single oritavancin dose of 15 mg/kg.
- **Cohort 5** (age from birth to <3 months [including neonates from 0 to 28 days]): a single oritavancin dose of 15 mg/kg

Cohorts 1 to 4 are completed. A cohort of 16 children aged from birth to less than 3 months (Cohort 5) is currently being investigated.

The oritavancin formulation used is identical to the formulation currently licensed for treatment of adults.

Outcomes/endpoints

Primary endpoint:

- Area under the plasma concentration-time curve (AUC).

Secondary endpoints:

- Maximum concentration (C_{max}), t½, time of maximum concentration (t_{max}), Vz, and CL.
- Safety assessed according to AEs, serious AEs (SAEs), vital signs (blood pressure, pulse rate, respiration rate, and temperature), electrocardiograms (ECGs), and clinical laboratory parameters (hematology and chemistry):

- Hematology: complete blood count with differential including white blood count (neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils), haemoglobin, haematocrit, and platelets.
- Chemistry: glucose, calcium, sodium, potassium, chloride, albumin, blood urea nitrogen (BUN), serum creatinine, alkaline phosphatase (ALP), ALT, AST, and total bilirubin.

Sample size

The total sample size (at least 52 evaluable subjects) was chosen based on judgment to provide adequate precision of the findings. At least 8 subjects per pediatric age cohort (and at least 16 for <3 month age cohort) were considered adequate to assess PK based on prior clinical experience.

Randomisation

Not applicable.

Blinding (masking)

Not applicable.

Statistical methods

Statistical analyses were performed using the following subject populations:

- Safety Population: All subjects who are dosed with oritavancin.
- PK Population: All subjects who are dosed with oritavancin and have at least one documented and evaluable blood concentration and documented dose records.

Results

Participant flow

A total of 46 subjects were enrolled in Cohorts 1-4 Of the 46 subjects enrolled, 38 subjects were dosed and 35 subjects completed the study (Table 1).

All 38 subjects that received the study drug (even those who did not receive a complete dose) were included in the Safety and PK Populations.

Table 1: Subject disposition (all dosed subjects)

	15 mg/kg				20 mg/kg
n (%)	**Cohort 1 12 to <18 years**	**Cohort 2 6 to <12 years**	**Cohort 3 2 to <6 years**	**Cohort 4 3 months to <2 years**	**Cohort 3b 2 to <6 years**
Subjects who received Study drug	8	8	8	7	7

Subjects who completed study drug	8/8 (100.0)	8/8 (100.0)	8/8 (100.0)	6/7 (85.7)	3/7 (42.9)
Subjects who discontinued study drug early	0	0	0	1/7 (14.3)	4/7 (57.1)
Primary reason for discontinuation					
Adverse event(s)	0	0	0	1/7 (14.3)	4/7 (57.1)
Safety subjects who completed the study	8/8 (100.0)	8/8 (100.0)	6/8 (75.0)	7/7 (100.0)	6/7 (85.7)
Safety subjects who discontinued the study	0	0	2/8 (25.0)	0	1/7 (14.3)
Primary reason for not completing the study					
Lost to follow-up	0	0	2/8 (25.0)	0	1/7 (14.3)

Conduct of the study

- Protocol amendments

The original study protocol was dated 12-Dec-2013 and there have been 3 protocol amendments that were detailed by the MAH.

- Protocol deviations

No major protocol deviations were reported for subjects in Cohorts 1, 2, 3b or 4. One subject in Cohort 3 had a major protocol deviation of not having been off vancomycin for more than 24 hours before the first dose of oritavancin on Day 1 of the study.

*Baseline characteristics***Table 2: Subject Demographics**

	15 mg/kg				20 mg/kg
n (%)	Cohort 1 12 to <18 years N=8	Cohort 2 6 to <12 years N=8	Cohort 3 2 to <6 years N=8	Cohort 4 3 months to <2 years N=7	Cohort 3b 2 to <6 years N=7
Age (months)					
N Mean (SD) Median Q1, Q3 Min, Max	8 189.5 (17.92) 192.0 187.0, 198.0 150, 212	8 114.9 (18.95) 111.0 99.0, 134.5 91, 139	8 32.0 (6.09) 32.0 26.5, 37.0 25, 40	7 14.6 (6.60) 14.0 9.0, 21.0 5, 22	7 48.6 (12.71) 47.0 35.0, 61.0 34, 66
Sex					
Male Female	4 (50.0) 4 (50.0)	2 (25.0) 6 (75.0)	4 (50.0) 4 (50.0)	5 (71.4) 2 (28.6)	4 (57.1) 3 (42.9)
Race n (%)					
White Black or African American American Indian or Alaska Native	6 (75.0) 2 (25.0) 0	7 (87.5) 1 (12.5) 0	6 (75.0) 2 (25.0) 0	6 (85.7) 0 1 (83.3)	6 (85.7) 1 (14.3) 0
Ethnic group					

Hispanic or Latino Not Hispanic or Latino	2 (25.0) 6 (75.0)	3 (37.5) 5 (62.5)	4 (50.0) 4 (50.0)	2 (28.6) 5 (71.4)	5 (71.4) 2 (28.6)
Weight (kg)					
N Mean (SD) Median Q1, Q3 Min, Max	8 69.3 (31.22) 64.5 57.1, 70.7 30, 139	8 41.5 (13.93) 37.9 32.6, 52.2 24, 63	8 14.0 (2.39) 13.2 12.0, 16.1 12, 18	7 11.6 (2.44) 11.7 10.3, 13.6 8, 15	7 17.4 (3.15) 18.8 13.4, 20.3 13, 20
Height (cm)					
N Mean (SD) Median Q1, Q3 Min, Max	8 167.1 (15.28) 167.9 155.0, 176.5 146, 192	8 141.4 (13.63) 139.1 129.3, 153.2 125, 163	8 92.7 (9.27) 91.3 85.3, 101.9 81, 104	7 79.8 (8.57) 84.0 71.1, 87.0 66, 88	7 102.4 (5.86) 103.0 96.5, 105.4 94, 112
Body Mass Index (kg/m^2)					
N Mean (SD) Median Q1, Q3 Min, Max	8 23.9 (6.64) 22.5 21.6, 25.4 14, 38	8 20.3 (3.82) 19.5 17.7, 23.1 15, 27	8 16.3 (1.64) 16.7 14.9, 17.8 14, 18	7 18.1 (1.69) 17.8 17.0, 20.3 16, 20	7 16.5 (1.72) 16.7 15.2, 17.8 14, 19
BMI-for-age (z-score)					
N Mean (SD) Median Q1, Q3 Min, Max	8 0.564 (1.369) 0.628 0.275, 1.177 -2.25, 2.60	8 1.015 (0.879) 1.059 0.301, 1.850 -0.33, 2.03	8 -0.028 (1.310) 0.237 -0.801, 0.984 -2.53, 1.47	7 1.167 (1.051) 0.547 0.400, 2.118 0.22, 2.95	7 0.465 (1.488) 0.710 -0.815, 1.609 -2.17, 2.17
Source: Section 14, Table 2.1					

Most subjects in Cohorts 1-3 had a single infection at baseline, and most subjects in Cohort 3b, and Cohort 4 had two infections at baseline. Two subjects in Cohort 3, one subject in Cohort 4 and one subject in Cohort 3b) had an MRSA infection.

Overall, the most frequent infections at baseline were pneumonia (including lobar pneumonia), appendicitis perforated, cellulitis, abscess, arthritis bacterial, bacteraemia, and sepsis.

- Primary endpoint – Interim analysis (Cohorts 1 to 4)

The target exposure range (AUC from baseline to 72 hours) in paediatric subjects was defined based on the PK analysis from the two pivotal Phase 3 studies in adults with ABSSSI (SOLO I and SOLO II):

Exposure Parameter	Adult Mean Coefficient of Variation (CV%)	Targeted Range in Pediatric Subjects
AUC_{0-72} (µg•h/mL)	1530 (36.9)	965-2095

For Cohorts 1 (12 to <18 years) and 2 (6 to <12 years) the single 15 mg/kg dose resulted in mean values of AUC_{0-72} that were within the lower limit of the target range (965 µg•h/mL) and 20% above the upper limit of the target range (2514 µg•h/mL). For Cohort 3 (2 to <6 years), the mean AUC_{0-72} of 1300 µg•h/mL was within the target range. However, one of the eight subjects of this cohort failed to meet the AUC_{0-72} target and one subject had an AUC_{0-72} value very close the lower limit of the target range. After reviewing these data, the Sponsor and the DSMB elected to amend the protocol to enrol additional subjects in this age group to receive a weight-based oritavancin dose of 20 mg/kg (Cohort

3b), with the expectation that this dose increase would achieve the target exposures. The mean AUC_{0-72} of Cohort 3b fell within the target range. However, in this cohort four subjects discontinued study drug infusion early due to the AE "red man syndrome" (see safety section for more details). AUC_{0-72} for the three subjects that completed oritavancin administration was increased compared to Cohort 3, however the mean value of 2170 µg•h/mL was above the target range, and two of the three subjects had exposures above the upper limit. Two of four subjects who discontinued the study drug early met the AUC_{0-72} and two did not.

In Cohort 4 (3 months to <2 years) the mean AUC_{0-72} fell within the target range and the AUC_{0-72} target was met for those subjects who received the complete dose of oritavancin. In this cohort, one subject discontinued study drug due to the adverse event "red man syndrome".

Mean AUC_{0-inf} ranged from 1641 µg•h/mL in Cohort 3 to 3161 µg•h/mL in Cohort 1 (Table 3); in adults mean AUC_{0-inf} was 2800 µg/ml.

Table 3: Summary of the derived PK parameter (PK population)

	15 mg/kg				20 mg/kg
	Cohort 1 12 to <18 years N=8	**Cohort 2 6 to <12 years N=8**	**Cohort 3 2 to <6 years N=8**	**Cohort 4 3 months to <2 years N=7**	**Cohort 3b 2 to <6 years N=7**
Cmax (µg)					
N	8	8	8	7	6
Mean (SD)	126.2 (20.9)	132.5 (34.6)	85.7 (16.2)	95.8 (27.8)	100 (31.3)
Median	130.1	122.9	86.5	96.4	99.6
Q1, Q3	120.7,139.7	115.7,148	81.6,87.3	80.1,114.2	74.8,120.7
Min, Max	88.7,148.2	81.8,195.9	64,118.6	54.3,131.4	63.8,145.4
Geometric mean	124.5	128.6	84.4	92.0	95.8
%CV	16.6	26.1	18.9	29.1	31.4
AUC0-72 (h·µg/mL)					
N	8	8	8	7	7
Mean (SD)	2205.4 (399.4)	2195 (829.5)	1304.8 (300.1)	1487.6 (540.4)	1546.7 (619.3)
Median	2290.7	2059.0	1422.7	1489.4	1688.6
Q1, Q3	1944.8, 2520.2	1823.5, 2276.5	1077.1, 1493.1	1232, 1802.8	984.6, 1997.1
Min, Max	1634.6, 2626.1	1212.3, 4047	831.4, 1673.5	664.2, 2190.2	837, 2337.7
Geometric mean	2172.0	2080.8	1271.4	1392.1	1433.1
%CV	18.1	37.8	23.0	36.3	40.0
AUC0-inf (h·µg/mL)					
N	8	8	8	7	7
Mean (SD)	3160.8 (542.8)	2826 (1072.8)	1640.7 (457.1)	1824.9 (697.8)	1945.4 (771)
Median	3243.1	2674.3	1839.7	1798.8	2146.8
Q1, Q3	2788.8, 3636.3	2296.3, 2934.9	1246.7, 2004.2	1451.7, 2182.3	1244.8, 2445.8
Min, Max	2383.3, 2626.1	1670.8, 4047	912, 1673.5	842.3, 2190.2	1065.5, 2337.7
Geometric mean	3118.4	2682.7	1576.6	1701.7	1807.1
%CV	17.2	38.0	27.9	38.2	39.6

%CV = coefficient of variation; AUC_{0-72} = area under the plasma concentration-time curve, from baseline to 72 hours post-dose; $AUC_{0-\infty}$ = area under the plasma concentration-time curve, total drug exposure over time; C_{max} = maximum plasma concentration; max = maximum; min = minimum; PK = pharmacokinetic; Q1 = first quartile (0.25); Q3 = third quartile (0.75); SD = standard deviation.
Based on exposure data from clinical studies in adult populations, the target range for AUC_{0-72} identified for the pediatric population in this study was 965 to 2095 µg•h/mL.

