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Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Tenkasi

Oritavancin

Procedure no: EMA/PAM/0000344073

Note

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

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1. Introduction

On 30 April 2026, the MAH submitted a completed paediatric study for Tenkasi, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Tenkasi (INN: Oritavancin) is a powder for concentrate for solution for infusion approved for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults and paediatric patients aged 3 month and older. The adult dose is 1200 mg, administered as a single dose by intravenous (IV) infusion over 3 hours; the paediatric dose is 15 mg/kg administered as a single dose by IV infusion over 3 hours (maximum 1200 mg). The parameter that best correlates with oritavancin efficacy is the area under curve (AUC) to minimum inhibitory concentration (MIC) ratio for the infecting organism.

The MAH has submitted the results of the completed study TMC-ORI-11-01 (ORKIDS) - An Open-label, Dose-finding, pharmacokinetics, Safety and Tolerability Study of Olivanic Single Dose Infusion in Paediatric Subjects <18 Years of Age with Suspected or Confirmed Bacterial Infections - that is part of the agreed Paediatric Investigation Plan (PIP), EMEA-001270-PIP01-12-M07, Study 2. The MAH stated that the PIP has been deferred and it is currently ongoing.

The interim clinical study report (CSR) of TMC-ORI-11-01 (dated 15 December 2021) relative to the first completed paediatric age Cohort 1-4 (aged 3 months to less than 18 years) was already submitted in August 2022. The data supported the extension of the paediatric indication for Tenkasi from 3 months to less than 18 years old on 15 May 2023. The study continued with Cohort 5 (birth to <3 months) but was closed by the Sponsor on 04 November 2025 with a total of 3 out of 16 planned participants. Safety and pharmacokinetic (PK) data from these 3 neonates were reviewed by the independent Data Safety Monitoring Board (DSMB) that recommended stopping the recruitment because the exposure achieved was lower than the anticipated efficacious one at the maximal tolerated dose of 15 mg/kg. Results of the study, together with the DSMB outcome were presented to the FDA that endorsed the closure of the study without any request for further data.

2.2. Information on the pharmaceutical formulation used in the study

Powder for concentrate for solution for infusion.

2.3. Clinical aspects

Introduction

The MAH submitted a final report for:

- TMC-ORI-11-01 (ORKIDS): An Open-label, Dose-finding, pharmacokinetics, Safety and Tolerability Study of Oritavancin Single Dose Infusion in Paediatric Subjects <18 Years of Age with Suspected or Confirmed Bacterial Infections.

Clinical study TMC-ORI-11-01 (ORKIDS)

Description

Study TMC-ORI-11-01 was a Phase 1, multicenter (US only), open-label, sequential study of a single dose of oritavancin in paediatric participants with a suspected or confirmed Gram-positive bacterial infection for which the participants were receiving standard antibiotic therapy or participants requiring peri-operative prophylactic use of antibiotics.

Methods

Study participants

Participants were enrolled in a stepwise approach, starting with the oldest age cohort (12 to <18 years), and then progressing down the age range after PK and safety analyses had been performed.

The protocol planned to enroll age-based cohorts sequentially (except for Cohorts 3b and Cohort 4 which were enrolled concurrently):

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

Inclusion Criteria

For inclusion into the study, participants were required to fulfil all the following criteria:

1. Males and females <18 years of age.
2. Neonates had to be at least 34 weeks gestational age.
3. Written informed consent provided before initiation of any study-related procedures; parent or legal guardian gave informed consent, as appropriate; and pediatric participants gave verbal assent where appropriate.
4. Suspected or diagnosed Gram-positive bacterial infection for which the participant was receiving standard antibiotic therapy or participants requiring peri-operative prophylactic use of antibiotics.
5. IV access to administer investigational medicinal product (IMP).
6. The participant would be observed in the emergency room or hospital for at least 1 hour after the IMP infusion was completed.

Exclusion Criteria

Participants meeting any of the following criteria were excluded from the study:

1. Septic shock or acute hemodynamic instability.
2. History of immune-related hypersensitivity reaction to glycopeptides (such as vancomycin, telavancin, or teicoplanin) or any of their excipients.
3. Participants 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 IMP. Participants who took dalbavancin were excluded if

dalbavancin was taken within the previous 2 weeks or if participants were anticipated to need dalbavancin within 48 hours after administration of IMP.

