NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Supplemental New Drug Application
Application Number(s)	NDA 021883/S-010
Priority or Standard	Standard
Submit Date(s)	September 23, 2020
Received Date(s)	September 23, 2020
PDUFA Goal Date	July 23, 2021
Division/Office	Division of Anti-Infectives/Office of Infectious Diseases
Review Completion Date	July 15, 2021
Established/Proper Name	Dalbavancin
Trade Name	DALVANCE®
Pharmacologic Class	Lipoglycopeptide antibacterial
Applicant	Allergan Sales, LLC
Dosage form	Intravenous injection
Applicant proposed Dosing Regimen	• Birth to less than 6 years: 22.5 mg/kg single dose • 6 to less than 18 years: 18 mg/kg single dose
Applicant Proposed Indication(s)/Population(s)	Acute bacterial skin and skin structure infections (ABSSSI) in patients (b) (4)
Recommended Indication(s)/Population(s)	Pediatric patients from birth to less than 18 years of age with acute bacterial skin and skin structure infections (ABSSSI)
Recommended Dosing Regimen	From birth to less than 6 years: a single dose of 22.5 mg/kg (maximum of 1500 mg); From 6 to less than 18 years: a single dose of 18 mg/kg (maximum of 1500 mg)
Recommendation on Regulatory Action	Approval

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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Glossary

ABSSSI acute bacterial skin and skin structure infections
AE adverse event
CABP community-acquired bacterial pneumonia
CNS central nervous system
CRP C-reactive protein
CSF cerebrospinal fluid
DAI Division of Anti-Infectives
DSUR Development Safety Update Report
EOT End-of-Therapy
FDA Food and Drug Administration
GA gestational age
HCT hematocrit
IND investigational new drug
IV intravenous
ITT intent-to-treat
LLOQ lower limit of quantification
LOS late-onset sepsis
MedDRA Medical Dictionary for Regulatory Activities
MIC minimum inhibitory concentration
Micro-ITT microbiological ITT
mITT modified ITT

NDA	new drug application
OCP	Office of Clinical Pharmacology
OSI	Office of Scientific Investigation
PADER	Periodic Adverse Drug Experience Report
PD	pharmacodynamics
PeRC	Pediatric Research Committee
PK	pharmacokinetics
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
sNDA	supplemental new drug application
TEAE	treatment-emergent adverse event
TOC	Test-of-Cure

1 Executive Summary

1.1 Product Introduction

DALVANCE (dalbavancin) is a lipoglycopeptide antibacterial drug that is currently approved for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Streptococcus anginosus* group. Dalbavancin acts by interruption of cell wall synthesis resulting in bacterial death.

Dalbavancin was initially approved on May 23, 2014, as a two dose regimen administered as a 1000 mg dose followed one week later by a 500 mg dose. In January 20, 2016, a single-dose regimen of 1500 mg IV was approved. The approval of the original NDA was supported by two Phase 3 randomized double-blind trials where dalbavancin was found to be non-inferior to intravenous vancomycin with the option to switch to oral linezolid, studies DUR001-301 and -302. The safety and efficacy of the single-dose regimen was supported by a Phase 3 trial comparing the single- and the two-dose regimen, study DUR001-303.

This NDA supplement is intended to extend the ABSSSI indication to the pediatric patient population from birth to less than 18 years of age. The submitted data include an open-label, randomized, multicenter, active-controlled trial evaluating safety and efficacy of a single-dose and two-dose once weekly regimen of dalbavancin in pediatric patients from birth to 17 years of age with ABSSSI. In addition, three open-label, uncontrolled, single dose pharmacokinetic (PK) studies were provided with the population PK and pharmacodynamic (PD) modeling and simulation data for the pediatric patient population.

DALVANCE is supplied as 500 mg vials for injection. The Applicant proposes the following dosing regimens for pediatric patients:

1. The dosage in pediatric patients from birth to less than 6 years is a single dose of 22.5 mg/kg (maximum of 1500 mg)
2. The dosage for pediatric patients from 6 to less than 18 years is a single dose of

18 mg/kg (maximum of 1500 mg)

This submission will fulfill the Pediatric Research Equity Act (PREA) postmarketing requirements (PMR 2145-2 and PMR 2145-10) that were issued at the time of the NDA approval (see section 3.1 of this review).

1.2 Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided adequate information to support the safety and effectiveness of DALVANCE for the treatment of ABSSSI in pediatric patients from birth to less than 18 years of age. The efficacy across all pediatric age groups is extrapolated from the efficacy in adults with ABSSSI. Comparable drug exposure between pediatric patients receiving the proposed dosage and adult patients receiving the approved dosage allows for extrapolation of effectiveness. The supportive evidence in pediatric patients is provided by Study DUR001-306, an open-label, randomized, active-controlled trial of dalbavancin in patients from birth to less than 18 years with ABSSSI.

Study DUR001-306 enrolled 186 patients from 3 months of age to less than 18 years, randomized to receive dalbavancin single-dose or two-dose regimen or active comparator, in a 3:3:1 randomization scheme (dalbavancin single-dose, n=78; dalbavancin two-dose, n=78; and active comparator, n=30). To enhance the enrollment of participants < 3 months of age, a separate cohort in this study recruited participants with a diagnosis of either ABSSSI or sepsis (n=5).

The trial was not powered for inferential testing of dalbavancin efficacy. The primary efficacy endpoint was the proportion of patients with an early clinical response at 48–72 hours defined as ≥ 20% reduction in lesion size compared to baseline. In patients aged 3 months to less than 18 years a positive early clinical response was reported in 97.3% (73/75) of patients in the dalbavancin single-dose arm, 93.6% (73/78) of patients in the dalbavancin two-dose arm, and 86.7% (26/30) of patients in the comparator arm. The difference in responder rates between the dalbavancin single-dose and comparator arms was 10.7%, with an exact 97.5% confidence interval (CI) of (-1.7%, 31.6%). The difference in responder rates between the dalbavancin two-dose and comparator arms was 6.9%, with an exact 97.5% CI of (-6.4%, 27.7%).

A secondary efficacy endpoint was proportion of patients with clinical cure at the test of cure (TOC) visit, which occured approximately 28 days after randomization. A positive response was defined as resolution of the clinical signs and symptoms of infection when compared to baseline and no additional antibacterial treatment for the disease under study. The positive response rates were 94.7% (71/75) in the dalbavancin single-dose arm, 92.3% (72/78) in the two-dose arm, and 100% (30/30) in the comparator arm. The difference in cure rates between the dalbavancin single-dose and comparator arms was -5.3%, with an exact 97.5% CI of (-15.1%, 10.5%). The difference in cure rates between the dalbavancin two-dose and comparator arms was -7.7%, with an exact 97.5% CI of (17.9%, 8.3%).

Patients in the youngest age cohort (birth to < 3 months of age) received a single-dose regimen of dalbavancin. There were a total of 5 patients enrolled in this cohort (4 patients with diagnosis of ABSSSI, and 1 patient with *S. aureus* sepsis). In 3 patients who received any amount of study drug and had a diagnosis of ABSSSI or suspected or confirmed sepsis not known to be caused exclusively by a Gram-negative organism(s), the early clinical response was 66.6% (2/3); and the clinical cure at TOC visit was 33% (1/3).

Safety findings in pediatric patients were comparable to those observed in adults and were similar across both dalbavancin dose regimens. There were no new safety signals observed in the pediatric studies (see Section 1.3, Benefit-Risk Assessment).

1.3 Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Dalbavancin has a well characterized safety and efficacy profile in the treatment of adult patients with ABSSSI. The benefit-risk assessment of the information provided in this submission supports the approval of dalbavancin for injection for the treatment of ABSSSI in pediatric patients from birth to less than 18 years of age. The recommended dosage regimen of dalbavancin is a single-dose regimen based on the age and weight of the pediatric patient. A single intravenous (IV) infusion provides therapeutic levels of dalbavancin for up to 14 days. This submission will fulfill the Pediatric Research Equity Act (PREA) postmarketing requirements (PMR 2145-2 and PMR 2145-10) that were issued at the time of the NDA approval (see Section 3.1 of this review).