The AUC/MIC ratio of oritavancin has been shown to correlate best with efficacy. Thus, AUC was chosen as primary endpoint to extrapolate efficacy. In Cohorts 1 and 2 mean AUC_{0-72} was higher than the defined upper limit, in Cohort 3 and 4 AUC_{0-72} was considerably lower but still within the predefined limits with the 15 mg/kg dose. With a higher dose of 20 mg/kg the number of AEs increased and 4 out of 7 subjects in Cohort 3b discontinued study drug infusion due to red man syndrome. Thus, the 20 mg/kg dose has not been further evaluated for the paediatric population. Based on the data of study TMC-ORI-11-01 and the PopPK model (described below) a single 15 mg/kg dose is applied for treatment of children >3 months of age and older with ABSSSI. From the PK point of view, this is generally considered acceptable.

- Secondary endpoints

Mean C_{max} was lower in all cohorts (range: 85.7-132.5 µg/ml; Table 3) compared to mean C_{max} in adults in the pivotal Phase 3 studies (138 µg/ml).

Summary statistics of primary and secondary PK parameters in adults and in children (overall and by cohort). In adults, half-life value corresponds to t1/2γ, whereas Vss and clearance values are derived with the PopPK model.

	Adults	Children (all cohorts)	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 3b
N	297	38	8	8	8	7	7
t1/2 (h)							
Median (IQR) Mean (SD) CV (%) Min – Max	242 (40) 244.6 (36.41) 14.88 139.0 – 435.0	162.95 (50.04) 173.2 (78.92) 45.55 86.67 - 576.0	180.56 (27.02) 183.7 (31.30) 17.03 145.1 – 230.3	191.71 (79.9) 237.1 (143.1) 60.35 128.4 – 576.0	125.41 (63.35) 133.9 (41.52) 31.00 86.67 - 197.9	143.8 (28.39) 158.2 (43.59) 27.55 107.6 – 241.1	142.25 (30.06) 148.1 (28.34) 19.13 106.4 – 194.3
Vss (L/kg)							
Median (IQR) Mean (SD) CV (%) Min – Max	1.14 (0.68) 1.318 (0.883) 67.01 0.159 – 8.945	0.508 (0.070) 0.509 (0.067) 13.16 0.382 – 0.739	0.44 (0.04) 0.46 (0.06) 13.04 0.38 - 0.59	0.475 (0.057) 0.49 (0.105) 21.42 0.39 – 0.73	0.55 (0.04) 0.55 (0.048) 8.7 0.47 – 0.61	0.484 (0.037) 0.50 (0.032) 6.4 0.47 – 0.56	0.53 (0.03) 0.53 (0.025) 4.7 0.507 – 0.575
CL (L/h/kg)							
Median (IQR) Mean (SD) CV (%) Min – Max	0.005 (0.002) 0.006 (0.002) 33.33 0.001 - 0.019	0.0069 (0.0032) 0.007 (0.002) 28.57 0.002 – 0.015	0.003 (0.001) 0.004 (0.0007) 16.27 0.003 – 0.005	0.005 (0.001) 0.005 (0.001) 20 0.002 – 0.008	0.007 (0.004) 0.009 (0.003) 33.33 0.007 – 0.015	0.007 (0.002) 0.007 (0.002) 28.5 0.005 – 0.012	0.007 (0.001) 0.007 (0.001) 14.28 0.006 – 0.009

IQR: inter-quartile range, SD: standard deviation, CV: coefficient of variation, Min: minimum, Max: maximum, t1/2: terminal elimination half-life, Vss: volume of distribution at steady state, CL: clearance.

The secondary PK parameters are mostly comparable between cohorts. Half-life of oritavancin is about 1.5-fold higher in adults compared to children (mean value all cohorts).

Population PK Analysis

The previously developed popPK model for adults was used to describe paediatric data of the ORKIDS study. Parameters were re-estimated using the full dataset of n=297 adults and n=38 paediatric patients of four different age cohorts (3 months to <18 years).

The data available from ORKIDS study (cut-off date 1st December 2020) were prepared using R. 38 patients, who contributed to 203 observations, were included in the analysis. BQL values (i.e. <0.5 µg/mL) were flagged in the dataset, such that the algorithm for population analysis considered them as normally distributed random values between negative infinity and the limit of quantification (Beal M3 method).

Assumptions on the appropriate compartment numbers were derived by plotting the time courses of log-transformed concentrations, and from previous oritavancin PK analysis documented in the ICPD report n. 00247-1. A three-compartment model with a zero-order intravenous infusion and first-order elimination was therefore tested for both adult and paediatric populations.

Allometric scaling was used to describe the covariate model linking body size measures to clearances and volumes. In addition to total body weight (BW), lean body mass (LBM) was also explored as potential covariate. No further covariates (e.g. age, BSA) were tested given their high collinearity. The impact of renal function on oritavancin elimination was not tested given its negligible role in oritavancin

excretion. This was also confirmed by the results of oritavancin popPK analysis in adults, where creatinine clearance was not found as a significant covariate. For the tested covariates BW and LBM a power model was implemented to describe the effects of size on all model parameters, via allometric scaling.

LBM was determined using Peters formula in children and Boer formula in adults, as follows:

- LBM (kg) = 3.8*(0.0215*WEIGHT(kg)^0.6469*HEIGHT(cm)^0.7236), in children

- LBM (kg) = 0.407*WEIGHT(kg) + 0.267*HEIGHT(cm) - 19.2, in male adults

- LBM (kg) = 0.252*WEIGHT(kg) + 0.473*HEIGHT(cm) - 48.3, in female adults.

Using the parameter estimates obtained from the final model, a series of simulation scenarios were implemented to assess the suitability of the 15 mg/kg dose for the paediatric population along with the predicted probability of target attainment across different age groups.

Population PK analyses were performed in Monolix, version 2019R1, whereas the application Sycomore, version 2019R1, was used for a visual and interactive exploration of the tested models. Dataset preparation, as well as model simulations, were performed in R.

Oritavancin plasma concentrations over time are presented on a semi-log scale as spaghetti-plots, by cohort (**Figure *1***). Oritavancin plasma concentrations were obtained after a single oritavancin dose of 15 mg/kg or 20 mg/kg, infused intravenously over 3 hours. Data demographics are summarised in **Table *4***.

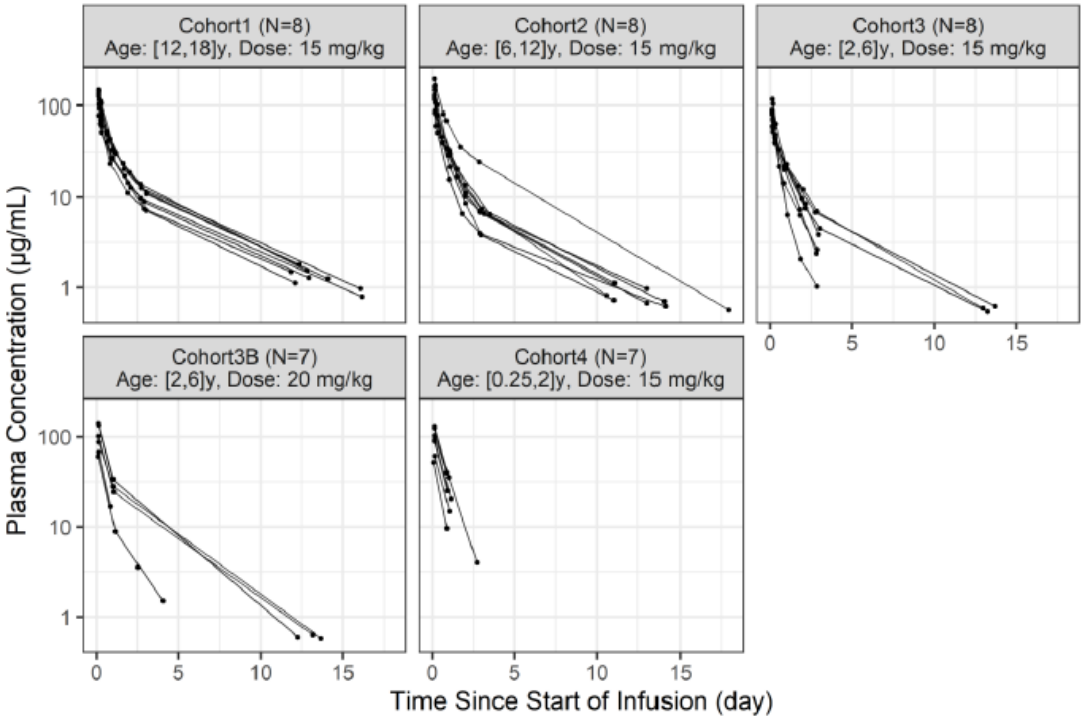


Figure 1: Semi-log spaghetti plots of oritavancin plasma concentration versus time since start of infusion, in children enrolled in ORKIDS study. Plots are displayed by treatment group.

Table 4: Summary of demographic characteristics of patients in ORKIDS study.

Cohort	N	age (y) – mean (min-max)	weight (kg) – mean (min-max)	height (cm) – mean (min-max)	LBM (kg) – mean (min-max)
1	8	15.8 (12.5,17.7)	69.3 (30.3,139.4)	167.1 (146,192)	51.2 (27.3,89.4)
2	8	9.6 (7.6,11.7)	41.5 (23.7,63.4)	141.3 (125.3,162.5)	32.7 (20.9,45.9)
3	8	2.7 (2.1,3.4)	14 (11.5,17.8)	92.7 (80.5,104)	11.9 (9.5,14.7)
3b	7	4.1 (2.9,5.5)	17.4 (12.7,20.4)	102.4 (94,111.8)	14.8 (11.5,17.4)
4	7	1.2 (0.4,1.8)	11.6 (7.9,15.4)	79.8 (66,87.5)	9.5 (6.4,12.1)

LBM: lean body mass

A popPK model was developed for oritavancin PK data based on a previous model (Table 5, Figure 2) collected from an adult population of 297 subjects. The best structural popPK model was a three-compartment model with zero-order infusion and fist-order elimination. The model was parameterized using total clearance (CL), volume of distribution of the central compartment (V1), distributional clearances and volume of distribution of the peripheral compartments (Q2,Q3 and V2,V3, respectively). CL, V1, and Q2 were modelled as correlated parameters. IIV was estimated for all PK parameters, using an exponential model. Lastly, the residual error model included a single proportional error term.

Covariate analysis identified LBM as a better descriptor of IIV compared to BW, for all model parameters. Covariate relationships between LBM and model parameters were implemented via power functions describing allometric scaling.

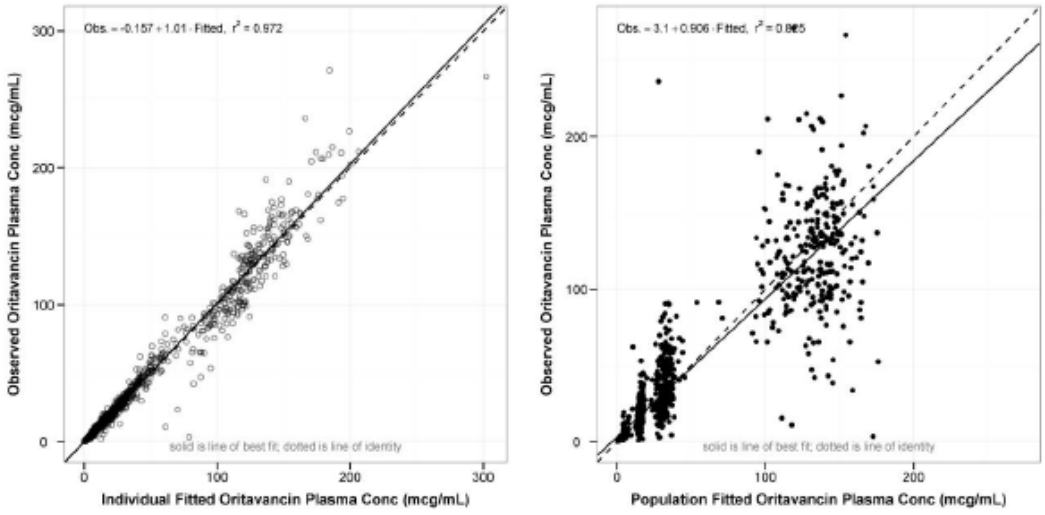
Population parameter estimates are listed in Table 6, GOF plots showed the ability of the final model to describe the observed concentration-time data in Figure 3.