4. Females who were of childbearing potential and unwilling to practice abstinence or use at least two methods of contraception (oral contraceptives, barrier methods, approved contraceptive implant) during the entire study period.
5. Female participants of childbearing potential who were lactating or who had a positive pregnancy test result at screening.
6. Males who were unwilling to practice abstinence or use an acceptable method of birth control during the entire study period (i.e., condom with spermicide).
7. Any surgical or medical condition which, in the opinion of the investigator, put the participants at increased risk or was likely to interfere with study procedures or PK of the IMP.
8. Participants whom the investigator considered unlikely to adhere to the protocol, comply with IMP administration, or complete the clinical study (e.g., unlikely to survive 60 days from initiation of IMP or unlikely to return for the Day 7 (Cohort 5)/Day 14 (Cohorts 1 through 4) follow-up visit).
9. Treatment with investigational medicinal product or investigational device within 30 days (or 5 times the t½ of the investigational medicine, whichever was longer) before enrollment and for the duration of the study.
10. Participants who were taking heparin or warfarin and/or required anticoagulant monitoring (activated partial thromboplastin time [aPTT], prothrombin time, international normalized ratio).
11. Participants who required anticoagulant monitoring with an aPTT.
12. Participants with an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 × the upper limit of normal (ULN) or total bilirubin ≥2 × ULN.
13. Neutropenia with absolute neutrophil count <500 cells/mm³.
14. Any clinically significant disease or condition affecting a major organ system, including but not limited to gastrointestinal, renal, hepatic, endocrinologic, broncho-pulmonary, neurological, metabolic, or cardiovascular disease.
15. Active exposure to cytotoxic chemotherapy or immunosuppressive therapy with tacrolimus or cyclosporine:
    a. Participants who received immunosuppressive treatment/chemotherapy within the 2 weeks prior to screening.
    b. Any chronic systemic immunosuppressive therapy equivalent to a prednisone dose higher than 15 mg/day.
16. Previously participated in this study.
17. Participant is the child of the investigator or his/her deputy, research assistant, pharmacist, study coordinator, other staff, or relative thereof directly involved in the conduct of the study.

Treatments

On Day 1, participants received a single dose of oritavancin at a weight-based regimen of 15 mg/kg (except for Cohort 3b, which was dosed at 20 mg/kg).

To minimize PK blood draws, each participant was only required to have PK samples drawn at three timepoints: 3 hours post infusion start time (i.e. end of infusion), 24 hours post infusion start time or 72 hours post infusion start time and 336 hours post infusion start time for Cohorts 1-4. The final collection time for Cohort 5 was 168 hours post-infusion start time.

Participants in Cohorts 1-4 were followed for 14 days post-dose to collect PK and safety measures and contacted by phone at Day 60 to collect any adverse events (AEs)/serious adverse events (SAEs) that

occurred between Day 14 and Day 60. Participants in Cohort 5 were followed for 7 days post-dose to collect PK and safety measures and contacted by phone Day 60 to collect any AEs/SAEs that occurred between Day 7 and Day 60.

Objective

The objective of the study was to evaluate the PK, safety, and tolerability of an IV infusion of oritavancin in paediatric participants with a suspected or confirmed Gram-positive bacterial infection for which they were receiving standard antibiotic therapy or paediatric participants requiring peri-operative prophylactic use of antibiotics.

Outcomes/endpoints

The primary endpoint was as follows:

- Area under the plasma concentration-time curve.

Secondary endpoints were the following:

- Maximum concentration (Cmax), t½, time of maximum concentration, the population mean total volume of distribution (Vz), and clearance (CL).
- Safety assessed according to AEs, SAEs, vital signs (blood pressure, pulse rate, respiration rate, and temperature), 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), hemoglobin, hematocrit, 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

Approximately 41 evaluable are planned.

- **Cohort 1:** 12 to <18 years; *enrollment complete; n=8*
- **Cohort 2:** 6 to <12 years; *enrollment complete; n=8*
- **Cohort 3:** 2 to <6 years; *enrollment complete; n=8*
- **Cohort 3B:** 2 to <6 years, dosed at 20 mg/kg; *enrollment complete; n=7*
- **Cohort 4:** 3 months to <2 years; *enrollment complete; n=7*
- **Cohort 5:** Birth to <3 months (includes 0-28 day neonates): n= 3 at the following age ranges:
  - Term neonates ages 7 to ≤28 days (gestational age 37 to 42 weeks)
  - Preterm neonates ages 7 to ≤28 days (gestational age 34 to <37 weeks)
  - Infants >28 days and <3 months

Randomisation and blinding (masking)

Not applicable since this was a non-comparative open-label study.

Statistical Methods

The total sample size (approximately 41 evaluable subjects) was chosen based on judgment to provide adequate precision of the findings. Approximately 8 subjects per paediatric age cohort were considered adequate to assess PK based on prior clinical experience. The <3 month age cohort was originally planned to have up to 16 subjects enrolled.