Efficacy

The efficacy of dalbavancin in the treatment of ABSSSI is extrapolated from adults and is supported by the results of Study DUR-306, a Phase 3, open label, randomized, comparator-controlled, multicenter trial in ABSSSI comparing dalbavancin to comparator in a 3:3:1 randomization scheme. The comparator regimen included either IV vancomycin for methicillin-resistant Gram-positive infections or IV oxacillin or flucloxacillin for methicillin-susceptible Gram-positive infections. Patients aged 3 months and older received either a single-dose dalbavancin regimen (n=83); a two-dose dalbavancin regimen,(n=78) or active comparator (n=30). The treatment duration in the comparator arm was for up to 14 days. Patients less than 3 months of age (n=5) received a single-dose regimen of dalbavancin. To enhance enrollment in this age group, patients were recruited with a diagnosis of ABSSSI or neonatal sepsis.

The trial was not powered for inferential testing of dalbavancin efficacy. The efficacy was assessed in 183 patients aged 3 months and older who received any dose of study drug. The primary efficacy endpoint was early clinical response defined as ≥20% reduction in lesion size compared to baseline 48–72 hours following the initiation of therapy. Early clinical response rates were 97.3% (73/75) in the dalbavancin single dose arm, 93.6% (73/78) in the dalbavancin two-dose arm, and 86.7% (26/30) in the comparator arm. A key secondary endpoint was the complete resolution of clinical signs and symptoms of ABSSSI at the test of cure (TOC) visit at Day 28. The response rates at TOC were 94.7% (71/75) in the dalbavancin single-dose arm, 92.3% (72/78) in the dalbavancin two-dose arm and 100% (30/30) in the comparator arm. Two of 5 patients aged less than 3 months were excluded from efficacy assessment due to the presence of Gram-negative infections. In 3 patients qualified for efficacy assessments, 2 had a positive early clinical response and 1 achieved clinical cure, defined as resolution of clinical signs and symptoms of infection at the Day 28 TOC visit.

Safety

The safety findings of dalbavancin in pediatric patients were similar to those in adults with ABSSSI infection. The safety population in Study DUR-306 included 161 pediatric patients from birth to less than 18 years who received at least one dose of dalbavancin and 30 patients who received comparator agents. The median age of pediatric patients treated with dalbavancin was 9 years, ranging from birth to 17 years. The majority of patients were male (62.3%) and white (89.0%). There were no deaths. There were no adverse events leading to drug discontinuation. Serious adverse events (SAEs) occurred in 3/161 (1.9%) of patients treated with dalbavancin, all in the single-dose arm ('bacterial abscess' in Cohort 5 (birth to <3 months), 'bacterial osteomyelitis' in Cohort 1 (12 to 17 years), and 'febrile convulsion' in Cohort 4 (3 months to <2 years). The SAEs were deemed unlikely to be related to study drug and all patients recovered. The most common treatment emergent adverse event (TEAE) was pyrexia (2/161, 1.2%) in the dalbavancin two-dose arm. Other reported adverse events, which occurred in one patient each (1/161, 0.6%), were diarrhea, dizziness, and pruritus. There were no significant differences in the rate of adverse events in patients who received a single- or a two-dose regimen. In addition, no significant safety findings were identified in 8 patients from birth to <3 months of age who were enrolled in PK studies. The most common TEAE observed in the PK study was pyrexia (3/8 [37.5%] patients).

Overall, dalbavancin has a favorable benefit-risk profile for the treatment of ABSSSI in pediatric patients from birth to less than 18 years of age. The safety profile of both dosing regimens is comparable to that in adults. The risks associated with dalbavancin use in the pediatric population are adequately addressed through the product labeling and routine post-marketing surveillance. Based upon the adult dosing and the trial results of DUR-306, either dosing regimen of dalbavancin would be acceptable for ABSSSI in pediatric patients. The single-dose regimen was selected for the pediatric population based upon ease of administration and enhanced compliance. The limitations of the data on the use of dalbavancin in pediatric patients include the absence of safety and efficacy data in patients with renal impairment as well as limited information in patients less than 3 months of age.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acute bacterial skin and skin structure infections (ABSSSI) may manifest as three clinical presentations in children and adults: cellulitis/ erysipelas, wound infections, and major cutaneous abscesses. The most common cause of cellulitis and erysipelas is Gram-positive bacteria such as beta-hemolytic streptococci, most commonly group A *Streptococcus* or *S. pyogenes* and *S. aureus*, including MRSA.	ABSSSI present overall similarly in pediatric adult patients. Regardless of the age of the patient, if inadequately treated, it has the potential to evolve into an invasive infection, sepsis, and death.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	The most common cause of skin abscesses is *S. aureus.* • In neonates, colonization with *S. aureus* may be an important risk factor for *S. aureus* infections. Hospitalized neonates, especially preterm and low birthweight infants are at higher risk of development of systemic staphylococcal infections due to an immature immune system. Omphalitis, an infection of the umbilicus and surrounding tissues represents a distinct clinical entity in neonates and is usually a mixed infection due to Gram-negative and Gram-positive pathogens.	
Current Treatment Options	• The management of patients with non-purulent infections like cellulitis or erysipelas consists of systemic antibacterial therapy, whereas patients with purulent infection such as abscess need incision and drainage in addition to antibacterial therapy. Duration of antibacterial treatment of ABSSSI caused by Gram-positive pathogens in the absence of bacteremia is generally 7 to 14 days. Multiple FDA approved treatment options are currently available for parenteral therapy of ABSSSI caused by Gram-positive pathogens in children, including vancomycin, daptomycin, telavancin, anti-staphylococcal penicillins, anti-staphylococcal cephalosporins, and oxazolidinones (linezolid and tedizolid). However, the majority of these antibacterials need to be administered twice or three times daily and some require therapeutic drug level monitoring.	• Dalbavancin offers an important treatment option for pediatric patients with ABSSSI caused by Gram-positive pathogens, including MRSA. It can be administered as a single IV infusion providing up to 14 days of drug exposure at therapeutic levels.
Benefit	• The Applicant conducted a Phase 3, open label, randomized, controlled trial comparing dalbavancin (a single- or a 2-dose regimen) or a comparator in a 3:3:1 randomization scheme: dalbavancin single-dose, n=83; dalbavancin two-dose, n=78; and an active comparator (either IV vancomycin for methicillin-resistant Gram-positive infections or IV oxacillin or flucloxacillin for methicillin-susceptible Gram-positive infections), n=30; Study DUR-(b) (4) Treatment duration was for up to 14 days.	• Expanding dalbavancin treatment of ABSSSI to the pediatric population is based on the evidence of efficacy from adequate and well-controlled studies in adults and supportive data from pediatric PK studies and Study DUR-306 in pediatric patients from birth to less than 18 years of age with ABSSSI.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	The randomization scheme did not include the youngest age cohort (birth to < 3 months of age), as all patients in this cohort were to receive a single-dose regimen of dalbavancin. • The efficacy analysis in Study DUR(b) (4) was conducted in 183 patients, 3 months of age to less than 18 years with ABSSSI (dalbavancin single-dose, n=75; dalbavancin two-dose, n=78; and active comparator, n=30). The primary efficacy endpoint of early clinical response was ≥ 20% reduction in lesion size compared to baseline without receipt of rescue antibacterial therapy at 48–72 hours. Clinical response rate was 97.3% (73/75) in the dalbavancin single dose arm, 93.6% (73/78) in the two-dose arm, and 86.7% (26/30) in the comparator arm. The trial was not powered for inferential testing of dalbavancin efficacy. • The key secondary efficacy endpoint of clinical cure at the TOC visit was 94.7% (71/75) in the dalbavancin single-dose arm, 92.3% (72/78) in the two-dose arm and 100% (30/30) in the comparator arm.	• In pediatric PK studies, the Applicant demonstrated similar exposures between pediatric patients (including preterm neonates) and adult patients with ABSSSI. • Study DUR-306 showed a similar early clinical response and clinical cure in the dalbavancin single-dose regimen, two-dose regimen, and comparator arms. In addition, the response rates were similar to the results observed for adults with ABSSSI in the previous registrational clinical trials. • Based on ease of administration and improved compliance, the Applicant has proposed to include the single-dose regimen for pediatric patients in the dalbavancin prescribing information (PI).
Risk and Risk Management	• The safety population in Study DUR-306 included 161 pediatric patients from birth to less than 18 years of age with ABSSSI, treated with dalbavancin (83 patients treated with a single-dose and 78 patients treated with a two-dose regimen) and 30 patients treated with comparator agents for a treatment period up to 14 days. There were no deaths or discontinuations of study drug due to adverse events in this study. SAEs were unlikely to be related to the administration of dalbavancin. • The most common treatment-emergent adverse event (TEAE) reported in this pediatric Phase 3 trial was pyrexia (2/161, 1.2% in the dalbavancin two-dose arm). Other adverse events occurred in 1 (1/161, 0.6%) patient each and included diarrhea, dizziness, and pruritus.	• The safety profile in pediatric patients was comparable to the previously established safety profile in adults. No new safety signals were observed. • Potential risks have been adequately conveyed in the product labeling. Routine pharmacovigilance would be acceptable and no additional risk mitigation strategies are recommneded at this time.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Safety findings from a PK study of 8 patients from birth to <3 months age who received a single-dose regimen of dalbavancin showed a similar safety profile. • There were no new adverse events identified in the pediatric population other than those already included in the dalbavancin PI as of the date of this review.	