Table 5: Previous adult population PK model using pooled data from SOLO I and SOLO II — Parameter estimates and standard errors

Parameter	Population mean		Magnitude of IIV (%CV)	
	Final estimate	%SEM	Final estimate	%SEM
CL (L/h)	0.445	—	27.2	21.6
Vc (L)	5.79	—	34.3	24.5
Q2 (L/h)	0.469	3.68	50.7	15.7
V2 (L)	75.5	5.63	48.3	14.5
Q3 (L/h)	0.666	4.78	87.2	22.9
V3 (L)	6.29	5.61	62.4	15.7
Vc-AGE Coefficient (L)	5.54	3.98	—	—
Vc-AGE Power	-0.641	11.0	—	—
CL-HTCM Coefficient (L/h)	0.446	2.57	—	—
CL-HTCM Power	0.695	84.8	—	—
SD_{in}	0.22	—	—	—
SD_{sl}	0.182	3.82	—	—
Minimum value of the objective function = 2636				

Abbreviations:

CL = Total clearance, Vc = Volume of distribution of the central compartment, Q2, Q3 = Distributional clearances, V2, V3 = Volume of distribution of the peripheral compartments, AGE = Patient age in years, HTCM = Patient height in cm, SD_{in} = Intercept (additive) term for residual variability model for plasma concentrations, SD_{sl} = Slope (proportional) term for residual variability model, %SEM = Standard error of the mean (percent standard error of the mean), IIV = Interindividual variability, %CV = Coefficient of variation (percent coefficient of variation)



Abbreviations: Conc=Concentration, Obs. = Observed, r^2 = Coefficient of determination (r-squared)

Figure 2: Goodness-of-fit plots for the previous adult population PK model — Individual and population fitted concentrations

Table 6: Values of population parameter estimates for the final popPK model fitted to adult data

Parameter	Fixed effects			Random effects			
	Estimate	RSE (%) s.a.	RSE (%) bootstrap	Standard deviation of the random effect	RSE (%) s.a.	RSE (%) bootstrap	Shrinkage (%)
CL (L/h)	0.509	1.59	1.50	0.236	4.64	7.07	-6.7
V1 (L)	8.01	3.11	3.90	0.183	14.1	20.9	0.13
Q2 (L/h)	0.479	3.67	3.46	0.583	4.6	5.90	-6.73
V2 (L)	152	5.46	7.34	0.455	8.51	12.7	-4.21
Q3 (L/h)	0.867	9.47	9.61	0.606	12.9	50.1	3.47
V3 (L)	10.8	3.32	6.05	0.151	23.7	37.9	6.44
Error model parameters							
Parameter	Estimate	RSE (%) s.a.	RSE (%) bootstrap				
b	0.244	2.97	3.99				
Correlations							
Parameter	Estimate	RSE (%) s.a.	RSE (%) bootstrap				
V1 – CL	0.50	20.7	31.3				
V1 – Q2	0.46	23.6	35.05				
Q2 – CL	0.99	0.05	0.03				

CL: clearance, V1: central volume, Q1: inter-compartmental clearance 1, V2: peripheral volume 2, Q2: inter-compartmental clearance 2, V3: peripheral volume 3, RSE: relative standard error, s.a.: stochastic approximation. RSE (%) bootsrap was calculated via bootstrapping (N=500). Shrinkage was calculated as $\eta = 1 - Var(\hat{\eta}) \Big/ \hat{\omega}^2$ $\eta = 1 - Var(\hat{\eta}) \Big/ \hat{\omega}^2$, where $Var(\hat{\eta}_i)$ is the empirical variance of the estimated random effects $\hat{\eta}_i$.

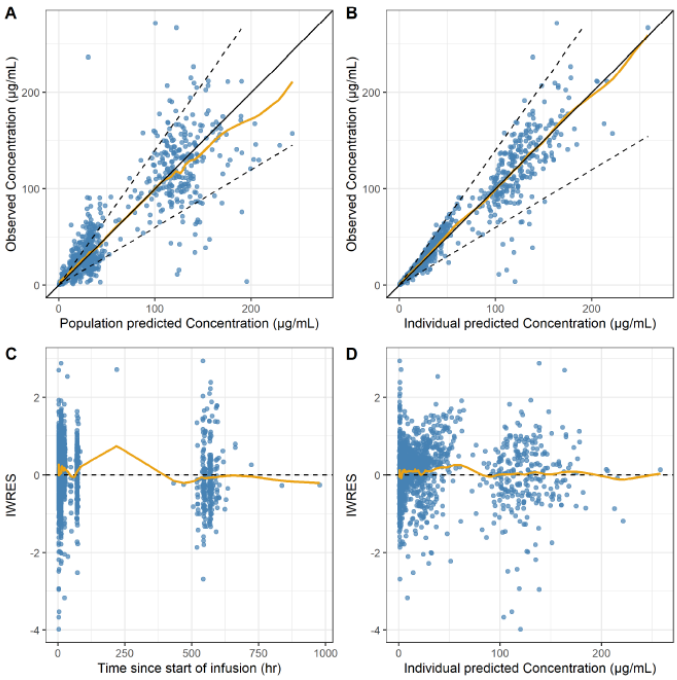


Figure 3: Goodness of fit plots for the final popPK model (adult population)

The same structural popPK model (three-compartment model with zero-order infusion and first order elimination) used for adults was adopted for the paediatric population. As for adult data, IIV was estimated using an exponential model for all PK parameters, and the residual error model included a single proportional error term. Given the sparse sampling scheme in the ORKIDS study, only correlation between CL and V1 could be identified.

Allometric principles were assumed as the only relevant factors. In addition to BW, also LBM was evaluated as an additional measure of body size. This analysis compared LBM as a descriptor of IIV compared to BW. Correlations between random effects and other covariates are showed in Figure 7.

Population parameters for paediatric data is reported in Table 7, and confidence intervals displayed in Figure 4. GOF plots showed the ability of the final model to describe the observed concentration-time data in Figure 5, the pcVPC is depicted in Figure 6.

Table 7: Values of population parameter estimates for the final popPK model fitted to paediatric data from ORKIDS study

Parameter	Fixed effects			Random effects			
	Estimate	RSE (%) s.a.	RSE (%) bootstrap	Standard deviation of the random effect	RSE (%)	RSE (%) bootstrap	Shrinkage (%)
CL (L/h)	0.405	4.54	4.17	0.264	12.2	15.9	-1.73
V1 (L)	9.05	6.25	6.76	0.241	17.7	27.6	1.92
Q2 (L/h)	0.111	11.9	16.59	0.475	22.2	29.1	-3.06
V2 (L)	26.6	18.6	18.62	0.31	32.3	48.1	0.99
Q3 (L/h)	0.724	19.8	26.38	0.559	26.3	28.0	-9.38
V3 (L)	7.29	8.95	9.02	0.218	36.8	38.6	-1.16
Error model parameters							
Parameter	Estimate	RSE (%) s.a.	RSE (%) bootstrap				
b	0.081	9.74	9.8				
Correlations							
Parameter	Estimate	RSE (%) s.a.	RSE (%) bootstrap				
V1 - CL	0.734	15.4	19.2				

CL: clearance, V1: central volume, Q1: inter-compartmental clearance 1, V2: peripheral volume 2, Q2: inter-compartmental clearance 2, V3: peripheral volume 3, RSE: relative standard error, s.a.: stochastic approximation. RSE (%) bootsrap was calculated via bootstrapping (N=500). Shrinkage was calculated from the conditional distribution as $\eta = 1 - Var(\eta)/\omega^2$, where $Var(\eta_i)$ is the empirical variance of the estimated random effects η_i.

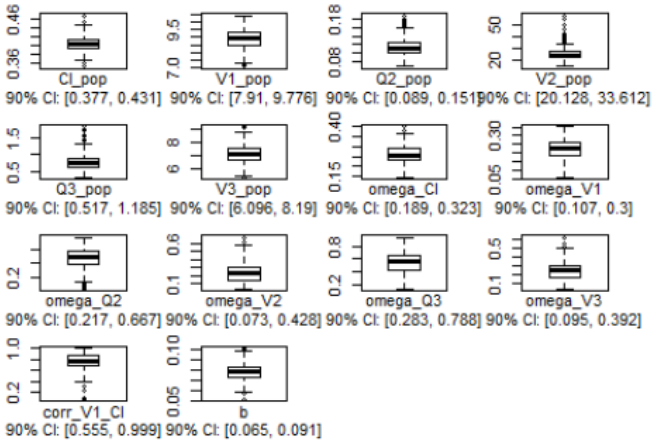


Figure 4: Distributions of the estimated population parameters for the final popPK model (paediatric population). Distributions were calculated from 500 bootstrap replicates.

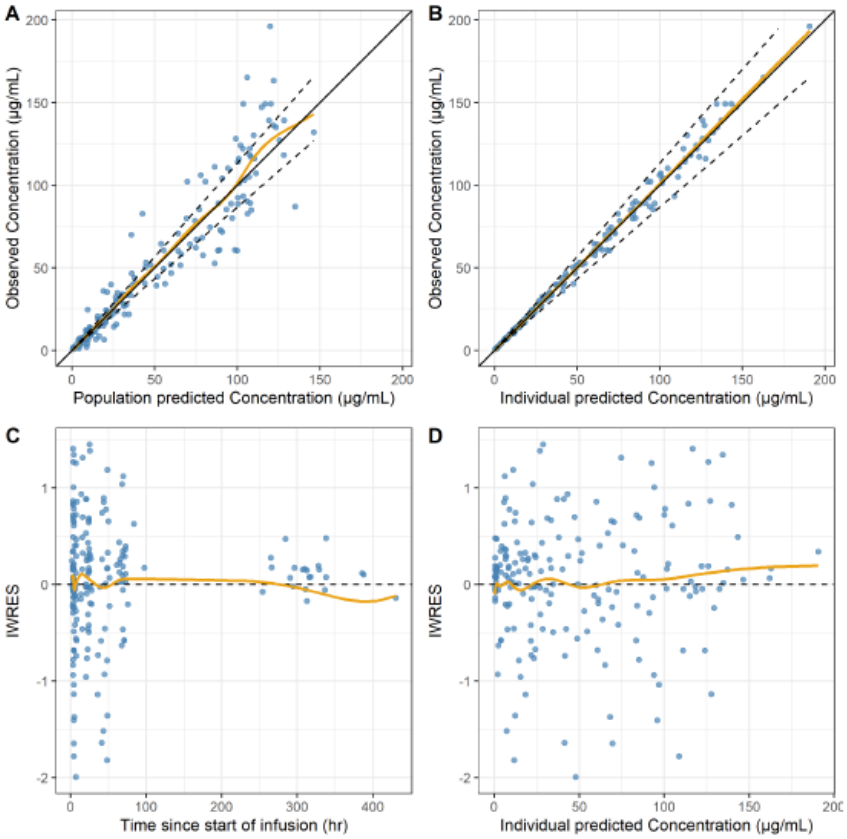


Figure 5: **Goodness of fit plots for the final popPK model (paediatric population)**

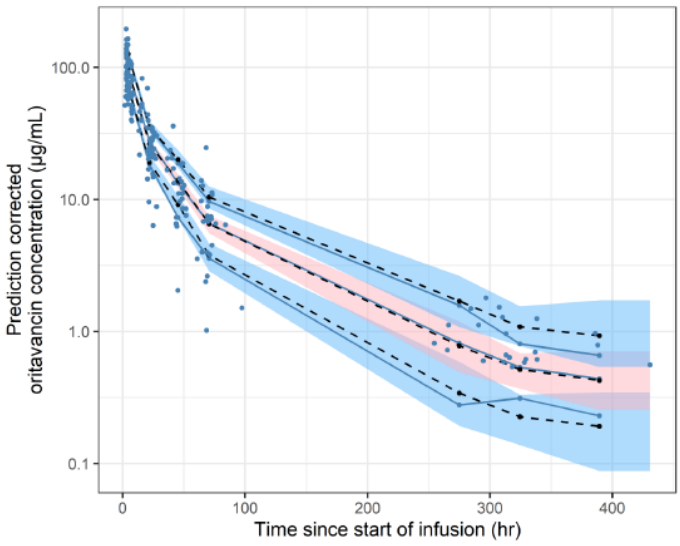


Figure 6: **Prediction-corrected VPCs generated with the final popPK model and paediatric data from ORKIDS study. Observed data (blue circles), their 5th, 50th, and 95th empirical percentiles (solid blue lines) are compared with the 5th, 50th, and 95th percentiles of predictions (dotted black lines) and corresponding 90% prediction intervals (pink area for the median, blue areas for 5th and 95th percentiles).**