Statistical analyses were performed using the following subject populations:

- Safety Population: All subjects who were dosed with oritavancin. This is the primary population used for safety analyses.
- PK Population: All subjects who were dosed with oritavancin and had at least one documented and evaluable blood concentration and documented dose records.

Descriptive statistics and graphic display were used to summarise the data collected in the case report form for all subjects and by age cohort. Continuous variables were summarised using mean, standard deviation, median, inter-quartile range, minimum, and maximum. Categorical variables will be summarised using frequency and percentage.

Results

Participant flow

A total of 49 participants were enrolled in Cohorts 1-5 (including Cohort 3b) in the study at 8 investigational sites in the US. Of the 49 participants enrolled, 41 were dosed.

Table 1: Number of participants dosed (TMC-ORI-11-01; Study 2)

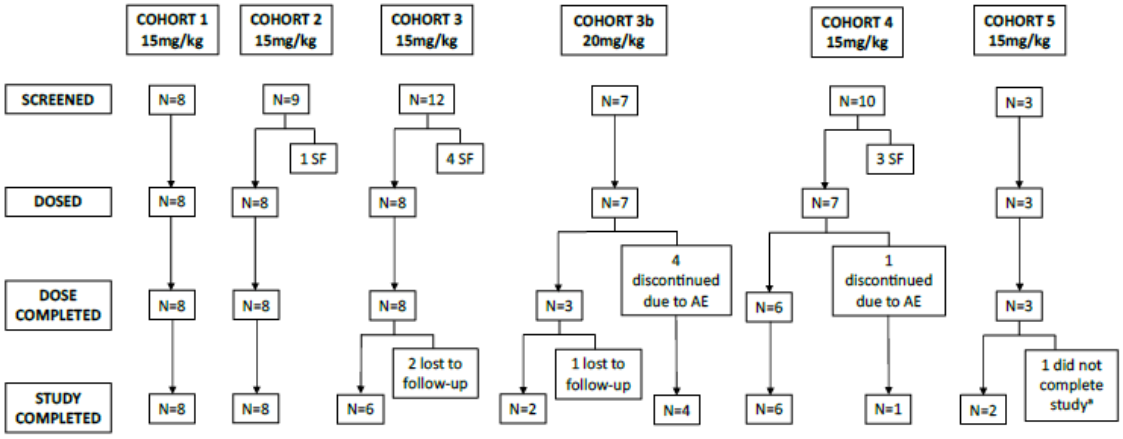
Cohort	Age Range	Number Dosed/Planned*	Dosing Regimen
1	12 to < 18 years	8/8	15 mg/kg
2	6 to < 12 years	8/8	15 mg/kg
3	2 to < 6 years	8/8	15 mg/kg
3b	2 to < 6 years	7/8	20 mg/kg
4	3 months to < 2 years	7/8	15 mg/kg
5	Birth to < 3 months	3/16	15 mg/kg

*Enrolment stopped at n= 7 due to high frequency of AE consistent with Red Man Syndrome in Cohort 3b and to COVID pandemic's impact on sites ability to enrol in Cohort 4. Enrolment stopped at n= 3 in Cohort 5 as per DSMB recommendation based on unfavourable risk/benefit no longer supporting the study of oritavancin in this subgroup.

All dosed participants in Cohort 1, Cohort 2, and Cohort 3 completed IMP (i.e., no treatment discontinuation). In Cohort 3b (i.e. the 20 mg/kg group) 4 participants discontinued IMP due to an AE of Red Man Syndrome (RMS) and 1 participant in Cohort 4 discontinued IMP due to an AE of RMS.

Up to 16 participants were planned for enrollment in Cohort 5. However, enrollment was stopped after 3 participants had been enrolled. The DSMB recommended that the risk-benefit no longer supported the study of oritavancin in children from birth to <3 months of age with the current dosing regimen.

Figure 1: Participant Disposition



Abbreviations: AE = Adverse event; SF = Screening failure.
*This participant did not complete the study for reasons listed as 'other'

Recruitment

First Participant Enrolled	17 September 2014
Last Participant Completed	27 September 2024

Baseline data

Most participants in Cohorts 1, 2, 3 and 5 had a single infection at baseline, most participants in Cohort 3b and in Cohort 4 had 1 or 2 infections at baseline. Two participants in Cohort 3, 1 participant in Cohort 4 and 1 participant in Cohort 3b had an Methicillin-Resistant Staphylococcus Aureus (MRSA) infection. The types of infections and pathogens varied in each of the cohorts with Pneumonia, Appendicitis perforated, Cellulitis, Abscess, and Lobar pneumonia being the most common.

Demographic data are summarized in Table 2.