1.4 Patient Experience Data

The Applicant used the "Skin and Soft Tissue Infections" (SSTI) Convenience questionnaire (section 14.4) to assess participant and parent/guardian satisfaction with therapy. Overall, the majority of participants in all treatment arms were reported as "*satisfied*" with their antibacterial treatment based on their responses to the questions. The proportion of positive responses was comparable in all treatment arms, except that more participants in both dalbavancin arms versus the comparator arm said that "*receiving the treatment did not interfere with usual daily activities".*

2 Therapeutic Context

2.1 Analysis of Condition

Acute bacterial skin and skin structure infections

Acute bacterial skin and skin structure infections (ABSSSI) are infections of skin and soft tissues, which may present in three different clinical varieties: cellulitis/ erysipelas, wound infections, and major cutaneous abscesses. ABSSSI are most frequently caused by Gram-positive organisms including *Staphylococcus aureus* (both methicillin-sensitive (MSSA) and methicillin-resistant strains (MRSA))*, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae,* and *Streptococcus anginosus group (*including *S. anginosus, S. intermedius, S. constellatus*). A small proportion of ABSSSI are caused by *Enterococcus faecalis*.[1] In an analysis of the dalbavancin surveillance program conducted by the Applicant over a period of 2014 to 2019, which was also a required post-marketing requirement, a total of 10,646 Gram-positive isolates were collected from documented infections in human clinical isolates collected from medical centers in the USA (5,566 isolates from 31 medical centers) and Europe (5,080 isolates from 37 medical centers in 19 countries). This surveillance program found *Staphylococcus aureus*, including MRSA, as the most common isolate followed by *S. pyogenes*, *S. agalactiae*, *S. dysgalactiae*, and *E. faecalis* in isolates from pediatric patients with ABSSSI from birth to 17 years (inclusive).[2] Similarly, other studies have found *S. aureus* to be the most frequently encountered pathogen isolated from cultures in pediatric patients with ABSSSI.

[1] Dennis L. Stevens, Alan L. Bisno, Henry F. Chambers, E. Patchen Dellinger, Ellie J. C. Goldstein, Sherwood L. Gorbach, Jan V. Hirschmann, Sheldon L. Kaplan, Jose G. Montoya, James C. Wade, Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America, Clinical Infectious Diseases, Volume 59, Issue 2, 15 July 2014, Pages e10–e52, https://doi.org/10.1093/cid/ciu296

[2] Surveillance of Dalbavancin Activity Tested Against Clinical Isolates Collected in the United States and Europe in 2019 and Summary of the 2014 to2019
Surveillance Program.

In neonates, specifically in the first few weeks of life, colonization with *S. aureus* and nasal carriage may be an important risk factor for *S. aureus* infections. Hospitalized neonates, especially preterm and low birthweight infants are at higher risk of development of staphylococcal infections likely due to an immature immune system, invasive procedures, and long hospital stays.

In all age cohorts, ABSSSI accounts for substantial morbidity and mortality and have the potential to evolve into serious invasive infections with fatal consequences if inadequately treated.

2.2 Analysis of Current Treatment Options

The management of patients with non-purulent ABSSSI like cellulitis or erysipelas consists of antibacterial therapy, whereas patients with purulent infection such as abscess need incision and drainage followed by systemic antibacterial therapy. The choice of antibacterial therapy should consider patient factors including the age, type and severity of infection, presence or absence of purulence, and local microbiological susceptibility patterns.

The following table (Table 1) provides a summary of therapeutic options available for the treatment of ABSSSI with comments indicating whether the drugs are FDA approved or used off-label for pediatric patients.

Table 1: Therapeutic options for skin and skin structure infections in pediatric patients

Product (s) Name	Common Trade Names	Formulation	Efficacy and Indications for Use	Important Safety and Tolerability Issues
FDA Approved Treatments for ABSSSI in Pediatric Patients				
Penicillins				
Amoxicillin-clavulanate	Augmentin	PO	Approved for SSSI caused by beta- lactamase producing *S. aureus, E. coli, Klebsiella* species	Modify dose in ≤12 weeks of age
Dicloxacillin		PO	Indicated in treatment of infections caused by penicillinase-producing *Staphylococci*	Neonatal data limited; advise frequent blood levels and monitoring for adverse effects
Nafcillin		IV	Indicated in treatment of infections caused by susceptible penicillinase-producing *Staphylococci*	Safety and effectiveness in pediatric patients established for IM nafcillin but not IV
Penicillin		IV		
Penicillin VK		PO	Approved for mild-to-moderate *Streptococcal* infections of upper respiratory tract, scarlet fever, mild erysipelas (without bacteremia). Approved for mild *Staphylococcal* infections of skin and soft tissues	
Cephalosporins				
Cefazolin	Ancef	IV	Approved for SSSI due to S. aureus (penicillin-sensitive and penicillin-resistant), group A beta-hemolytic *Streptococci*, and other strains of *Streptococci*	Safety and effectiveness for use in premature infants and neonates not established
Ceftaroline	Teflaro	IV	Approved for ABSSSI ≤ 34 weeks gestational age and ≥12 days postnatal age	
Cefaclor		PO	Approved for SSSI caused by *S. aureus* and *S. pyogenes*	Safety and effectiveness not established in infants <1 month
Cefadroxil		PO	Approved for SSSI caused by *Staphylococci* and/or *Streptococci*	
Cefotaxime		IV, IM	Approved for SSSI caused by *S. aureus, S. epidermidis, S. pyogenes* and other Streptococci, *Enterococcus* species, *Acinetobacter* species, *E. coli, Citrobacter* species (including *C. freundii*), *Enterobacter* species, *Klebsiella* species, *Proteus mirabilis, Proteus vulgaris, Morganella morganii, Providencia rettgeri, Pseudomonas* species, *Serratia marcescens, Bacteroides* species, and anaerobic cocci (including *Peptostreptococcus* species and *Peptococcus* species	
Cefoxitin		IV	Approved in ≥3 months for SSSI caused by *S. aureus, S. epidermidis, S. pyogenes* and other Streptococci (excluding Enterococci), *E. coli, Proteus mirabilis, Klebsiella* species, *Bacteroides* species, *Clostridium* species, *Peptococcus niger*, and *Peptostreptococcus* species	Safety and efficacy in pediatric patients from birth to 3 months of age not established. For ≥3 months, higher doses of associated with increased incidence of eosinophilia and elevated SGOT