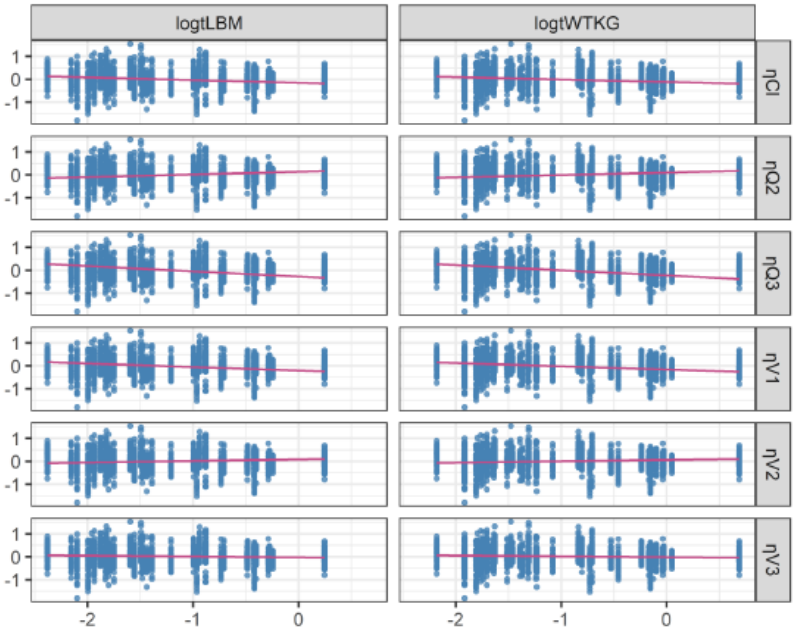


Figure 7: **Scatter plots of random effects (η) associated with model parameters versus log-transformed body weight and log-transformed lean body mass values (log(WTKG/70), and log(LBM/70), respectively). Regression lines are displayed in pink.**

Simulations

A virtual population of 10000 paediatric subjects (aged 0 - <18 years) was created to perform simulations. Six age groups (12-18 y, 6-12 y, 2-6 y, 3 m-2 y, 14 d-3 m, and 0-14 d) of 2000 subjects each were created sampling age from random uniform distributions, and sex from random binomial distributions. Body weights and heights were generated based on the Center for Disease Control (CDC) growth charts.

Children and adults are expected to show similar response to treatment, if exposures over the 72-hour period are comparable across the two populations. Thus, the AUC_{0-72} target range for an effective treatment in children was set as 965-2095 µg•h/mL, which corresponds to the mean AUC_{0-72} ± 1 standard deviation obtained from adult Phase 3 studies. Simulations of oritavancin concentrations in the virtual paediatric population showed that the 15 mg/kg dose resulted in median AUC_{0-72} values within the target range for all age groups, including neonates (Figure 8, Figure 9) (blue boxplots). On the other hand, simulations of lower doses of 10 mg/kg in neonates revealed that this dose results in an AUC_{0-72} range which is considerably lower than the target exposure for a large proportion of subjects. In fact, the corresponding median AUC_{0-72} value fell below the therapeutic range, Figure 13, and the overall distribution of exposures in this group diverged from the reference AUC_{0-72} distribution in adults (Figure 10).

About 17% of all children had simulated exposures higher than the upper cut-off of the target range (2095 µg•h/mL), and 5% of all simulated children had exposures higher than 2514 µg•h/mL. These high exposure values corresponded mainly to children who received the 20 mg/kg dose, or subjects with values of LBM greater than 33 kg.

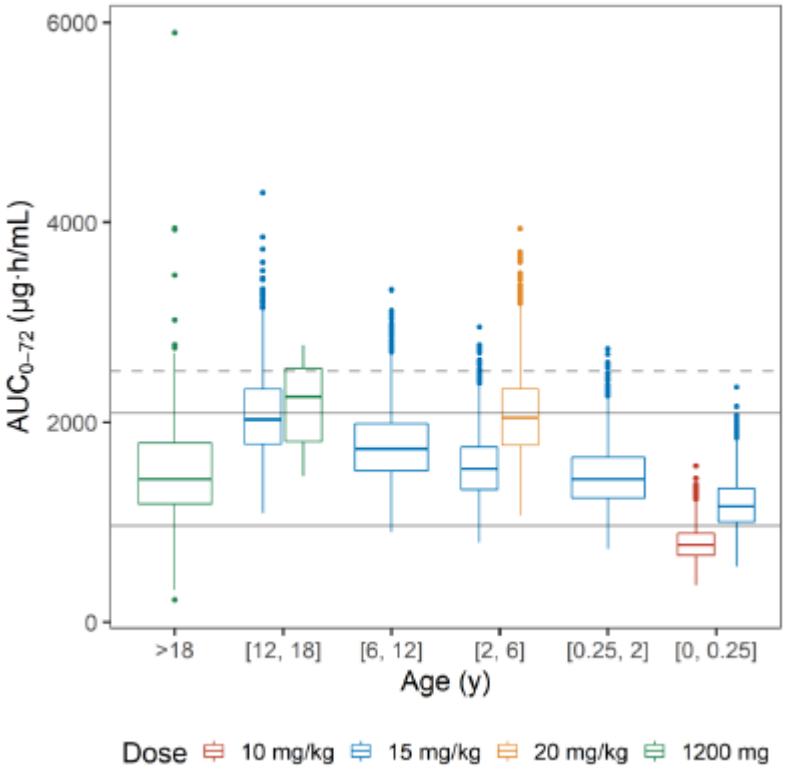


Figure 8: **Boxplots of oritavancin AUC_{0-72} for adult (green) and paediatric (blue, yellow, and red) patients. Exposures in adults were taken from simulations in the ICPD reports [4], [9], whereas exposures in children were simulated using the final paediatric popPK model and the virtual population of 10000 children (2000 for each age/dose group). Horizontal solid grey lines show the AUC_{0-72} target range (965-2095 µg•h/mL) for the paediatric population. Horizontal dotted grey line shows 20% above the upper cut-off of the target range.**

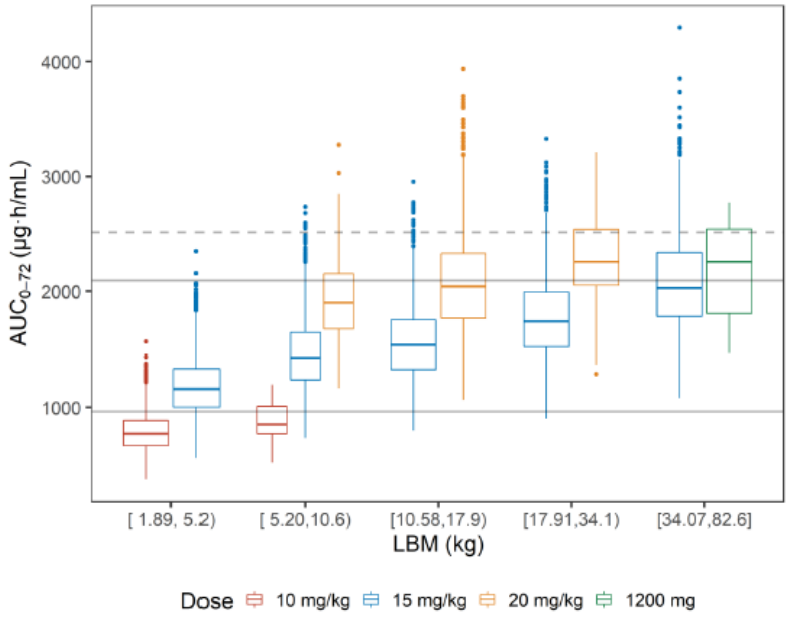


Figure 9: **Boxplots of oritavancin AUC_{0-72} for pediatric patients versus LBM groups. Exposures in children were simulated using the final paediatric popPK model and the virtual population of 10000 children (2000 for each age/dose group).**

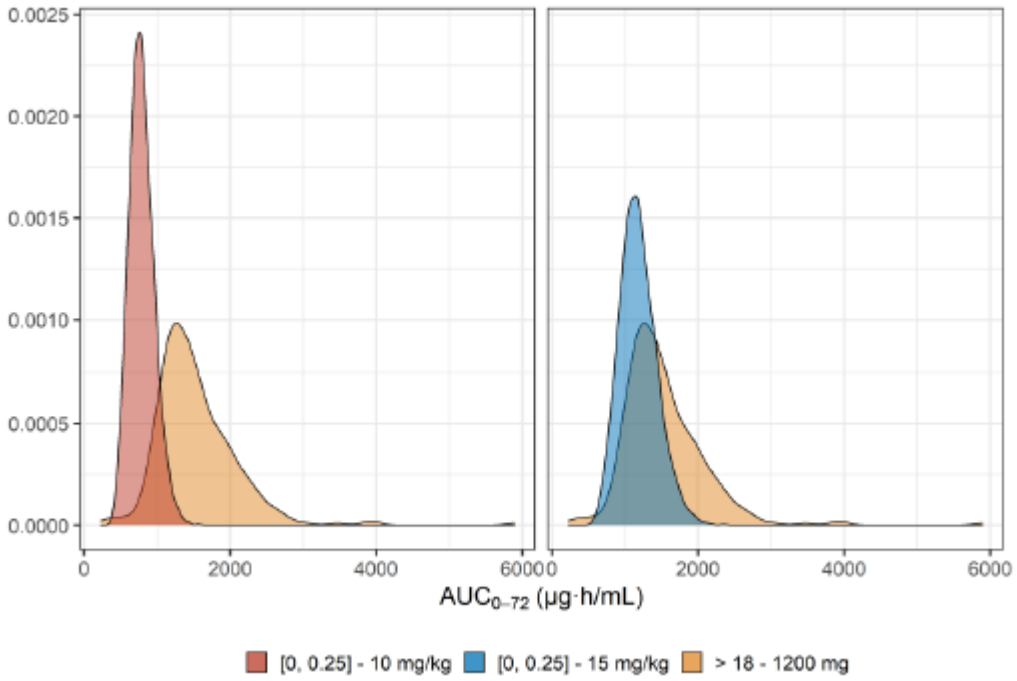


Figure 10: Comparison between simulated AUC_{0-72} in adults and neonates. Distribution of AUC0-72 reached in the adult population (1200 mg dose) is compared with those reached in neonates who received oritavancin 10 mg/kg (panel A) and neonates who received oritavancin 15 mg/kg (panel B).

2.3.1. Pharmacodynamics

Not applicable since no new PD data have been submitted.

2.3.2. PK/PD modelling

Post-hoc AUC_{0-72} estimates were derived to obtain individual AUC_{0-72}/MIC ratios. AUC_{0-72}/MIC ratio greater than the preclinical PK-PD target value (3941 and 4581 for net bacterial stasis and 1-$\log_{10}$ CFU reduction, respectively) was defined as the desired therapeutic target, and used for the calculation of the probability of target attainment.