Table 2. Participant Demographics (Safety population)

	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 5 Birth to <3 months N=3	Cohort 3b 2 to <6 years N=7
Age (years)						
N	8	8	8	7	3	7
Mean (SD)	15.83 (1.5)	9.6 (1.58)	2.72 (0.52)	1.25 (0.55)	0.04 (0.02)	4.08 (1.06)
Median	16.05	9.28	2.72	1.23	0.04	3.95
Q1, Q3	15.62, 16.58	8.30, 11.22	2.25, 3.16	0.80, 1.79	0.02, 0.05	2.97, 5.16
Min, Max	12.5, 17.7	7.6, 11.7	2.1, 3.4	0.4, 1.9	0.0, 0.0	2.9, 5.5
Sex						
Male	4 (50.0)	2 (25.0)	4 (50.0)	5 (71.4)	2 (66.7)	4 (57.1)
Female	4 (50.0)	6 (75.0)	4 (50.0)	2 (28.6)	1 (33.3)	3 (42.9)
Race n (%)						
White	6 (75.0)	7 (87.5)	6 (75.0)	6 (85.7)	3 (100.0)	6 (85.7)
Black or African American	2 (25.0)	1 (12.5)	2 (25.0)	0	0	1 (14.3)
American Indian or Alaska Native	0	0	0	1 (14.3)	0	0
Ethnic group						
Hispanic or Latino	2 (25.0)	3 (37.5)	4 (50.0)	2 (28.6)	1 (33.3)	5 (71.4)
Not Hispanic or Latino	6 (75.0)	5 (62.5)	4 (50.0)	5 (71.4)	2 (66.7)	2 (28.6)
Weight (kg)						
N	8	8	8	7	3	7
Mean (SD)	69.3 (31.22)	41.5 (13.93)	14.0 (2.39)	11.6 (2.44)	4.1 (0.57)	17.4 (3.16)
Median	64.5	37.9	13.2	11.7	3.9	18.8
Q1, Q3	57.1, 70.7	32.6, 52.2	12.0, 16.1	10.3, 13.6	3.6, 4.7	13.4, 20.3
Min, Max	30, 139	24, 63	12, 18	8, 15	4, 5	13, 20
Height (cm)						
N	8	8	8	7	3	7
Mean (SD)	167.1 (15.28)	141.4 (13.63)	92.7 (9.27)	79.8 (8.58)	52.1 (4.00)	102.4 (5.86)
Median	167.9	139.1	91.3	84.0	52.2	103.0
Q1, Q3	155.0, 176.5	129.3, 153.2	85.3, 101.9	71.1, 87.0	48.0, 56.0	96.5, 105.4
Min, Max	146, 192	125, 163	81, 104	66, 88	48, 56	94, 112
BMI (kg/m²)						
N	8	8	8	7	3	7
Mean (SD)	23.9 (6.64)	20.3 (3.83)	16.3 (1.64)	18.1 (1.70)	15.0 (0.66)	16.5 (1.71)
Median	22.5	19.5	16.7	17.8	15.0	16.7
Q1, Q3	21.6, 25.4	17.7, 23.1	14.9, 17.8	17.0, 20.4	14.3, 15.6	15.2, 17.8
Min, Max	14, 38	15, 27	14, 18	16, 20	14, 16	14, 19
BMI-for-age (z-score)						
N	8	8	8	7	3	7
Mean (SD)	0.544 (1.348)	0.978 (0.842)	-0.003 (1.300)	1.170 (1.052)	1.002 (0.632)	0.430 (1.411)
Median	0.614	1.059	0.268	0.572	0.896	0.729
Q1, Q3	0.264, 1.173	0.287, 1.774	-0.793, 1.012	0.410, 2.107	0.429, 1.680	-0.836, 1.626
Min, Max	-2.25, 2.50	-0.33, 1.92	-2.47, 1.47	0.23, 2.98	0.43, 1.68	-2.10, 1.81

Abbreviations: BMI = Body mass index; Max = Maximum; Min = Minimum; Q1 = First quartile; Q3 = Third quartile.

Number analysed

Table 3. Participant Disposition (All dosed participants)

	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 5 Birth to <3 months	Cohort 3b 2 to <6 years
Participants who received IMP	**8**	**8**	**8**	**7**	**3**	**7**
Number of participants receiving full dose	**8/8 (100.0)**	**8/8 (100.0)**	**8/8 (100.0)**	**6/7 (85.7)**	**3/3 (100.0)**	**3/7 (42.9)**
Participants who did not receive full dose	0	0	0	1/7 (14.3)	0	4/7 (57.1)
Primary reason for not receiving full dose						
Adverse event(s)	0	0	0	1/7 (14.3)	0	4/7 (57.1)
Safety participants who completed the study	**8/8 (100.0)**	**8/8 (100.0)**	**6/8 (75.0)**	**7/7 (100.0)**	**2/3 (66.7)**	**6/7 (85.7)**
Safety participants who discontinued the study	0	0	2/8 (25.0)	0	1/3 (33.3)	1/7 (14.3)
Primary reason for not completing the study						
Lost to follow-up	0	0	2/8 (25.0)	0	0	1/7 (14.3)
Other*	0	0	0	0	1/3 (33.3)	0