Ceftriaxone	Rocephin	IV, IM	Approved for SSSI caused by *S. aureus, S. epidermidis, S. pyogenes,* Viridans group *Streptococci, E. coli, Enterobacter cloacae, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Morganella morganii, Pseudomonas aeruginosa, Serratia marcescens, Acinetobacter calcoaceticus, Bacteroides fragilis* or *Peptostreptococcus* species	Should not be administered to hyperbilirubinemic neonates, especially premature infants. Contraindicated in neonates (≤ 28 days) if they require calcium-containing IV solutions
Ceftazidime	Fortaz, Tazicef	IV	Approved in neonates and children for SSSI caused by *Pseudomonas aeruginosa; Klebsiella* spp.; *E. coli; Proteus* spp.; *Enterobacter* spp.; *Serratia* spp.; MSSA; *S. pyogenes*	
Cephalexin	Keflex	PO	Approved for >1-year-old patients for SSSI caused by *S. aureus* and *S. pyogenes*	
β-lactam/β-lactamase inhibitor combinations				
Ampicillin-sulbactam	Unasyn	IV	Approved in ≥1 year of age for SSSI strains of *S. aureus, E. coli, Klebsiella* spp., *Proteus mirabilis, Bacteroides fragilis, Enterobacter* spp., *Acinetobacter calcoaceticus*	
Monobactams				
Aztreonam		IV	Approved in pediatric patients >9 months of age for SSSI caused by *E. coli, Proteus mirabilis, Serratia marcescens, Enterobacter* spp., *P. aeruginosa, Klebsiella pneumoniae*, and *Citrobacter* spp.	Insufficient data available for <9 months of age and for SSSI suspected or known to be due to *H. influenzae* type b)
Aminoglycosides				
Amikacin		IV, IM	Approved in SSSI caused by *Pseudomonas* species, *E. coli, Proteus* spp., *Providencia* spp., *Klebsiella-Enterobacter-Serratia* spp., and *Acinetobacter* spp.	Caution in premature infants and neonates due to renal immaturity and resulting prolongation of serum half-life
Gentamicin		IV, IM	Approved in skin, bone, and soft tissue infections caused by *Pseudomonas aeruginosa, Proteus* species, *E. coli, Klebsiella-Enterobacter-Serratia* species, *Citrobacter* species, and *Staphylococcus* species	
Tobramycin		IV	Approved for skin, bone, and skin-structure infections caused by *P. aeruginosa, Proteus* spp., *E. coli, Klebsiella* spp., *Enterobacter* spp., and *S. aureus*	
Glycopeptides				
Vancomycin		IV	Approved for SSSI due to *Staphylococci*	When infections are localized and purulent, antibiotics used as adjuncts to appropriate surgical measures
Macrolides				
Erythromycin		PO	Indicated for mild to moderate SSSI caused by *S. pyogenes* or *S. aureus*	Reports of infantile hypertrophic pyloric stenosis after erythromycin therapy. Benefits of treatment need to be weighed carefully against risks in infants

Tetracyclines				
Demeclocycline	Declomycin	PO	SSSI caused by *S. aureus*	Not for use <8 years of age. Tetracyclines are not the drugs of choice in treating any *Staphylococcal* infection
Minocycline		IV, PO	As above	As above
Tetracycline		PO	SSSI caused by *S. pyogenes, S. aureus*	As above
Cyclic lipopeptides				
Daptomycin	Cubicin	IV	Indicated for adults with cSSSI caused by MSSA, MRSA, *S. pyogenes, S. agalactiae, S. dysgalactiae* subsp. *equisimilis*, and *Enterococcus faecalis* (vancomycin-susceptible isolates only). Pediatric use information is approved for Cubicin, manufactured by Merck & Co., Inc. which has marketing exclusivity rights	Safety and effectiveness not established <1 year of age. Dose not established in pediatric patients with renal impairment
Oxazolidinones				
Linezolid	Zyvox	IV, PO	Indicated in pediatric patients starting from birth for cSSSI caused by MSSA, MRSA, *S. pyogenes, S. agalactiae*	
Lincomycins				
Clindamycin		IV, PO	Indicated in pediatric patients from birth for SSSI caused by *S. pyogenes, S. aureus*, and anaerobes	
Carbapenems				
Ertapenem	Invanz	IV, IM	Indicated in pediatric patients ≥3 months of age with cSSSI due to MSSA, *S. agalactiae, S. pyogenes, E. coli, Klebsiella pneumoniae, Proteus mirabilis, Bacteroides fragilis, Peptostreptococcus* spp., *Porphyromonas asaccharolytica*, or *Prevotella bivia*	Not approved <3 months of age (no data available)
Imipenem and cilastatin	Primaxin	IV	Indicated in pediatric patients from birth onward for treatment of SSSI caused by *E. faecalis, S. aureus* (penicillinase-producing isolates), *S. epidermidis, Acinetobacter* spp., *Citrobacter* spp., *Enterobacter* spp., *E. coli, Klebsiella* spp., *Morganella morganii, Proteus vulgaris, Providencia rettgeri, P. aeruginosa, Serratia* spp., *Peptococcus* spp., *Peptostreptococcus* spp., *Bacteroides* spp. including *B. fragilis, Fusobacterium* spp.	Not recommended in pediatric patients <30 kg with renal impairment (no data available)
Meropenem		IV	Approved in pediatric patients ≥3 months for treatment of cSSSI due to MSSA, *S. pyogenes, S. agalactiae*, viridans group *Streptococci*, *E. faecalis* (vancomycin-susceptible isolates only), *P. aeruginosa*, *E. coli, Proteus mirabilis, Bacteroides fragilis*, and *Peptostreptococcus* spp.	
Oxazolidinones				
Tedizolid	Sivextro	IV, PO	Approved in pediatric patients >12 years of age ABSSSI caused by MSSA, MRSA, *S. pyogenes, S. agalactiae, S. anginosus* group, and *E. faecalis*	

Used Off-Label for Pediatric ABSSSI				
β-lactam/β-lactamase inhibitor combinations				
Piperacillin-tazobactam	Zosyn	IV	Approved in adults for uncomplicated and cSSSI including cellulitis, cutaneous abscesses and ischemic/diabetic foot infections caused by beta-lactamase producing isolates of *S. aureus*	
Fluoroquinolones				
Ciprofloxacin	Cipro	IV, PO	Approved in adults for SSSI caused by *E. coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, Pseudomonas aeruginosa*, MSSA, *S. epidermidis, S. pyogenes*	Although effective in clinical trials, not a drug of first choice in pediatric age group due to increased incidence of adverse reactions (caused arthropathy in juvenile animals)
Levofloxacin	Levaquin	IV, PO	Approved in adults for uncomplicated SSSI (mild to moderate) including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections due to MSSA or *S. pyogenes* and complicated SSSI (cSSSI) due to MSSA, *E. faecalis, S. pyogenes, Proteus mirabilis*	Caused arthropathy and osteochondrosis in juvenile animals
Moxifloxacin		IV, PO	Indicated in adults for treatment of uncomplicated SSSI caused by susceptible *S. aureus* or *S. pyogenes* as well as cSSSI caused by MSSA, *E. coli, Klebsiella pneumoniae, E. cloacae*	Effectiveness not established in ≤18 years of age. Causes arthropathy in juvenile animals
Tetracyclines				
Doxycycline		IV	Used off-label in patients >8 years old	
Nitroimidazoles				
Metronidazole	Flagyl	IV, PO	Approved in adults for treatment of SSSI caused by *Bacteroides* spp. (e.g. *B. fragilis* group), *Clostridium* spp., *Peptococcus* spp., *Peptostreptococcus* spp., and *Fusobacterium* spp.	Safety and effectiveness in pediatric patients have not been established, except for treatment of amebiasis
Sulfonamide and trimethoprim combination				
Trimethoprim - sulfamethoxazole	Bactrim, Sulfatrim	PO		Contraindicated in pediatric patients <2 months of age due to potential risk of bilirubin displacement and kernicterus
Approved for Treatment of ABSSSI in Adults				
Cephalosporins				
Cefotetan		IV	Approved in adults for SSSI due to MSSA, *S. epidermidis, S. pyogenes, Streptococcus* species, *E. coli, Klebsiella pneumoniae, Peptococcus niger, Peptostreptococcus* spp.	Safety and effectiveness in pediatric patients have not been established
Lipoglycopeptides				
Telavancin	Vibativ	IV	Approved in adults for cSSSI caused by susceptible MSSA and MRSA, *S. pyogenes, S. agalactiae, S. anginosus* group, or *E. faecalis* (vancomycin-susceptible isolates only)	
Oritavancin	Orbactiv	IV	As above	

Dalbavancin	DALVANCE	IV	As above	

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

NDA 21-883 for DALVANCE® (dalbavancin hydrochloride) was approved on May 24, 2014, for the indication of acute bacterial skin and skin structure infections. At the time of approval, the Agency deferred submission of pediatric studies for ages 0 to 17 years until June 30, 2020, because the product was ready for approval for use in adults, and the pediatric studies had not been completed. The required postmarketing studies listed in the approval letter were as follows:

> **PMR 2145-1:** Conduct a single dose pharmacokinetic (PK) study in children from 3 months to less than 12 years of age.
>
> **PMR 2145-2:** Conduct a single dose PK study in neonates/infants from 0 to less than 3 months of age.
>
> **PMR 2145-3:** Conduct a Phase 3, randomized, comparator-controlled study of dalbavancin in children from 3 months to 17 years of age with ABSSSI.
>
> **PMR 2145-4:** Conduct a Phase 3, randomized, comparator-controlled study of dalbavancin in neonates/infants from birth to less than 3 months of age with ABSSSI.