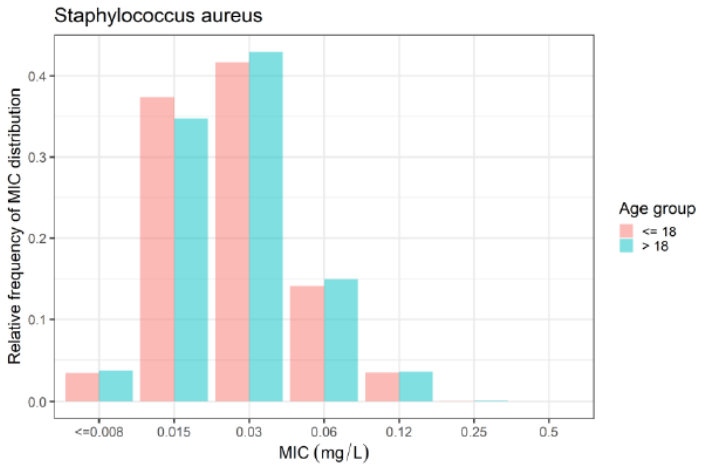


Figure 11: Barplots of the MIC distribution for oritavancin against *S. aureus*, by age groups. Source data: surveillance data of clinical isolates from medical centres in the US and Europe (2008-2019)

MIC distributions displayed in Figure 11 show the comparison in the susceptibility distribution of the pathogen between adults and children. The combined distribution of adult and paediatric isolates was used for the analysis. The probability of target attainment (PTA) in the paediatric population was estimated using the $AUC_{0\text{-}72}$ values for simulated paediatric patients in combination with the non-clinical $AUC_{0\text{-}72}$/MIC ratio targets for efficacy against *S. aureus*. Percent probabilities of PK-PD target attainment were assessed at individual fixed MIC values spanning the MIC distribution for oritavancin against *S. aureus* based on surveillance data collected from medical centres in the USA and Europe (2008-2019). Overall PTA was calculated as the weighted average of PTA values, using MIC distribution values as weights.

Oritavancin susceptibility breakpoint for *S. aureus* was set to 0.12 mg/L. High probabilities of target attainment for *S. aureus* were predicted in adults for the MIC value of 0.25 mg/L for net bacterial stasis (85%; Table 8, Table 9). PTA analysis in the virtual paediatric population showed that, at a MIC value of 0.12 mg/L, oritavancin 15 mg/kg dose resulted in percent probabilities of PK-PD target attainment equal to 100% for all age groups. Results associated with all tested doses and age groups are displayed in Table 8 and Figure 12 for net bacterial stasis, and in Table 9 and Figure 13 for 1-$\log_{10}$ CFU reduction from baseline. Noteworthy, in children aged 2-6 years both 15 mg/kg and 20 mg/kg doses resulted in PTA values above 97% for the 0.25 mg/L MIC value, supporting the recommendation of 15 mg/kg as target dose in this age group.

A dose of 10 mg/kg resulted in 131/2000 neonates (around 6.5%) not reaching the PK-PD target at 0.12 mg/L MIC value; Table 9 (1-$\log_{10}$ CFU reduction from baseline). A substantial drop in the PTA value was observed for the 10 mg/kg dose at the MIC value of 0.25 mg/L, compared with the 15 mg/kg dose in the same age group, and in older subjects. Specifically, PTA values dropped from 78% to 11.95% for net bacterial stasis, and from 52.8 to 2.95 for 1-$\log_{10}$ CFU reduction from baseline.

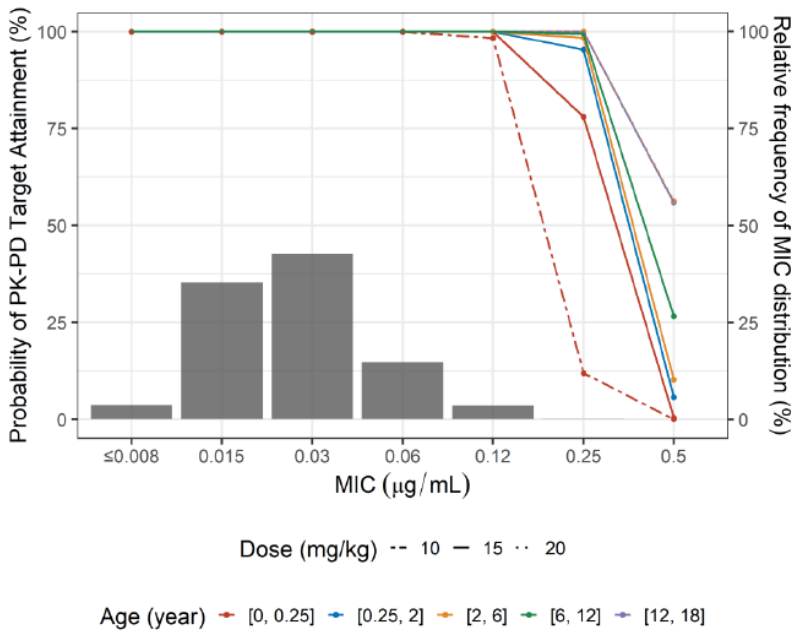


Figure 12: Percent probabilities of PK-PD target attainment by MIC for *S. aureus*, based on net bacterial stasis (lines). Bars overlaid on the figure show the oritavancin MIC distribution against *S. aureus* from surveillance of clinical isolates in the US and Europe

Table 8: Summary of oritavancin PTAs by MIC and overall PTA for *S. aureus* (for net bacterial stasis)

MIC mg/L	0 - 0.25 y 10 mg/kg	0 - 0.25 y 15 mg/kg	0.25 - 2 y 15 mg/kg	2 - 6 y 15 mg/kg	2 - 6 y 20 mg/kg	6 - 12 y 15 mg/kg	12 - 18 y 15 mg/kg	> 18 y 1200 mg
<=0.008	100	100	100	100	100	100	100	100
0.015	100	100	100	100	100	100	100	100
0.03	100	100	100	100	100	100	100	100
0.06	100	100	100	100	100	100	100	100
0.12	98.35	100	100	100	100	100	100	99.8
0.25	11.95	78	95.35	98.40	100	99.5	100	85.1
0.5	0.0	0.45	5.70	10.20	56.35	26.55	55.9	20
Overall	99.8	99.9	99.9	100	100	100	100	99.8

MIC: minimum inhibitory concentration (mg/L)

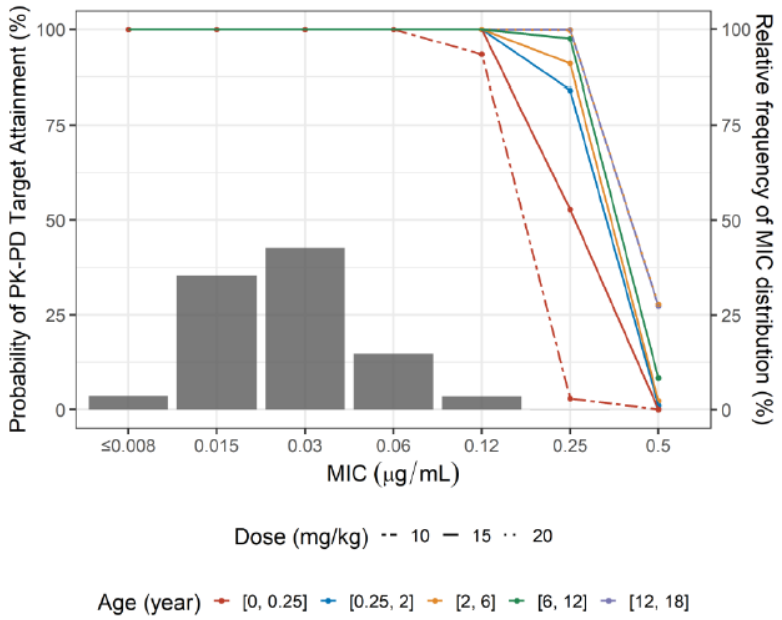


Figure 13: Percent probabilities of PK-PD target attainment by MIC for *S. aureus* based on 1- log_{10} CFU reduction from baseline (lines). Bars overlaid on the figure show the oritavancin MIC distribution against *S. aureus* from surveillance of clinical isolates in the US and Europe

Table 9: Summary of oritavancin PTAs by MIC and overall PTA for *S. aureus* (1-log_{10} CFU reduction from baseline)

MIC mg/L	0 - 0.25 y 10 mg/kg	0 - 0.25 y 15 mg/kg	0.25 - 2 y 15 mg/kg	2 - 6 y 15 mg/kg	2 - 6 y 20 mg/kg	6 - 12 y 15 mg/kg	12 - 18 y 15 mg/kg	> 18 y 1200 mg
<=0.008	100	100	100	100	100	100	100	100
0.015	100	100	100	100	100	100	100	100
0.03	100	100	100	100	100	100	100	100
0.06	100	100	100	100	100	100	100	100
0.12	93.45	100	100	100	100	100	100	99.4
0.25	2.95	52.8	84.1	91.05	99.75	97.55	99.9	74.8
0.5	0.0	0.05	1.1	2.25	27.75	8.30	27.35	10
Overall	99.7	99.9	99.9	99.9	100	99.9	100	99.6

MIC: minimum inhibitory concentration (mg/L)

2.3.3. Discussion on clinical pharmacology

The application relies on the concept of extrapolation of clinical efficacy based on comparable plasma exposures in children and adults. The acceptance of extrapolation is based on assumptions that the disease, mechanism of action and thus PK/PD are the same in paediatric patients as in adults and therefore the selected dose should achieve similar plasma exposures and probability of PK/PD target attainment (PTA) in children as in adults. AUC/MIC ratio of oritavancin has been shown to correlate best with efficacy. Thus, AUC after a single oritavancin dose was chosen as primary endpoint in study TMC-ORI-11-01. A target range of 965-2095 µg•h/ml for AUC0-72 had been defined based on pooled data of the two pivotal Phase 3 studies SOLO I and SOLO II. A popPK model developed in 2013 using adult data (n=297) from phase 3 clinical studies was updated with paediatric data (n=38) to predict

exposure of oritavancin in children from 3 months to <18 years of age. Allometric scaling was used to link body size measurements to paediatric clearances and volumes; this methodology is regarded as appropriate. The MAH also further clarified that as only sparse samples were collected in ORKIDS study, the MAH adopted an extrapolation approach (Cella et al., Clin Pharmacol Ther. 2010) based on leveraging extensive PK data from Phase 3 studies in adults and applying allometric principles. Despite limited paediatric data were available, this approach ensured the definition of an appropriate popPK model to characterise oritavancin pharmacokinetics in children. Adult and paediatric data were not pooled together because the merged dataset, comprising rich adult data (n = 297) and limited paediatric data (n = 38), would result not balanced in representing both populations.

The previous PK model in adults and the new model in adults have different covariates. In the "previous" PK model in adults, age was found statistically significant on central volume of distribution (V1) and height on clearance (CL) with estimated coefficients of -0.641 and 0.695, respectively. No other covariates were found statistically significant on the other parameters. However, in terms of allometry, age and height are not physiologically relevant, contrary to measures of body size, such as body weight, lean body mass (LBM), etc. In the "new " allometry-based adult model, all volumes and clearances have been allometrically scaled by LBM, fixing the exponents to 1 for volumes and 0.75 for clearances, as recommended by allometry theory.

Despite these differences, when the distributions of the individual model parameter values are compared, no significant differences can be observed between the "previous" and the "new" model for all parameters. More precisely, the distributions of model parameters of the new model are comparable with the distributions of model parameters from the previous model.

In the popPK model allometric scaling was used with fixed exponents for Cl and V (0.75 and 1, respectively), whereas allometry was not taken into account for dosing (15 mg/kg for all age cohorts). This lead to high exposures predicted in older patients (Cohort 1) and lower exposures in younger patients (Cohort 3, Cohort 4). Medians of the simulated exposures were simulated to be within the predefined range of 965-2095 hr*µg/mL.

Simulations showed decreasing exposures with decreasing age as a general trend, whereas observed exposure data revealed higher exposure in Cohort 4 compared to Cohort 3. This effect was not described by the popPK model and is therefore not apparent in simulations, which is revealing further insecurities of the model. One aspect regarding this issue could be that initially no maturation factor was included into the model although the indication included patients from an age of three months. The MAH has subsequently explained that variability and changes in oritavancin PK due to developmental growth were best described by LBM, which is a measure of body size and therefore could account for both modification in body composition and developmental changes, as maturation. It was then considered a new model in which both size and maturation would shape the clearance process presented. However, adding a maturation factor did not improve the predictions for the youngest age group due to limited data available for patients <2 years of age. The MAH assured to re-evaluate a maturation factor for modelling when data of Cohort 5 (age from birth to 3 months) will be available (recruitment is open).

The submitted PTA analysis for S. aureus are considered supportive that the chosen 15 mg/kg is effective in the paediatric population.

2.3.4. Conclusions on clinical pharmacology

Based on the submitted PK data described above, the 15 mg/kg dose for treatment of paediatric patients aged >3 months and older is generally considered acceptable to extrapolate efficacy.

2.4. Clinical efficacy

Not applicable since no new efficacy data have been submitted.