Abbreviations: IMP = Investigational medicinal product

*Note: the reason for 'other' was that the family did not return Day 60 phone call. The participant had a routine well-child visit with their pediatrician on Day 62, and this was used to review physical examination, history and to assess for AEs

Efficacy results

The clinical pharmacology data obtained in children aged from 3 months to < 18 years old (corresponding to Cohorts 1-3) were submitted in the interim CSR of trial TMC-ORI-11-01 (Study 2), dated 15 Dec 2021, together with the PopPK and PopPK/PD modelling and simulation analyses that supported the oritavancin dosing recommendation of 15 mg/kg and the approval of use in this paediatric population with ABSSSI. To note, the PK data of Cohorts 1–4 included in Interim CSR were re-estimated with the revised PopPK model updated in June 2025. Compared with the previous PopPK model developed in 2021 (PK-ORI-01), the updated model included data collected from the 3 neonates in Cohort 5 and data from an ongoing paediatric ABSSSI study (ML-ORI-201), which provided PK data from an overall n = 63 children aged >3 months and treated at the same approved dose of 15 mg/kg.

The PK of oritavancin was adequately described by a 3-compartment linear model, consistently with the previous analysis from which Bayesian priors were derived. In this updated model, the effect of weight was included on all parameters in an allometric fashion with estimated allometric exponents using Bayesian priors of 0.75 for clearance parameters and 1 for volumes, as per the previous analysis. After accounting for the effect of weight, no further correlations were observed between model parameters and age, even in the neonatal age group, consistently with the previous analysis. This updated model showed good performance, with the 10th, median, and 90th percentiles consistently within the 95% confidence interval (CI) of model predictions. Moreover, diagnostic plots demonstrated an adequate model fit with no significant bias.

The key PK parameters of interest, namely Cmax, AUC0-72 and AUC72-168, are reported in Table 4 for all cohorts.

Table 4. Summary of Pharmacokinetic parameters (Pharmacokinetic 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 5 Birth to <3 months N=3	Cohort 3b 2 to <6 years N=7
C_{max} (µg/mL)						
N	8	8	8	7	3	7
Mean (SD)	123.9 (19.23)	126.7 (27.84)	85.6 (13.12)	86.0 (21.96)	69.3 (3.89)	94.8 (32.96)
Median	129.4	123.4	86.2	90.3	67.8	97.2
Min, Max	91.7, 140.8	83.8, 175.5	67.0, 111.1	44.4, 108.8	66.4, 73.7	48.1, 132.9
Geometric mean	122.4	124.0	84.8	83.0	69.2	89.3
%CV	15.5	22.0	15.3	25.5	5.6	34.8
AUC_{0-72} (h·µg/mL)						
N	8	8	8	7	3	7
Mean (SD)	2009.8 (350.99)	1990.5 (671.62)	1264.3 (268.59)	1339.9 (445.68)	1095.3 (118.73)	1443.3 (577.64)
Median	2092.0	1895.3	1382.6	1410.1	1094.8	1523.8
Min, Max	1442.3, 2356.6	1199.9, 3494.1	824.0, 1555.0	580.3, 1861.3	976.8, 1214.3	753.1, 2111.5
Geometric mean	1981.1	1907.6	1236.6	1262.5	1091.0	1335.1
%CV	17.5	33.7	21.2	33.3	10.8	40.0
AUC_{72-168} (h·µg/mL)						
N	8	8	8	7	3	7
Mean (SD)	481.4 (96.72)	367.2 (240.10)	183.5 (70.10)	209.5 (72.25)	125.8 (26.03)	235.4 (83.74)
Median	467.3	329.3	195.0	217.7	126.3	234.7
Min, Max	366.8, 586.8	179.0, 935.9	63.1, 260.3	91.0, 296.2	99.5, 151.6	123.2, 370.5
Geometric mean	472.9	322.2	168.3	196.6	123.9	222.4
%CV	20.1	65.4	38.2	34.5	20.7	35.6

Abbreviations: %CV = Coefficient of variation; AUC_{0-72} = Area under the plasma concentration-time curve, from baseline to 72 hours post-dose; AUC_{72-168} = Area under the plasma concentration-time curve, from 72 to 168 hours post-dose; C_{max} = Maximum plasma concentration; Max = Maximum; Min = Minimum; PK = Pharmacokinetic; 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.