It should be noted that on June 19, 2017, Allergan Sales, LLC (applicant) was released from PMRs 2145-3 and 2145-4, as they elected to modify the study and combine the age groups to be studied from "less than 3 months" to "birth to 18 years of age" in a single PMR. At the time of release, PMR 2145-10 was issued to incorporate the age group modification as follows:

> **PMR 2145-10:** Conduct a Phase 3, randomized, comparator-controlled study of dalbavancin in children from birth to 18 years of age with ABSSSI.

In accordance with PREA, the Applicant conducted 2 clinical studies: DUR001-106 (PMR 2145-1) and DAL-PK-02 (PMR 2145-2), and 1 clinical study: DUR001-306 (PMR 2145-10). This sNDA includes the results from completed Study DAL-PK-02 and DUR001-306, combined with population PK/PD modeling and simulation data, to support fulfillment of PREA PMR 2145-2 and 2145-10. Based on this data, the Applicant proposes to add pediatric patients 0-17 years of age to the approved indication of ABSSSI and to incorporate the relevant data into the DALVANCE labeling.

3.2 Summary of Presubmission Regulatory Activity

- **May 24, 2014:** DALVANCE® is approved for ABSSSI.

- **February 24, 2015:** The Agency grants a 6-month deferral extension for the Final Report for PMR 2145-1 (a single dose pharmacokinetic (PK) study in children from 3 months to less than 12 years of age) from September of 2015 to March of 2016.

- **April 22, 2015:** The Agency grants a 6-month deferral extension for the Final Report for PMR 2145-2 (PK study in neonates/infants from 0 to less than 3 months of age) from May of 2017 to November of 2017 due to the need for dose adjustments in this age group and necessary protocol revisions.

- **December 16, 2015:** The Agency grants a 6-month deferral extension for the Final Report for PMR 2145-3 (Phase 3, randomized, comparator-controlled study of dalbavancin in children from 3 months to 17 years of age with ABSSSI) from June 2017 to December 2017 due to ongoing discussions with the Applicant on the conduct of the study.

- **March 28, 2017:** The Agency informs the Applicant that the requirements for PMR 2145-1 have been fulfilled.

- **October 3, 2018:** The Agency agrees to grant a deferral extension for the Final Study report for PMR 2145-2 from May of 2019 to April of 2020 due to enrollment issues.

- **May 14, 2020:** The Agency agrees to grant a deferral extension for the Final Study Report for PMR 2145-10 from June 2020 to September of 2020.

Allergan Sales, LLC has submitted their efficacy supplement for pediatric labeling changes for the prescribing information for DALVANCE® on September 23, 2020.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

Clinical site inspections were not requested. In conjunction with OSI, the review team determined that inspections were not mission critical and would not warrant the risks associated with travel during the COVID-19 pandemic. Several of the Applicant's sites had been previously inspected for earlier supplements in the NDA and appeared to be compliant with good clinical practices. In this supplement, the number of patients enrolled at each site was small and there were no concerning findings regarding safety or efficacy identified at any particular site.

4.2 Product Quality

There are no proposed changes related to product quality or chemistry and manufacturing. Through an amendment dated 01/06/2021, the Applicant requested categorical exclusion for the environmental assessment (EA) as per 21 CFR 25.31(b) based on the calculation that estimated concentration of the active pharmaceutical substance at the point of entry into the aquatic environment will be below 1 ppb. The NDA supplement is acceptable from CMC standpoint.

4.3 Clinical Microbiology

The Gram-positive clinical isolates (*Staphylococcus aureus* including methicillin-resistant *S. aureus* (MRSA), methicillin-susceptible *S.aureus* (MSSA) , *Streptococcus pyogenes*, *Streptococcus dysgalactiae* and vancomycin-susceptible *Enterococcus faecalis*) collected from children with ABSSSI in the 2019 IDEA surveillance program were 100% susceptible to dalbavancin based on the FDA approved breakpoint for target pathogens (minimum inhibitory concentration (MIC) ≤0.25 mcg/mL). The dalbavancin MIC for *S. aureus*, *S. pyogenes*, *S. anginosus*, and *E. faecalis* baseline isolates for subjects in the clinical study DUR001-306 were below the FDA approved breakpoints.

5 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

There were no nonclinical pharmacology or toxicology data submitted. The reader is referred to Dr. Terry Miller's review of the pharmacology/toxicology data in the original NDA submission.

6 Clinical Pharmacology

6.1 Executive Summary

The clinical pharmacology information in this sNDA supports extending the approved adult indication of DALVANCE to pediatric patients from birth to less than 18 years of age. Of note, the Division does not agree with granting (b) (4). Refer to Section 8.1.3 for details.

The effectiveness of dalbavancin in pediatric patients with ABSSSI, including neonates, is based principally on an *a priori* probability of target attainment (PTA[3]) and comparable drug exposure between pediatric patients receiving the proposed dosage and adult patients receiving the approved dosage to allow for extrapolation of effectiveness in adults with ABSSSI to pediatric patients with ABSSSI. Additional efficacy data in pediatric patients was obtained from the Phase 3 pediatric safety, efficacy, and PK trial [trial DUR001-306, See Sections 8.1 and 8.2]. Exposure similarity between pediatric patients (including preterm neonates) and adult patients with ABSSSI were demonstrated and PTAs were above 90% up to the current dalbavancin susceptible breakpoint of 0.25 mcg/mL, supporting the efficacy of the Applicant's proposed pediatric age- and weight-based dosage (Table 2).

Table 2: Dosage of DALVANCE in Pediatric Patients

Age Range	Dosage
0 to < 6 years	22.5 mg/kg (maximum 1500mg)
6 to less than 18 years	18 mg/kg (maximum 1500mg)

Sufficient evidence of safety is based on one Phase 3 trial [Study DUR001-306], together with data from three Phase 1 PK studies (Studies A8841004 [previously submitted], DUR001-106, and DAL-PK-02) (See Section 8.2). PK data in pediatric patients from these studies were used for population PK modeling and simulation and PTA by MIC (Report DAL-MS-02).

6.2 Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The Applicant's Population PK (PopPK) modeling and probability of PK-PD target attainment (PTA) simulations support the extrapolation of clinical efficacy observed in adults with ABSSSI to the pediatric population (including preterm neonates) administered with the Applicant's proposed pediatric dosing regimens. From a clinical pharmacology perspective,

[3] PTA analysis compares free-drug plasma exposure following an antibiotic dosing regimen in a patient population against a target exposure (expressed relative to the minimum inhibitory concentration [MIC]) associated with a PD endpoint (e.g., 1-$\log_{10}$ bacterial kill) thought to predict efficacy.

there is sufficient evidence of effectiveness because it is expected that disease progression and response to intervention are similar between children and adults.