2.5. Clinical safety

Introduction

The original MAA included safety data from 3017 oritavancin-treated adults from 22 clinical trials, including data from 2149 adult patients from Phase 3 ABSSSI trials.

The primary safety analysis relies on pooled safety data from the two identical designed, pivotal Phase 3 studies in adults (SOLO I and SOLO II) in which 976 adults treated with oritavancin.

The most commonly reported adverse reactions (≥5%) were nausea, hypersensitivity reactions, infusion site reactions, and headache. The most commonly reported serious adverse reaction was cellulitis (1.1%). The most common reported reasons for discontinuation were cellulitis (0.4%) and osteomyelitis (0.3%).

Patient exposure

In study TMC-ORI-11-01 (described in the PK section) 38 paediatric patients aged 3 months to less than 18 years received a single dose of 15-20 mg/kg oritavancin (31 patients: 15 mg/kg, 7 patients: 20 mg/kg) and were included in the safety population. Patients were followed for 14 days and also contacted by phone at Day 60 to collect any AEs.

The mean total dose of oritavancin in the first three age cohorts was 926.3 mg (mean weight 69.3 kg), 622.5 mg (mean weight 41.5 kg), 210 mg (mean weight 14.0 kg), respectively. In Cohort 3b the mean total dose of oritavancin was 270.7 mg (mean weight 17.4 kg), and in Cohort 4 it was 155.2 mg (mean weight 11.6 kg).

Adverse events

In study TMC-ORI-11-01, considering all dosed patients (oritavancin doses 15 mg/kg or 20 mg/kg), 25 (65.8%) patients reported at least one AE; 14 (36.8%) reported at least one ADR; 5 (13.2%) experienced an AE leading to treatment discontinuation; and 5 (13.2%) experienced at least one serious adverse event (SAE).

Considering the patients who received oritavancin 15 mg/kg, 18 (58.1%) patients reported at least one AE; 9 (29.0%) reported at least one ADR; 1 (3.2%) experienced an AE leading to treatment discontinuation; and 4 (12.9%) experienced at least SAE (Table 7).

Table 10: AEs reported by age and dose cohort, overall by dose and overall in study TMC-ORI-11-01 and in the oritavancin arm of the Phase 3 studies SOLO I and II in adults (safety population).

	Trial TMC-0RI-11-01							Trials SOLO I & SOLO II
Oritavancin Single Dose	15 mg/kg					20 mg/kg	15 mg/kg or 20 mg/kg	1200mg
	Cohort 1	Cohort 2	Cohort 3	Cohort 4	All Cohorts	Cohort 3b	All Cohorts	SOLO pool
Age	12 to < 18 years	6 to < 12 years	2 to < 6 years	3 months to < 2 years	3 months to < 18 years	2 to < 6 years	3 months to < 18 years	Adults ≥ 18 years
	N = 8	N = 8	N = 8	N = 7	N = 31	N = 7	N = 38	N = 976
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of patients with any AE	4 (50.0)	5 (62.5)	5 (62.5)	4 (57.1)	18 (58.1)	7 (100.0)	25 (65.8)	540 (55.3)
Number of patients with study drug related[a] AE	2 (25.0)	3 (37.5)	3 (37.5)	1 (14.3)	9 (29.0)	5 (71.4)	14 (36.8)	217 (22.2)
Number of patients with any AE leading to study drug discontinuation	0	0	0	1 (14.3)	1 (3.2)	4 (57.1)	5 (13.2)	36 (3.7)
Number of patients with SAE	1 (12.5)	1 (12.5)	1 (12.5)	1 (14.3)	4 (12.9)	1 (14.3)	5 (13.2)	57 (5.8)
Number of patients with any AE leading to death	0	0	0	0	0	0	0	2 (0.2)

AE: adverse event; N: total number of patients in Cohort/s; n: number of patients with AE/SAE; SAE: serious adverse event
a Includes AEs considered by the Investigator as definitively related or possibly related to the study drug.
Source: Interim Clinical Study Report 2 TMC-0RI-11-01, Table 13; Original 2.7.4 Summary of Clinical Safety for Oritavancin from 04th February 2014, Table 6

Considering all dosed patients in study TMC-ORI-11-01 (oritavancin doses 15 mg/kg or 20 mg/kg), the ADRs reported in more than one patient were red man syndrome (5/38 [13.2%] patients), hepatic enzyme increased (2/38 [5.3%]) and vomiting (2/38 [5.3%]) (

Table 11).

Considering the patients who received oritavancin 15 mg/kg, the ADRs reported in more than one patient were hepatic enzyme increased (2/31 [6.5%]), and vomiting (2/31 [6.5%]) (

Table **11**).

Vomiting was also common in the adult population who received oritavancin in the SOLO pool, hepatic enzyme increased was reported by only 1 (0.1%) patient in the SOLO pool and no cases of red man syndrome were reported.

The majority of AEs were mild or moderate in severity.

Considering all dosed patients in study TMC-ORI-11-01 (oritavancin doses 15 mg/kg or 20 mg/kg), severe AEs occurred in 4 (10.5%) patients: headache (Cohort 2), red man syndrome (Cohort 3b), chest pain (Cohort 3b), and enterococcal endocarditis and diarrhoea (Cohort 3).

Considering the patients who received oritavancin 15 mg/kg, severe AEs occurred in 2 (6.5%) patients.

Table 11: All related AEs reported by age and dose cohort, overall by dose and overall in study TMC-ORI-11-01 and their comparison with frequencies in the the Phase 3 studies SOLO I and II in adults (safety population)

	Trial TMC-0RI-11-01							Trials SOLO I & SOLO II
Oritavancin Single Dose	15 mg/kg					20 mg/kg	15 mg/kg or 20 mg/kg	1200mg
	Cohort 1	Cohort 2	Cohort 3	Cohort 4	All Cohorts	Cohort 3b	All Cohorts	SOLO pool
Age	12 to < 18 years	6 to < 12 years	2 to < 6 years	3 months to < 2 years	3 months to < 18 years	2 to < 6 years	3 months to < 18 years	Adults ≥ 18 years
	N = 8	N = 8	N = 8	N = 7	N = 31	N = 7	N = 38	N = 976
AE by PT	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of Patients with any ADR	**2 (25.0)**	**3 (37.5)**	**3 (37.5)**	**1 (14.3)**	**9 (29.0)**	**5 (71.4)**	**14 (36.8)**	**217 (22.2)**
Skin and Subcutaneous tissue disorders	**0**	**0**	**0**	**1 (14.3)**	**1 (3.2)**	**5 (71.4)**	**6 (15.8)**	**50 (5.1)**
Red Man Syndrome	0	0	0	1 (14.3)	1 (3.2)	4 (57.1)	5 (13.2)	0
Rash	0	0	0	0	0	1 (14.3)	1 (2.6)	4 (0.4)
Investigations	**2 (25.0)**	**2 (25.0)**	**1 (12.5)**	**0**	**5 (16.1)**	**0**	**5 (13.2)**	**35 (3.6)**
Hepatic enzyme increased	2 (25.0)	0	0	0	2 (6.5)	0	2 (5.3)	1 (0.1)
AST increased	0	1 (12.5)	0	0	1 (3.2)	0	1 (2.6)	13 (1.3)
ECG QT prolonged	0	0	1 (12.5)	0	1 (3.2)	0	1 (2.6)	0
Liver function test abnormal	0	1 (12.5)	0	0	1 (3.2)	0	1 (2.6)	6 (0.6)
Gastrointestinal disorders	**0**	**1 (12.5)**	**1 (12.5)**	**0**	**2 (6.5)**	**0**	**2 (5.3)**	**84 (8.6)**
Vomiting	0	1 (12.5)	1 (12.5)	0	2 (6.5)	0	2 (5.3)	23 (2.4)
General disorders and administration site conditions	**0**	**0**	**1 (12.5)**	**0**	**1 (3.2)**	**0**	**1 (2.6)**	**59 (6.0)**
Pyrexia	0	0	1 (12.5)	0	1 (3.2)	0	1 (2.6)	4 (0.4)
Immune system disorders	**0**	**0**	**1 (12.5)**	**0**	**1 (3.2)**	**0**	**1 (2.6)**	**2 (0.2)**
Hypersensitivity	0	0	1 (12.5)	0	1 (3.2)	0	1 (2.6)	1 (0.1)
Infections and Infestations	**0**	**1 (12.5)**	**0**	**0**	**1 (3.2)**	**0**	**1 (2.6)**	**10 (0.1)**
Clostridioides difficile colitis	0	1 (12.5)	0	0	1 (3.2)	0	1 (2.6)	1 (0.1)
Nervous system disorders	**0**	**1 (12.5)**	**0**	**0**	**1 (3.2)**	**0**	**1 (2.6)**	**30 (3.1)**
Headache	0	1 (12.5)	0	0	1 (3.2)	0	1 (2.6)	23 (2.4)
Psychiatric disorders	**0**	**0**	**1 (12.5)**	**0**	**1 (3.2)**	**0**	**1 (2.6)**	**11 (1.1)**
Irritability	0	0	1 (12.5)	0	1 (3.2)	0	1 (2.6)	0

AE: adverse event; AST: aspartate aminotransferase; ECG: electrocardiogram; N: total number of patients in Cohort/s; n: number of patients with TEAE; PT: preferred term

a AEs reported in ≥ 1 patient in All Cohorts (including Cohort 3b) of Trial TMC-ORI-11-01 are highlighted in grey.

b There are differences in wording of this AE between trials (reported as swelling face in SOLO trials and as face oedema in Trial TMC-ORI-11-01).

Source: Interim Clinical Study Report 2 TMC-0RI-11-01, Table 16; Original 5.3.5.3 Integrated Summary of Safety for Oritavancin, Table 02.6.5.P4

Cases of red man syndrome:

• Study participant from Cohort 4 dosed at **15 mg/kg**, 22-month-old American Indian or Alaska Native male Hispanic or Latino with a diagnosis of appendicitis perforated with periappendiceal abscess treated non-operatively. The patient experienced the non-serious AE "red man syndrome" on Day 1 that lead to the study drug discontinuation. The AE was of mild severity and definitively related to the study drug. After 73 minutes of oritavancin infusion was discontinued as the subject was itching, fussy, red on face and ears. The event was treated with diphenhydramine and resolved 25 minutes later. The subject also experienced the SAE device occlusion (occlusion of peripherally inserted central device) on Day 2, the event was of mild intensity, unrelated and resolved after 2 days. Final dose received was 91.3 mg (5.93 mg/kg) at an infusion rate of 4.06 mL/kg/hour.

• Study participant from Cohort 3b dosed at **20 mg/kg**, a 2-year-old white male Hispanic or Latino with a diagnosis of device related infection (Broviac line); pathogens: *Staphylococcus aureus* (Gram positive). On Day 1 the subject experienced the non-serious AE "red man Syndrome". It was of mild severity, definitively related to the study drug, and led to study drug discontinuation. After 90 minutes oritavancin infusion it was discontinued as the subject presented red rash to face, ears and under chin. The event was treated with diphenhydramine and resolved 1 hour and 24 minutes later. The patient experienced also the following SAEs: pyrexia (start on Day 3), neutropenia (start on Day 50), pyrexia (start on Day 50), thrombophlebitis superficial (start on Day 55) and medical device complication (start on Day 62). All were reported as of mild intensity, unrelated to the study drug and recovered. Final dose received was 130 mg (9.7 mg/kg) at an infusion rate of 5.40 mL/kg/hour.

• Study participant from Cohort 3b dosed at **20 mg/kg**, a 5-year-old Black or African American female Hispanic or Latino, with a diagnosis of abscess of right external ear and mastoiditis; pathogens: Streptococcus Grp A (Gram positive) and Beta-haemolytic Streptococcus (Gram positive). On Day 1, the subject experienced the non-serious AE "red man syndrome". It was of severe intensity, definitively related to the study drug, and lead to study drug discontinuation. After 60 minutes of oritavancin infusion the subject developed some mild itching over body and scalp, at about 90 minutes of oritavancin infusion a mild rash began to develop at her neck and an urticarial lesion began to develop in a single location (approx. 4-6 cm proximal to the IV catheter tip). The sensation of itching of the scalp increased at this time. The infusion was permanently discontinued after 109 minutes due to Red man syndrome. The event was treated with Benadryl (diphenhydramine) and resolved 1 hour and 34 minutes later. The patient did not experience any other AE. Final dose received was 224.7 mg (12.0 mg/kg) at an infusion rate of 5.59 mL/kg/hour.