Mean exposure in terms of Cmax, AUC0-72, AUC72-168 decreased with decreasing age from Cohorts 1-5, except for Cohort 4 where the PK parameters were slightly higher in comparison to Cohort 3. For this reason, oritavancin was tested in an additional Cohort 3b at 20 mg/kg dose, reaching higher exposure but with an unacceptable high rate of infusion-related reaction resembling RMS.

Despite the decreasing exposure with decreasing age, the median AUC0-72 achieved at the dose of 15 mg/kg in children aged from 3 months to <18 years (Cohorts 1 to 4) is within the adult target range (965–2095 mcg·h/mL). In contrast, the AUC0-72 is considered suboptimal in Cohort 5, with a median value (1094.8 mcg·h/mL) close to the lower limit of the target exposure range in adults. Similar conclusions can be drawn for the other parameters (Cmax and AUC72-168), with median values in neonates being 52.4% and 27% of the corresponding values in the oldest age group (Cohort 1).

Model-based simulations were performed using the updated PopPK model in a virtual population of N = 2000 subjects per age group (50% of each sex), created by sampling ages from a random uniform distribution within each age group and body weights obtained by randomly sampling from the weight-for-age and sex distributions described by the Center for Disease Control (CDC) growth charts.

Boxplots of predicted exposures by age group are shown in Figure 2. Table 5 contains summary statistics of predicted exposures.

The PK simulations confirmed that exposure generally decreases with decreasing age, which is of concern for the youngest age cohort (birth to <3 months). In this population, the median predicted AUC0-72 (917 mcg·h/mL) falls below the 25th percentile of the corresponding predicted adult AUC0-72 distribution and is outside the target range in adults. A more pronounced effect is observed for Cmax and AUC72-168, which fall below or approach the 5th percentile of the corresponding predicted adult exposure (Figure 2).

Comparable results were obtained when the predicted exposures were presented by body weight.

Figure 2. Boxplots of predicted exposures by age group

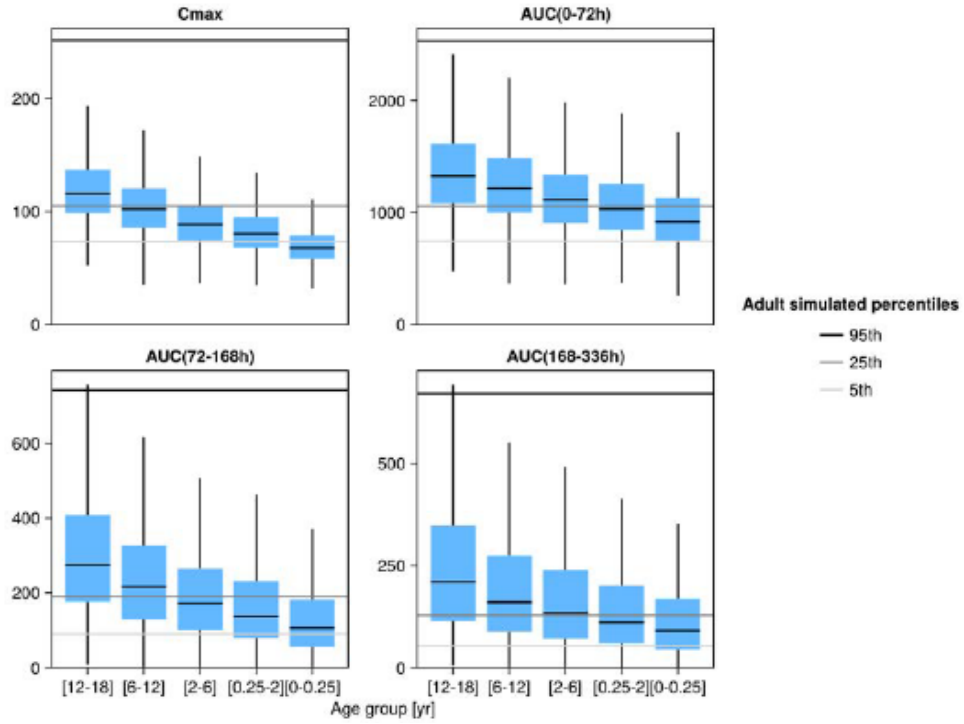


Table 5. Summary of predicted exposures by age group

Parameter	Adults (1200 mg)	[12-18] yr (15 mg/kg)	[6-12] yr (15 mg/kg)	[2-6] yr (15 mg/kg)	[0.25-2] yr (15 mg/kg)	[0-0.25] yr (15 mg/kg)
C_{max} (mcg/mL)						
Median	134	116	102	88.7	80.8	67.9
5th-95th percentile	(73-252)	(76-173)	(66-152)	(60-131)	(54-117)	(46-99)
$AUC_{(0-72)}$ (mcg/mL*h)						
Median	1370	1329	1217	1112	1033	917
5th-95th percentile	(746-2539)	(829-2092)	(755-1935)	(679-1746)	(634-1734)	(545-1541)
$AUC_{(72-168)}$ (mcg/mL*h)						
Median	300	275	216	172	138	106
5th-95th percentile	(90-743)	(76-626)	(52-542)	(34-460)	(29-422)	(18-336)