Simulated Day 1 unbound (free) dalbavancin exposures in plasma between pediatric age groups (including preterm neonates) and adults administered the recommended age-dependent single dose of DALVANCE demonstrated no clinically meaningful differences in exposures because cumulative response probabilities (CRP[4]; expressed as a percentage) were at least 90% in all simulated pediatric age groups, suggesting a high likelihood for treatment success across the pediatric population from preterm neonates to 17 years. This is in line with a CRP of 100% and clinical effectiveness observed in patients enrolled in the single-dose Phase 3 safety and exploratory efficacy pediatric trial DAL001-306 with the Applicant's proposed pediatric dosing regimens (See Section 8.1.2). Of note, the highest MIC_{90} of dalbavancin labeled organisms was 0.06 mg/L and used for simulations (2017 United States of America surveillance data; Report 14-DUR-01). For DAL001-306, the highest MIC_{90} of dalbavancin labeled organisms was 0.06 mg/L. For dalbavancin labeled pathogens the CLSI/FDA susceptible breakpoint is ≤ 0.25 mg/L. See section 14.6.3 and 14.6.3.3 for further details of the PTA analyses.

Accordingly, the review team has determined that use of dalbavancin PopPK modeling and simulation approach is appropriate as supportive evidence of effectiveness in pediatric populations with ABSSSI.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The Applicant's Population PK (PopPK) modeling and probability of PK-PD target attainment (PTA) analyses supports the proposed recommended pediatric dosing regimens up to the FDA/CLSI breakpoint MIC of ≤ 0.25 mg/L because: (i) the PTA at the proposed dosing regimen were ≥ 91.6% for MICs of ≤ 0.25 mg/L in all simulated pediatric populations (including preterm neonates) and (ii) in Study DAL001-306, 97.6% of pediatric patients, all having pathogen MICs of ≤ 0.25 mg/L, achieved the PK/PD target.

From a clinical pharmacology-regulatory perspective, the Applicant's analyses and conclusion are adequate based on the following:

- The PK/PD index (i.e., *f*$AUC_{0\text{-}24}$ h/MIC) associated with effectiveness of dalbavancin has been confirmed in neutropenic murine thigh infection models (Andes and Craig 2007; Lepak, et al. 2015) and used in previous PTA assessments for clinical and regulatory decisions in adults (e.g., Breakpoint update).
- The PK/PD targets used by the Applicant were conservative because: (i) the PK/PD target value was largest for *S. aureus* compared to other gram positives (i.e., *S. pneumoniae*) in the neutropenic murine thigh infection model and the arithmetic mean rather than median used was also larger (Andes and Craig 2007) (Lepak, et al. 2015);

[4] This is the expected population probability of target attainment for a specific drug dose and a specific population of bacteria.

(ii) the PK/PD target value is determined as the value required for 1-log bacteria killing rather than net-stasis of bacteria killing. Note, net bacterial stasis has been an endpoint used to guide development in indications such as ABSSSI probably because of source control (incision and drainage) and high no-pharmacotherapy response rate. This thinking is concordant with exposure-response findings for linezolid and tigecycline to treat ABSSSI (Ambrose, 2007); (iii) PK/PD targets (value of *f*AUC/MIC) determined based on the same plasma protein binding between mice and humans were used in the PTA analyses although literature (Lepak, et al. 2015) reported a higher plasma protein binding in mice compared to humans. As a result, an approximately 4-fold higher *f*AUC/MIC value (compared to that based on a higher plasma protein binding in mice than humans) were used in the PTA analyses. See Section 14.6.1.1 for further details and discussion; and (iv) the daily average of the 5-day plasma AUC of DAL in humans ($AUC_{0\text{-}120h}/5$) is smaller that $AUC_{0\text{-}24h}$, and were used for PTA analyses.

- Residual uncertainties are acceptable based on additional TA analyses conducted by the review team. The PTA results using a random PK/PD target approach that incorporated PD variability were similar to that using the arithmetic mean as the PK/PD target for all individuals. Furthermore, using the exact $AUC_{0\text{-}24h}$ (rather than $AUC_{0\text{-}120\ h}/5$) and arithmetic mean as the PK/PD target for all individuals, PTAs for the pediatric populations were > 80% for targets associated with 2-log bacterial kill.

Therefore, considering the totality of evidence, we find the proposed recommended pediatric dosing regimens to be adequate for efficacy with MIC's up to the FDA/CLSI breakpoint MIC of ≤ 0.25 mg/L. Population pharmacokinetic modeling and simulations, together with PTA analyses, demonstrated that there are no clinically meaningful differences in drug exposure between pediatric age groups and adults following administration of the age-dependent recommended single dose of DALVANCE. Of note, the simulated (expected) median plasma AUC from 0 to 120 hours ($AUC_{0\text{-}120h}$) of dalbavancin in pediatric patient age groups from term neonates at birth to less than 18 years were comparable and ranged between 82% to 96% that in adult patients ($AUC_{0\text{-}120h}$, 10400 mg*h/L). The expected median plasma $AUC_{0\text{-}120h}$ of dalbavancin in preterm neonates at birth (gestational age 26 weeks to <37 weeks) was approximately 62% of that in adult patients. The expected median maximum plasma concentrations (C_{max}) of dalbavancin for pediatric patient age groups ranged between approximately 70% to 53% that in adult patients (C_{max}, 412 mg/L). However, the PTA up to MIC of 0.25 mg/L in preterm neonates was still > 90%, supporting that lower median value of simulated AUC and C_{max} in preterm neonates than those in adults will not affect effectiveness of the proposed dosing of dalbavancin (see Section 14.6.3.2).

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Currently, we agree with the Applicant's proposed dosage regimens in pediatric patients with creatinine clearance (CLcr) ≥30 mL/min/1.73m^2. We agree with the Applicant that there is insufficient information to recommend a dosage adjustment in pediatric patients with severe renal impairment (i.e., an age appropriate creatinine clearance (CLcr) or estimated glomerular

filtration rate (eGFR) consistent with an adult CLcr < 30 mL/min). This is based on: (i) no pediatric patients with CLcr < 30 mL/min/1.73m^2 participating in the clinical studies/trial; (ii) the PopPK model suggesting renal function had less impact on dalbavancin CL and AUC in pediatrics compared to adults; (iii) already lower exposures ($AUC_{0\text{-}120}$) in pediatrics relative to adults administered the proposed pediatric or approved adult single-dose dalbavancin regimens, respectively. Therefore, precise quantitative recommendations regarding dose reductions in pediatric patients with severe renal impairment is currently unavailable.

Note that the proposed (b) (4) .

During our review, we found the recommended dosage adjustments for both the single-dose regimen and two-dose regimen in adults with severe renal impairment (CLcr <30 mL/min) may not be warranted when considering the potential risk to an individual's safety likely acceptable without a dosage adjustment. The following comment was sent to the Applicant:

> *Currently, we agree with your proposed dosage regimens in pediatric patients with creatinine clearance (CLcr) ≥30 mL/min/1.73m^2. However, during our review, we found the recommended dosage adjustments for both the single-dose regimen and two-dose regimen in adults may not be warranted as the potential risk to an individual's safety are likely acceptable without a dosage adjustment. This is based on (i) only a 25% reduction of the total dose based on a little relative increase in $AUC_{0\text{-}14days}$ in patients with stable CLcr <30 mL/min compared to patients with normal renal function; (ii) a generally considered broad therapeutic index (i.e., no known concentration dependent adverse events); (iii) safety information from studies with extended duration dosing or larger 2-dose regimen (e.g., 1500 mg QW) in adult patients with osteomyelitis; and (iv) single-dose regimens, much akin to a loading dose, typically do not need adjustment.* (b) (4)

Question on clinically relevant specifications

Plasma Protein Binding (PPB) of DAL

In the original submission, the Applicant used higher PPB values of dalbavancin in mice than that in humans (98.4% *vs.* 93%) based on a literature (Lepak et al., 2015). However, we found other reports showed dalbavancin PPB being the same between humans and other animal species. We concluded that comparable PPB of dalbavancin between mice and humans should be used for PTA analysis (see Section 14.6.1.1 for further details and discussion regarding PPB of dalbavancin). Accordingly, we requested the Applicant reconduct all PK/PD analyses. The PTA analyses reconducted with the same PPB between mice and humans (i.e., approximately 4.3-fold greater fAUC/MIC as a dalbavancin PK/PD target) demonstrated that PTA is still greater than or close to 90% for MIC of up to 0.25 mg/L for all age-groups of pediatric patients including term and preterm neonates (See Sections 14.6.1.1 and 14.6.3.3) for further details and discussion regarding PPB and PTA, respectively).