• Study participant from Cohort 3b dosed at **20 mg/kg**, a 3-year-old white male Hispanic or Latino, with a diagnosis of pneumonia; pathogens: Streptococcus species (Gram positive). On Day 1 the subject experienced the non-serious AE "red man syndrome". It was of moderate intensity, definitively related to the study drug, and lead to study drug discontinuation. After 133 minutes of oritavancin infusion the subject began to cry and developed some mild itching which started at his head and progressed down to his arms, hands, and torso. The infusion was permanently discontinued and the redness decreased significantly with just small erythematous patches under his eyes. The event was treated with Benadryl (diphenhydramine) and resolved within 1 hour and 30 minutes after the infusion was stopped. The patient did not experience any other AE. Final dose received was 252.0 mg (14.5 mg/kg) at an infusion rate of 5.44 mL/kg/hour.

• Study participant from Cohort 3b dosed at **20 mg/kg**, a 2-year-old white female with a diagnosis of left neck abscess and lymphadenitis; pathogens: *Staphylococcus aureus* (methicillin resistant) (Gram positive). On Day 1, the subject experienced the non-serious AE "red man syndrome". It was of moderate intensity, definitively related to the study drug, and lead to study drug discontinuation. After 73 minutes of oritavancin infusion the subject began to complain of itching which started on scalp and

progressed down to her forehead. The infusion was permanently discontinued and Benadryl (diphenhydramine) was administered. The redness began to decrease within 30 minutes. Subject continued to complain of scalp itching for another 30 minutes. All symptoms resolved 2 hours after the infusion was stopped. The patient did not experience any other AE. Final dose received was 101.8 mg (8.0 mg/kg) at an infusion rate of 5.49 mL/kg/hour.

Serious adverse event/deaths/other significant events

Deaths

There were no deaths reported in study TMC-ORI-11-01.

Serious adverse events (SAEs)

Five subjects, one in each age cohort, had SAEs. SAEs included small intestinal obstruction in Cohort 1, *C. difficile* colitis in Cohort 2, Enterococcal endocarditis in Cohort 3, Pyrexia, Neutropenia, Thrombophlebitis superficial, and Medical device complication in Cohort 3b (2 to <6 years), and Device occlusion in Cohort 4 (3 months to <2 years). Only the *C. difficile* colitis was assessed by the investigator as possibly related to oritavancin

SAEs reported in subjects dosed at 15 mg/kg were:

• Study participant from Cohort 1 dosed at 15mg/kg, a 15-year-old white male, Hispanic or Latino, with a polymicrobial (intra-abdominal) infection, experienced small intestinal obstruction on Day 1, the event was considered serious, of moderate severity, unrelated to the study drug and resolved after 15 days. The patient also had a non-serious AE, hepatic enzyme increased, that started on Day 8, the event was mild, possibly related, and recovered after 51 days.

• Study participant from Cohort 2 dosed at 15 mg/kg, a 9-year-old white female with community-acquired left lower lung pneumonia, experienced *Clostridioides difficile* colitis on Day 23, the event was considered serious, of mild severity, possibly related to the study drug, and resolved after 7 days. The patient had also AST increased (start on Day 5), viral upper respiratory tract infection (start on Day 11), and skin exfoliation (start on Day 11). All were non serious, of mild intensity and resolved. AST increase was possibly related to the study drug.

• Study participant from Cohort 3 dosed at 15 mg/kg, a 2-year-old white female Hispanic or Latino with bacteraemia (*Enterococcus faecalis* [Gram-positive] and *Pseudomonas aeruginosa* [Gram-negative]). On Day 25, the subject had severe enterococcal endocarditis that was reported as a serious adverse event, of severe intensity and unrelated to the study drug. The central line was removed and the treatment with ampicillin was initiated.

Enterococcal endocarditis was considered resolved with sequelae 28 days after.

• Study participant from Cohort 4 dosed at 15 mg/kg, a 22-month-old American Indian or Alaska Native male Hispanic or Latino with a diagnosis of appendicitis perforated with periappendiceal abscess treated non-operatively. The subject experienced the SAE device occlusion (occlusion of peripherally inserted central device) on Day 2, the event was of mild intensity, unrelated and resolved after 2 days. The patient experienced the nonserious AE red man syndrome on Day 1 that lead to the study drug discontinuation. The AE was of mild severity and definitively related to the study drug.

SAEs reported in the subject dosed at 20 mg/kg were:

• Study participant from Cohort 3b, a 2-year-old white male Hispanic or Latino with a diagnosis of device related infection (Broviac line); pathogens: *Staphylococcus aureus* (Gram positive), experienced the following SAEs: pyrexia (start on Day 3), neutropenia (start on Day 50), pyrexia (start on Day 50),

thrombophlebitis superficial (start on Day 55) and medical device complication (start on Day 62). All were reported as of mild intensity, unrelated to the study drug and recovered. The patient experienced the non-serious AE red man syndrome on Day 1 that lead to the study drug discontinuation. The AE was of mild severity and definitively related to the study drug.

Other significant adverse events

Five (13.2%) patients experienced the AE red man syndrome leading to study drug discontinuation; 4 in Cohort 3b (age 2 to < 6 years who received oritavancin 20 mg/kg) and 1 in Cohort 4 (age 3 months to < 2 years who received oritavancin 15 mg/kg). In all 5 cases the red man syndrome was reported as non-serious, definitively related to the study drug, and resolved after study drug discontinuation and treatment with diphenhydramine. Two cases were of mild intensity, two moderate and one severe (details described in section adverse events).

Adverse Events of Special Interest (AESI)

Hypersensitivity

There were no reports of serious hypersensitivity reactions including anaphylactic shock in study TMC-ORI-11-01.

Considering all patients, overall 10 (26.3%) had potentially hypersensitivity, of which 5 (13.8%) were red man syndrome and the rest of AEs affected one patient each. All cases of red man syndrome, hypersensitivity, and rash were considered as definitively related to the study drug.

Infusion-related reactions

Three AEs were identified (infusion site extravasation, vessel puncture site swelling, and thrombophlebitis superficial) that occurred to patient in Cohort 3b (dosed at 20 mg/kg). Thrombophlebitis superficial starting on D55 was reported as a SAE of mild intensity, unrelated to the study drug, and resolved after 8 days. Infusion site extravasation and vessel puncture site swelling starting on Day 43 and Day 62 respectively, were reported as non-serious AEs of mild intensity, unrelated to the study drug and resolved after 2 and 5 days, respectively.

Red man syndrome

Red man syndrome occurred in a greater number of patients who received oritavancin 20 mg/kg than in those who received oritavancin 15 mg/kg (4/7 [57.1%] vs 1/31 [3.2%], respectively).

Pseudomembranous colitis/*Clostridioides difficile* associated diarrhoea

Clostridioides difficile colitis occurred in 1 patient (Cohort 2, dosed at 15 mg/kg; see section SAEs for details).

Osteomyelitis

There were no reports of osteomyelitis in study TMC-ORI-11-01.

Nephrotoxicity/Increase in uric acid levels

Uric acid concentrations were not monitored during trial TMC-ORI-11-01, however, no AEs related to increased uric acid concentrations were observed.

Increase in transaminases

In study TMC-ORI-11-01, 5 patients experienced AEs related to transaminase increase (hepatic enzyme increased, AST increased, and liver function test abnormal). All of them occurred in the age

cohorts dosed at 15 mg/kg, none of them were serious, all were of mild intensity and in 4 cases were considered as related to the study drug:

• Study participant from Cohort 1, a 15-year-old white male, Hispanic or Latino, with a polymicrobial (intra-abdominal) infection, had an AE of hepatic enzyme increased starting on Day 8. The values of ALT and AST were within the normal range at Screening (16 U/L and 22 U/L, respectively) and on Day 3 (22 U/L and 30 U/L, respectively) that increased on Day 8 (66 U/L and 51 U/L, respectively), the peak value for ALT was reached on Day 15 (114 U/L >3 × ULN) and for AST on Day 36 (56 U/L < 1.5 × ULN). On Day 58 ALT and AST normalised (24 U/L and 28 U/L, respectively).

Concomitant medications immediately prior to the hepatic enzymes increase included acetaminophen 1000 mg IV as needed, ibuprofen 600 mg orally as needed, and erythromycin 200 mg IV once daily, and these are known to cause hepatotoxicity. The event was mild, considered possibly related to the study drug and recovered after 51 days. This patient had also an SAE of post-operative worsening of small intestinal obstruction due to adhesions.

• Study participant from Cohort 1, a 12 year old white female with pelvic abscess and peritonitis had an AE of hepatic enzyme increased starting on Day 3. The values of ALT and AST were within the normal range at Screening (28 U/L and 23 U/L, respectively), on Day 3 ALT increased (36 U/L) and AST was within the normal range (35 U/L). On Day 13, both peaked (49 U/L and 54 U/L, < 2 × ULN respectively); 155 after the study drug administration ALT was over the normal limit (39 U/L) and AST was within the normal range (37 U/L) and 169 days after the study drug administration ALT and AST were increased (38 U/L and 49 U/L, respectively). The adverse event was reported as non serious, of mild intensity, possibly related to the study drug and not resolved. The patient did not experience any other AE.

• Study participant from Cohort 2, a 9-year-old white female with community-acquired left lower lung pneumonia, had an AE of AST increase starting on day 5. The values of AST were within the normal range at Screening (43 U/L) and on Day 3 (39 U/L) and on Day 5 increased to 69 U/L (< 2 × ULN). By Day 15, AST was within the normal range (34 U/L). The event was non serious, of mild intensity, possibly related to the study drug and resolved. The patient also experienced the SAE *Clostridioides difficile* colitis on Day 23.

• Study participant from Cohort 2, an 11-year-old white male with bacterial arthritis of the right hip, had an AE of liver function test abnormal starting of Day 3. The values of ALT and AST were within the normal range at Screening (22 U/L and 28 U/L, respectively) and increased considerably on Day 3 (234 U/L and 307 U/L, > 5 × ULN respectively). The concomitant medications immediately prior to the elevation in ALT and AST included Valium 4 mg orally as needed for muscle spasm prophylaxis, cefazolin 1000 mg IV every 8 hours and cephalexin 250 mg orally every 6 hours for the septic arthritis that may have played a role in the event. ALT and AST decreased to 28 U/L and 29 U/L on Day 14, respectively. The event was non serious, of mild intensity, definitively related to the study drug and resolved. Total bilirubin concentrations remained below the ULN during the study (Screening: 12.0 µmol/L, Day 3: 13.7 µmol/L, and Day 15: 6.8 µmol/L). The patient did not experience any other AE.

• Study participant from Cohort 3, a 2-year-old white female, Hispanic or Latino, with bacteraemia, had an AE of hepatic enzyme increased starting on Day 18. The value of ALT was slightly increased at Screening (43 U/L) and AST was within the normal range (40 U/L), both were within the normal range on Day 3 (40 U/L and 28 U/L, respectively) and increased on Day 12 (42 U/L and 71 U/L, < 2 × ULN respectively). The AE was considered resolved 42 days after its onset, however, no further lab results were reported. The AE was not serious, of mild intensity, and unlikely related to the study drug. This patient also experienced the SAE on Day 25 and several other AEs.

<u>Vestibular toxicity/ototoxicity</u>

In study TMC-ORI-11-01, the only AE consistent with vestibular toxicity was dizziness in 1/38 (2.6%) patient (Cohort 3b) and there were no AEs related to ototoxicity. In addition, 2/38 (5.3%) patients had acute otitis media.

Haematologic effects (cytopenia)

Considering all patients, overall 4 (10.5%) had cytopenia related AEs, out of them 3 (7.9%) had anaemia, 2 (5.3%) had neutropenia which were considered unrelated to study drug. One case of neutropenia was reported as a SAE.

Considering all patients dosed at 15 mg/kg, overall 3 (9.7%) had cytopenia related AEs.

Laboratory findings

Haematology

In trial TMC-ORI-11-01, mean changes in haematology parameters from Baseline over time showed slight fluctuations, but these changes were similar across the paediatric cohorts and were not considered clinically significant.