Figure 3. Boxplots of predicted exposures by body weight

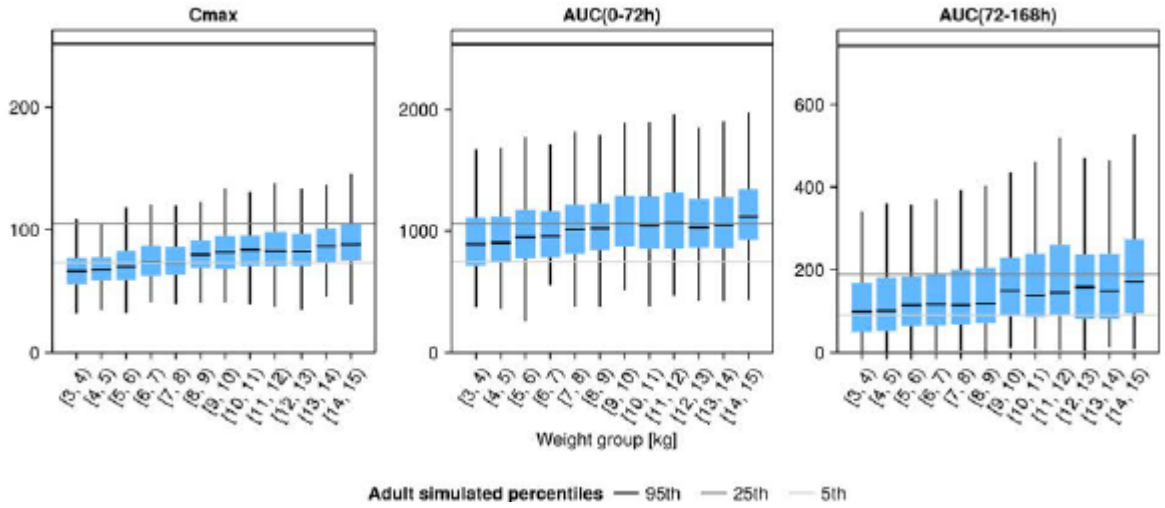


Table 6. Probability of target attainment for *S. aureus*

			MIC (ug/mL)					
			0.015	0.03	0.06	0.125	0.25	0.5
Endpoint	**Age group**	**Dose regimen**	**Probability of Target Attainment (%)**					
1-log10 CFU reduction from baseline	Adults	1200 mg	100	100	100	99.2	67.8	9.45
	[12-18]	15 mg/kg	100	100	100	99.8	68.7	2.35
	[6-12]	15 mg/kg	100	100	100	99.4	58.6	0.95
	[2-6]	15 mg/kg	100	100	100	98.4	45.9	0.3
	[0.25-2]	15 mg/kg	100	100	100	97.4	35.6	0.1
	[0-0.25]	15 mg/kg	100	100	100	93.2	23.8	0
Net bacterial stasis	Adults	1200 mg	100	100	100	99.8	80.7	17.3
	[12-18]	15 mg/kg	100	100	100	99.9	85	8.05
	[6-12]	15 mg/kg	100	100	100	99.8	76.2	4.15
	[2-6]	15 mg/kg	100	100	100	99.3	66	1.9
	[0.25-2]	15 mg/kg	100	100	100	99.1	57	1.05
	[0-0.25]	15 mg/kg	100	100	100	97.3	41.2	0.35

Current EUCAST MIC breakpoints are 0.125 for *S. aureus* and 0.25 for *S. anginosus* group and *Streptococcus* groups A, B, C and G.

Safety results

In Study TMC-ORI-11-01 (Study 2), safety and tolerability were assessed through physical examinations, 12-lead ECGs, vital signs monitoring, and safety laboratory tests (haematology and chemistry) over 14 days and 7 days post dose (Cohorts 1–4 and Cohort 5, respectively), i.e. until the last PK measurement, and at Day 60 by phone contact to collect AEs/SAEs occurring after Day 14 or Day 7.

In addition, the results of an interim analysis of safety and PK data after the completion of each age cohort were presented to an external, independent DSMB, which ensured that safety criteria were met and that the PK profile was comparable to that of adults receiving the labelled dose of 1200 mg.