7 Sources of Clinical Data and Review Strategy

7.1 Table of Clinical Studies

The clinical safety and efficacy data were based on a single Phase 3 pediatric trial in patients with ABSSSI (Study DUR001-306). The Table 3 summarizes this study, which was a multicenter, open-label, randomized, comparator-controlled, and descriptively analyzed trial. Table 3 also summarizes Studies A8841004, DUR001-106, and DAL-PK-02 which were Phase 1 single-dose PK studies conducted to determine dosing and evaluate safety.

Table 3 : List of Clinical Trials Relevant to this NDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	Countries (No. of Centers)
		Controlled Studies to Support Efficacy and Safety						
DUR001-306	NCT02814916	Phase 3, multicenter, open-label, randomized, comparator-controlled trial	Study drug regimen, either: • A single dose of IV dalbavancin [1] • Or a 2-dose regimen of once-weekly IV dalbavancin [2] • Comparator regimen, either: o IV vancomycin (for methicillin-resistant Gram-positive infections) o Or IV oxacillin or flucloxacillin (for methicillin-sensitive Gram-positive infections)	Primary: Safety Secondary: Clinical response at 48-72 hours, EOT visit (14 ± 2 days), TOC visit (28 ± 2 days), and follow-up visit (54 ± 7 days)	**Treatment duration:** Dalbavancin: single-dose and 2-dose regimen of once weekly (total 14 days of coverage) Comparator: 10-14 days **Follow up - clinical response at:** -48-72 hours after randomization -End of treatment (14 ± 2 days after start of therapy) -Test of cure visit (28 ± 2 days after start of therapy) -Last follow-up visit (54 ± 7 days after start of therapy)	191	Pediatric patients from birth to 17 years of age with ABSSSI caused by either known or suspected susceptible Gram-positive organisms organized into 5 cohorts: Cohort 1: 12 to 17 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 (including preterm neonates with gestational age ≥ 32 weeks)	United States (6), Guatemala (2), Mexico (1), Panama (1), Bulgaria (8), Georgia (4), Ukraine (2), Latvia (1), Greece (2), Spain (1), South Africa (2)
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
A8841004	NCT00678106	Phase 1, open-label, multicenter study	Single-dose IV dalbavancin	PK parameters, safety, tolerability	Treatment: single IV infusion over 30 minutes on Day 1 Follow-up: Blood	10	Pediatric patients 12-17 years of age (inclusive)	United States

					samples (13 per participant) collected over 56 days for PK assessment			
DUR001-106	NCT01946568	Phase 1, open-label, single-dose study	Single-dose IV dalbavancin	PK parameters, safety, tolerability	Treatment: single IV infusion over 30 minutes Follow-up: Blood samples (6 per participant) collected over 28 days for PK assessment	36	Pediatric patients 3 months to 11 years of age organized into 3 cohorts: Cohort 1: ≥5 years to 11 years Cohort 2: <5 years Cohort 3: 3 months to <2 years	United States
DAL-PK-02	NCT02688790	Multicenter, randomized, open-label, single-dose study	Single-dose IV dalbavancin	PK parameters, safety, tolerability	Treatment: single IV infusion over 30 minutes on Day 1 Follow-up: PK samples (6 per participant) collected over 28 days	8	Pediatric patients <28 days to 3 months organized into 3 cohorts: • Cohort 1: aged ≥28 days to <3 months • Cohort 2: term neonates aged ≤28 days (gestational age ≥37 weeks) • Cohort 3: preterm neonates aged ≤28 days (gestational age ≥32 to <37 weeks)	United States (5)

[1] 3 months to < 6 years old: 22.5 mg/kg (maximum 1500 mg) on Day 1; ≥ 6 years to 17 years old (inclusive): 18 mg/kg (maximum 1500 mg) on Day 1

[2] 3 months to < 6 years old: 15 mg/kg (maximum 1000 mg) on Day 1, and 7.5 mg/kg (maximum 500 mg) on Day 8; ≥ 6 years to 17 years old (inclusive): 12 mg/kg (maximum 1000 mg) on Day 1, and 6 mg/kg (maximum 500 mg) on Day 8

7.2 Review Strategy

For the indication of ABSSSI, efficacy in pediatrics is traditionally extrapolated from adults. Therefore, the pediatric studies were designed with relatively small sample sizes and with the primary objectives of evaluating safety and tolerability. Efficacy results were assessed descriptively.

This review focuses on Study DUR-306, a Phase 3, open-label, randomized, comparator controlled, multicenter trial of the safety and efficacy of dalbavancin versus active comparator in pediatric patients with ABSSSI. This study submitted with this sNDA provided supportive evidence of safety as well as efficacy in pediatric patients aged from birth to less than 18 years of age with ABSSSI.

Data Sources
Data sources reviewed included patient-level datasets, study reports, protocols, statistical analysis plans, and case report forms.

The SDTM and ADaM datasets are available at the following location in the Agency's Electronic Document Room: \\CDSESUB1\evsprod\NDA021883\1157\m5\datasets

Data and Analysis Quality
The quality of submitted data was sufficient for review purposes. It was possible to reproduce the Applicant's main analysis results without complex manipulations. The protocols and statistical analysis plans were sufficiently precise and comprehensive, and the Applicant's reported analyses were consistent with planned analyses.

8 Statistical and Clinical and Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 Study Design - DUR001-306

Trial Design

This was a Phase 3, multicenter, open-label, randomized, active controlled trial evaluating the safety and efficacy of a single-dose of IV dalbavancin and a 2-dose regimen of once weekly IV dalbavancin for the treatment of ABSSSI known or suspected to be due to susceptible Gram-positive organisms in children. The comparator regimen was either IV vancomycin (for methicillin-resistant Gram-positive infections) or IV oxacillin or flucloxacillin (for methicillin-susceptible Gram-positive infections) for 10-14 days. Patients could be switched from IV oxacillin or flucloxacillin to oral cefadroxil after at least 72 hours of study drug treatment, if they met specified criteria for oral therapy. Similarly, if infection with methicillin-resistant *S. aureus*

was documented, then patients could be switched from IV vancomycin to oral clindamycin after at least 72 hours of parenteral antibiotic therapy, if they met specified criteria for oral therapy. If an alternate comparator regimen was indicated by local susceptibility patterns or recommended by local treatment guidelines, this had to be discussed with the medical monitor.

The trial planned to enroll approximately 188 patients into five age cohorts: Cohort 1: 12 – 17 years with 54 patients; Cohort 2: 6 – < 17 years with 54 patients; Cohort 3: 2 – < 6 years with 35 patients; Cohort 4: 3 months – < 2 years with 35 patients; and Cohort 5: birth – < 3 months with 10 patients. Patients in Cohorts 1 – 4 were to be randomized to receive dalbavancin (single-dose or two-dose regimen) or comparator in a 3:3:1 randomization scheme.
For the dalbavancin single-dose treatment group, patients 3 months to < 6 years old received 22.5 mg/kg (maximum 1500 mg) of dalbavancin on Day 1 and patients ≥ 6 years to 17 years old (inclusive) received 18 mg/kg (maximum 1500 mg) of dalbavancin on Day 1.
For the dalbavancin two-dose arm, patients 3 months to < 6 years old received dalbavancin dosed at 15 mg/kg (maximum 1000 mg) on Day 1, and 7.5 mg/kg (maximum 500 mg) on Day 8 and patients ≥ 6 years to 17 years old (inclusive) received dalbavancin dosed at 12 mg/kg (maximum 1000 mg) on Day 1, and 6 mg/kg (maximum 500 mg) on Day 8. The randomization scheme did not include the youngest age cohort (birth to < 3 months of age), as all patients in this cohort were to receive the single-dose regimen of dalbavancin. The two youngest age cohorts were the most difficult to enroll and strategies were developed during the trial by each site to improve enrollment. In order to support enrolment of patients < 3 months of age, this cohort recruited patients with either ABSSSI or neonatal sepsis.

The Baseline (predose) period was from Day -1 to Day 1. The first dose of study intervention was administered on Day 1, followed by assessments at 48-72 hours postdose and on Day 8 ± 1. The EOT Visit was on Day 14 ± 2, the TOC Visit on Day 28 ± 2, and the Follow-Up Visit on Day 54 ± 7.