Liver Function Tests

In study TMC-ORI-11-01, there was no evidence of liver toxicity with oritavancin in any of the cohorts. Mean changes from Baseline over time in LFTs were minimal and similar between the cohorts. Shifts in LFTs over time did not reveal any meaningful differences in any of the cohorts.

No patient met Hy's law criteria. Potentially clinically significant LFT abnormalities (i.e., ALT ≥ 3 × ULN, AST ≥ 3 × ULN, alkaline phosphatase ≥ 1.5 × ULN, or total bilirubin ≥ 1.5 × ULN) were observed in 2/38 (5.3%) subjects.

Renal function

No evidence of renal toxicity was seen in any of the cohorts. Mean change from Baseline in BUN and creatinine showed slight fluctuations, but these changes were similar across the cohorts and were not considered clinically significant.

No consistent trend was seen over time for shifts in either BUN or creatinine in any of the cohorts and no patient had an abnormality in renal function tests reported as an AE. Only one AE of haematuria was reported in Cohort 3 that was not drug related.

Other serum chemistry tests

In trial TMC-ORI-11-01, mean change from Baseline in other serum chemistry tests were minimal and similar across the cohorts. No consistent trend was seen over time for shifts in other serum chemistry tests and no patient had an abnormality in the other serum chemistry tests reported as an AE.

Electrocardiograms

Most patients in each of the cohorts had normal ECG findings at Baseline and post-baseline, with most of the ECG abnormalities seen at Baseline resolving post-baseline. The mean (SD) ΔQTcF was 1.20 (27.80) ms and the 90% CI was -14.97 to 17.37. Treatment-emergent new or worsening ECG findings were seen in 3 patients overall. In one patient (Cohort 3) prolonged QT interval (baseline: 377 ms, 470 ms on the day of oritavancin administration) was reported as non serious, moderate and definitely related to study drug. It resolved and was not associated with any other AEs. Unfortunately, no repeat ECG was recorded. Concomitant medications included acetaminophen 240 mg as needed, amoxicillin

720 mg twice daily, and ampicillin 800 mg IV every 6 hours. The patient did not experience any other AE.

Discontinuation due to adverse events

Four subjects in Cohort 3b (age 2 to < 6 years who received oritavancin 20 mg/kg) and one subject in Cohort 4 (age 3 months to < 2 years who received oritavancin 15 mg/kg) discontinued study drug due to the AE red man syndrome. Two cases were reported as mild (15 mg/kg dose), two as moderate and one severe (each at 20 mg/kg dose). All resolved with treatment.

2.5.1. Discussion on clinical safety

Thirty-eight subjects were dosed in study TMC-ORI-11-01, of which five discontinued study drug early due to developing AEs consistent with red man syndrome. Four of seven subjects discontinued study drug early due to developing AEs of red man syndrome at the dose level of 20 mg/kg (Cohort 3b). In contrast, only one of 31 subjects discontinued drug early due to developing an AE of red man syndrome at the dose level of 15 mg/kg. Consistently, AEs were reported by more patients from Cohort 3b (2 to less than 6 years of age) who received oritavancin 20 mg/kg with all 7/7 (100%) patients reporting AEs. In contrast, AEs were reported by 5/8 (62.5%) patients from the same age group (Cohort 3) who received oritavancin 15 mg/kg. Hence, this dose has not been further evaluated for the paediatric population.

Hypersensitivity reactions and infusion related reactions that resemble red man syndrome have been reported with oritavancin and are included in the product information (SmPC sections 4.4 and 4.8). The risk of red man syndrome may increase with the concentration or infusion rate. The MAH further explained that increasing infusion time would impact C_{max} (and not AUC), therefore it was explored if any relationship between C_{max} and probability of RMS could be retrieved from the available data. Results from logistic regression showed that, based on the available data, changes in C_{max} would not impact the probability of RMS (p-value of 0.15, not significant). A greater number of RMS cases were reported in patients who received oritavancin 20 mg/kg (4/5) than in those who received oritavancin 15 mg/kg (1/5). Patients who received the 20 mg/kg dose had a higher infusion rate than patients who received 15 mg/kg, and this may have increased the risk for infusion-related reactions. It is agreed that the 3-hour infusion time is considered adequate for the paediatric population.

Overall, in subjects receiving the 15 mg/kg dose, the AEs reported during this study were consistent with the known safety profile for oritavancin in adults. Three probably related AEs (one case each) ECG QT prolonged, irritability and Clostrioides difficile colitis were reported which are currently not listed in the product information of Tenkasi based on data of the Phase 3 studies SOLO I and II in adults.

2.5.2. Conclusions on clinical safety

The paediatric safety data base is very limited but overall, the safety data of the 15 mg/kg dose in the paediatric population are comparable to safety data in adults and no safety concern is posed based on the measured C_{max} values.

2.5.3. PSUR cycle

Based on lack of long-term safety data in paediatric population, the CHMP is of the opinion that the already existing entry in the EURD list for oritavancin needs to be amended as follows: the PSUR cycle

for the medicinal product should follow a yearly cycle (instead of 3-yearly cycle). The next data lock point (upon extension of indication approval and after current DLP) will be 19 March 2024.

2.6. Risk management plan

The MAH submitted an updated RMP version 5.0 with DLP 31 Mar 2022 with this application.

The RMP has been updated to include information on oritavancin used in the paediatric population aged 3 months to <18 years, in order to support the extension of oritavancin's indication to this age group.

The MAH has updated the RMP to version 5.1 during this procedure, Part II Module SVI has been updated to align with EMA's Paediatric Investigation Plan (PIP) assessment, dated 20 May 2022 (procedure number: EMA/PDCO/117516/2022), on potential long term safety/efficacy issues in relation to paediatric use.

The PRAC considered that the risk management plan version 5.1 is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

Summary of safety concerns	
Important identified risks	• Hypersensitivity and histamine-like infusion reactions
Important potential risks	• Pseudomembranous colitis / Clostridium difficile-associated diarrhea (CDAD) • Osteomyelitis
Missing information	• none

Pharmacovigilance plan

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

• Specific adverse reaction follow-up questionnaires for oritavancin immunological (hypersensitivity and histamine-like infusion reactions) adverse events (Important Identified Risk), for oritavancin pseudomembranous colitis / CDAD adverse events (Important Potential Risks) and for oritavancin osteomyelitis adverse events (Important Potential Risk):

The aim of these questionnaires is to obtain structured and detailed information on reports of these adverse reactions. The forms are provided in Annex 4 of this RMP.

• Other forms of routine pharmacovigilance activities:

Not applicable.

A review of the safety concerns will be performed at each PSUR elaboration.

There are no ongoing or planned additional pharmacovigilance activities in place for oritavancin products.

The PRAC, having considered the data submitted, is of the opinion the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Pharmacovigilance Activities**
Hypersensitivity and histamine-like infusion reactions	Routine risk minimisation measures: - SmPC section 4.3 Contraindications - SmPC section 4.4 Special warnings and precautions for use - SmPC section 4.8 Undesirable effects The PL of the concerned products is in line with the information contained in the SmPC previously described. Such information is given in the following sections of the PL: - PL Section 2 What you need to know before you take – You must not be given – Warnings and precautions - PL Section 4 Possible side effects Legal status: prescription only medicine Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction. Additional pharmacovigilance activities: None
Important Potential Risks: Pseudomembranous colitis / Clostridium difficile-associated diarrhea (CDAD)	Routine risk minimisation measures: - SmPC section 4.4 Special warnings and precautions for use - SmPC section 4.8 Undesirable effects	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction. Additional pharmacovigilance activities:

Safety concern	Routine risk minimisation measures	Pharmacovigilance Activities
	The PL of the concerned products is in line with the information contained in the SmPC previously described. Such information is given in the following sections of the PL: - PL Section 2 What you need to know before you take – Warnings and precautions - PL Section 4 Possible side effects Legal status: prescription only medicine Additional risk minimisation measures: No risk minimisation measures	None
Important Potential Risks: Osteomyelitis	Routine risk minimisation measures: - SmPC section 4.4 Special warnings and precautions for use - SmPC section 4.8 Undesirable effects The PL of the concerned products is in line with the information contained in the SmPC previously described. Such information is given in the following sections of the PL: - PL Section 2 What you need to know before you take – Warnings and precautions - PL Section 4 Possible side effects Legal status: prescription only medicine Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction. Additional pharmacovigilance activities: None

2.7. Additional risk minimisation measures

Routine risk minimisation activities as described in Part V.1 of the RMP are sufficient to manage the safety concerns of the medicinal product.

2.8. Conclusions on risk minimisation measures

The PRAC, having considered the data submitted, was of the opinion the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

2.9. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details.

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reason:

the information given in the PL only slightly differs from the approved PL in regard to the paediatric information included.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The following extension of indication is applied:

Treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults and paediatric patients aged 3 months and older.

3.1.2. Available therapies and unmet medical need

There is a need for making new antibacterial agents available also to the paediatric population that will effectively treat infections caused by Gram-positive bacteria including resistant pathogens such as methicillin-resistant S. aureus.

3.1.3. Main clinical studies

Study TMC-ORI-11-01 is an ongoing Phase 1, open-label, multicentre, sequential study to evaluate the PK, safety and tolerability of single-dose oritavancin in paediatric patients aged less than 18 years. The

study is part of the Paediatric Investigation Plan for oritavancin. Thirty-eight paediatric patients >3 months of age (Cohorts 1 to 4) with a confirmed or suspected Gram-positive infection received a single dose (15 mg/kg or 20 mg/kg) of oritavancin which was infused over 3 hours. Primary endpoint of the study was AUC to extrapolate efficacy.

3.2. Favourable effects

In all age groups AUC0-72 was higher than the lower limit of the predefined target range (965 µg•h/ml) with the applied 15 mg/kg dose. PTA analyses support that the chosen dose is effective in the paediatric population.

3.3. Uncertainties and limitations about favourable effects

The primary objectives of study TCM-ORI-11-01 were to evaluate PK and safety/tolerability of oritavancin in the paediatric population. No clinical efficacy data are available and conclusion of efficacy is solely based on PK/PD data.

3.4. Unfavourable effects

Five subjects discontinued study drug early due to developing AEs consistent with red man syndrome. Four of these patients received the 20 mg/kg dose indicating that the risk of infusion-related reactions may increase with the concentration or infusion rate. Based on the available data an infusion time of 3 hours is considered adequate for the paediatric population and the applied dose of 15 mg/kg.

Overall, in subjects receiving the 15 mg/kg dose, the AEs reported during this study were consistent with the known safety profile for oritavancin in adults. Three probably related AEs (one case each) ECG QT prolonged, irritability and C. difficile colitis were reported which are currently not listed in the product information of Tenkasi.

3.5. Uncertainties and limitations about unfavourable effects

The paediatric safety database is of limited size.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The application relies on the concept of extrapolation of clinical efficacy based on comparable plasma exposures in children and adults. The acceptance of extrapolation is based on assumptions that the disease, mechanism of action and thus PK/PD are the same in paediatric patients as in adults and therefore the selected dose should achieve similar plasma exposures and probability of PK/PD target attainment (PTA) in children as in adults. The proposed dose in children >3 months of age is a single dose of 15 mg/kg (maximum 1,200 mg) infused over 3 hours. Based on similar exposure in the paediatric population as in adults and satisfactory PTA it is anticipated that the recommended paediatric doses will be effective and safe in the paediatric population.

The paediatric safety database is of limited size but could be acceptable. No new risks were identified and based on the data provided the safety profile in the paediatric population and the dosage applied for seems to be comparable to that established in adults.

3.6.2. Balance of benefits and risks

The balance of benefits and risks for the extension of indication of Tenkasi to include paediatric patients >3 months of age and older is positive.

3.6.3. Additional considerations on the benefit-risk balance

Not applicable.

3.7. Conclusions

The overall benefit/risk balance of Tenkasi is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of paediatric population, aged between 3 months and less than 18 years for Tenkasi (oritavancin) 400 mg based on interim results from study TMC-ORI-11-01.
As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC were updated. The Package Leaflet is updated in accordance.
In addition, the MAH has taken the opportunity to make minor editorial amendments and QRD updates (v10.2) to the SmPC/PL..
Furthermore, the PI is brought in line with the latest QRD template version 10.2 rev 1.
Version 5.1 of the RMP has also been approved.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0236/2022 and the results of these studies are reflected in the

Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Tenkasi-H-C-003785-II-0037'.