The final CSR includes safety data from the completed Cohorts 1 through 4 that had already been submitted in the application leading to the extension of oritavancin's indication to paediatric patients with ABSSSI aged 3 months to <18 years.

Overall, in this population, the safety data demonstrated that oritavancin was safe and well tolerated at a dose of 15 mg/kg. Infusion-related reactions resembling RMS, a protocol-specified adverse event

of special interest (AESI), were the most frequently reported treatment-emergent adverse events (TEAEs) leading to discontinuation (N = 5; 12.2%). Notably, the rate of discontinuation due to RMS was significantly higher at the 20 mg/kg dose, affecting 4 out of 7 participants (57.1%).

Infusion-related reactions resembling RMS were reported in up to 3.5% of adults treated with oritavancin. They are mentioned in SmPC section 4.4, *Special warnings and precautions for use* and are known to be associated with glycopeptide antibiotics.

The new safety data included in the final CSR for TMC-ORI-11-01 were collected from 3 neonates treated in Cohort 5 with 15 mg/kg. The TEAEs reported in this cohort affected the same System Organ Classes (SOCs) as those seen in older paediatric populations: Gastrointestinal (GI) disorders, Infections and Infestations, and Skin and Subcutaneous Tissue disorders.

Within the GI disorders SOC, vomiting was reported in two neonates. In the Skin and Subcutaneous Tissue disorders SOC, erythema, flushing, and neonatal rash were each reported in one neonate. None of these events were assessed by the investigator as related to the IMP. For the events of erythema and flushing that occurred in the same child, IMP causality cannot be ruled out because of their coincident occurrence with the IMP infusion (1.5 hours after the start of infusion and lasting approximately 40 minutes).

Furthermore, no cases of RMS, nor any serious or severe TEAEs, were reported in the neonatal cohort.

No significant abnormalities in vital signs, laboratory parameters, or ECGs with IMP causality were reported, nor were any trends in these parameters detected in any pediatric cohort.

Discussion on clinical aspects

PK and safety data from the clinical trial TMC-ORI-11-01 (Study 2) for the population aged 3 months to less than 18 years, i.e. from Cohorts 1-4, have been already reported in the Interim CSR (dated 15 December 2021) together with PopPK and PopPK / PD modelling and simulation (PK-ORI-01, dated 28 June 2021) and supported the Extension of Indication to use of oritavancin at a dose of 15 mg/kg in the paediatric population aged 3 months to less than 18 years for the treatment of ABSSSI. Hence, the focus in this report is on the data for the population aged less than 3 months, i.e. Cohort 5.

Study TMC-ORI-11-01 was terminated in November 2025 with a total of 3 out of the planned up to 16 neonates recruited in Cohort 5 following the recommendation by the DSMB and endorsed also by FDA to close the cohort because of suboptimal achieved exposure at the dose of 15 mg/kg and consequent risk of lack of efficacy.

Dose increase to 20 mg/kg to compensate for a lower achieved exposure was already tested for the population aged 2 to 6 years as Cohort 3b. The dose increase was associated with the occurrence of RMS in 4 of 7 (57.1%) recruited paediatric patients of Cohort 3b (as opposed to 0/8 (0%) in Cohort 3 and 1/34 (2.9%) in all cohorts dosed at 15 mg/kg and 1.9% in adults) and discontinuation in all affected cases. Previous studies involving the glycopeptide antimicrobial vancomycin have demonstrated a link between higher dose concentrations, shorter infusion durations, and an increased risk of RMS (Myers et al., 2012). Due to the high rate of TEAEs of RMS in participants dosed with 20 mg/kg oritavancin, 15 mg/kg was considered the maximum tolerated dose. Hence, dose increase in paediatric patients aged less than 3 months to compensate for the suboptimal exposure achieved at 15 mg/kg is not considered a viable option. In consequence, it is agreed that paediatric patients aged less than 3 months very likely cannot be effectively dosed with the current formulation.

3. CHMP overall conclusion and recommendation

The applicant reported the findings from paediatric study TMC-ORI-11-01 that investigated the PK and safety of oritavancin in different age cohorts of paediatric patients. Data on Cohorts 1 – 4 had been presented and the focus in this report is on the data for the population aged less than 3 months (Cohort 5). Due to the observed suboptimal exposure in this population at the standard dose of 15 mg/kg combined with the observed unacceptably high occurrence of TEAE of Red Man Syndrome in Cohort 3b in which higher dosing at 20 mg/kg was investigated, it is agreed that paediatric patients aged less than 3 months very likely cannot be effectively dosed with the current formulation.

☒ **Fulfilled:**

No regulatory action required.