Study Endpoints

Primary:

- Physical examination, vital signs, adverse events, deaths (Cohort 5 only), and clinical laboratory tests
- Audiologic testing in at least 20 children < 12 years old performed at Baseline and repeated at Day 28 (± 2 days)
- Impact of dalbavancin on bowel flora evaluated in all patients from birth to < 2 years by performing PCR for *Clostridium difficile* and culture for VRE on a stool specimen or rectal swab

Secondary

The following are the secondary endpoints assessed in this trial. Patients who died or received given rescue medication were considered non-responders or failures. The efficacy endpoints roughly follow the Agency Guidance for Industry: Acute Bacterial Skin and Skin Structure

Infections: Developing Drugs for Treatment[5], with the exception of Cohort 5, which had different definition of clinical response.

- Clinical response at 48-72 hours after randomization was defined as
    - Cohorts 1-4: ≥ 20% reduction in lesion size compared to baseline
    - Cohort 5 patients with ABSSSI: cessation of increase in lesion size and decreased erythema or tenderness compared to baseline with no appearance of new lesions
    - Cohort 5 patients with sepsis: improvement of at least one abnormal clinical and laboratory parameter related to sepsis
- Clinical response at remaining time-points based primarily on the global clinical assessment of the patient made by the investigator at that evaluation time-point.
    - Clinical response at EOT visit (14 ± 2 days) defined as Cure, Improvement, Failure, or Unknown
    - Clinical response at the TOC visit (28 ± 2 days) and at the follow-up visit (54 ± 7 days) defined as Cure, Failure or Unknown
    - Clinical response categories are defined below:
        - Cure: Resolution of the clinical signs and symptoms of infection, when compared to baseline. No additional antibacterial treatment was required for disease under study.
        - Improvement (only used at the EOT visit): Reduction in severity of 2 or more, but not all, clinical signs and symptoms of infection, when compared with baseline (Cohorts 1-4, and ABSSSI patients in Cohort 5). In sepsis patients in Cohort 5 (birth to < 3 months), improvement was defined as reduction in severity of at least 1 abnormal clinical and laboratory parameter related to sepsis, when compared with baseline. For Cohorts 1-4 only, no additional antibacterial treatment was required for disease under study. For Cohort 5, no rescue medication was required after at least 48 hours of start of study treatment.
        - Failure: Persistence or progression of baseline clinical signs and symptoms of infection after at least 2 days (48 hours) of treatment or development of new clinical findings consistent with active infection.
        - Unknown: Extenuating circumstances preclude classification to one of the above.
- Clinical response was determined by baseline pathogen at 48-72 hours post randomization, EOT, TOC, and last follow-up visit, as described above.
- Microbiological response at 48-72 hours post randomization, EOT, TOC, and last follow-up visit
    - Direct demonstration of eradication or persistence of the causative organism had to be attempted in all patients where it was considered standard practice. However, this had to be done in all patients who were considered treatment failures.

[5] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acute-bacterial-skin-and-skin-structure-infections-developing-drugs-treatment

  - Microbiological responses were defined as:
    - Eradication: Source specimen demonstrates absence of the original baseline pathogen.
    - Presumed eradication: Source specimen was not available to culture and the patient was assessed as a clinical responder (48-72 hours post randomization), cure of improvement (EOT visit), cure (TOC and follow-up visit).
    - Persistence: Source specimen demonstrates continued presence of the original baseline pathogen.
    - Presumed persistence: Source specimen was not available to culture and the patient was assessed as a clinical non-responder (48-72 hours post randomization), failure (EOT, TOC and follow-up visit)
    - Indeterminate: Source specimen was not available to culture and the patient's clinical response was assessed as unknown or missing (EOT, TOC and follow-up visit)
  - Eradication and presumed eradication were considered favorable microbiological responses and persistence and presumed persistence were considered unfavorable microbiological outcomes.
- All-cause mortality
  - For Cohort 5 only (birth to < 3 months): all-cause mortality was determined at test of cure visit (28 ± 2 days after start of therapy)
- Concentration of dalbavancin in plasma.
  - The population PK profile of dalbavancin was assessed using a sparse sampling approach and will be reported separately.

Statistical Analysis Plan

The following Analysis Populations were defined.

- Screened: All screened patients who sign informed consent
- Intent-to-Treat (ITT): All randomized patients regardless of whether or not they received study drug.
- Safety: All patients in the ITT population who received at least 1 dose of study drug
- Modified Intent-to-Treat (mITT): All randomized patients who received at least one dose of study drug and had a diagnosis of ABSSSI (or a suspected or confirmed sepsis for Cohort 5) not known to be caused exclusively by a Gram-negative organism.
- Clinically Evaluable (CE): Four CE populations will be defined based on the timing of the outcome assessment, CE-48-72 hours (post randomization), CE-EOT, CE-TOC, and CE-Follow-up visit. Patients who meet all of the following criteria will be considered to be clinically evaluable at the respective visit:
  - Fulfilled inclusion/exclusion criteria such that the clinical response is not confounded (if a patient is subsequently found to have violated an enrollment criteria, even if not noted at the baseline visit, the patient will not be included in the clinical evaluable population);
  - For patients randomized to dalbavancin, received at least 1 dose of active study

medication. For patients randomized to comparator, received at least 5 days of study drug therapy;
    - For Cohorts 1-4: received no more than one dose of another systemic antibacterial therapy (with the exception of systemic aztreonam, oral or IV metronidazole or oral vancomycin) with documented activity against the causative organism from study drug initiation until the outcome assessment (visit) for a non-ABSSSI indication. [Note: Patients receiving a new non-study systemic antibacterial treatment (with the exception of aztreonam or metronidazole) for treatment of the ABSSSI from initiation of study drug through the outcome assessment (visit) will be assessed as Evaluable Failures]. Note: Cohort 5 are permitted to receive allowed concomitant antibacterials.
    - Had an outcome assessment at which a clinical response could be evaluated for the time point specified;
    - Received appropriate adjunctive antibacterial coverage if the patient had a culture-documented mixed ABSSSI (one or more Gram-positive pathogens with one or more Gram-negative aerobic or anaerobic organisms).
- Microbiological ITT (microITT): This population consist of all patients in the ITT population who had at least 1 Gram-positive pathogen isolated at Baseline
- Microbiologically Evaluable (ME):
    - This population consist of patients who meet all of the criteria for the CE population and microITT population.
    - There are four ME populations: ME-48-72 hours, ME-EOT, ME-TOC, and ME-Follow-up visit.

Sample Size
The trial was designed to determine the safety and descriptive efficacy of dalbavancin for the treatment of ABSSSI known or suspected to be caused by susceptible Gram-positive organisms, including MRSA. Since the study is primarily a safety study, the sample size was not calculated based on a power calculation for a hypothesis test.

The trial was designed to enroll approximately 188 patients, with 178 patients enrolled in Cohorts 1 – 4 (76 in the single-dose arm of dalbavancin, 76 in the two-dose arm of dalbavancin, and 26 in the comparator arm). There was an enrollment target of 10 patients for Cohort 5 (birth to < 3 months), which includes at least 5 patients ≤ 28 days (including pre-term neonates).

Statistical Methods
Descriptive statistics were calculated, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided. Safety results and adverse events were tabulated by separate treatment regimens, including those who did and did not receive additional agents (aztreonam and/or metronidazole), in order to analyze safety in these respective groups.

Summary of efficacy variables were done by age and treatment group for all patients.

Protocol Amendments

The following are the major protocol amendments that were put in place after the trial was initiated on 3/30/2017.

Amendment 5 (6/27/2017)

- A fifth cohort, Cohort 5 (birth to < 3 months of age) was added to this study and the randomization scheme was modified to include that Cohort 5 would only be assigned to the single-dose regimen of dalbavancin, with dose to be determined by results of Study DAL-PK-02.
- Statement that for Cohort 5 only, patients with sepsis may be included in this study was added.
- Information added that patients in Cohort 5
    - Will be allowed concomitant antibacterial therapy.
    - Will undergo audiologic testing
    - Will have mpact on bowel flora determined
    - 'All-cause mortality analyses' were added
- Hy's law criteria assessment was added

Amendment 6 (4/26/2018)

- Updated the planned total number of patients to 188 from the previous total of 175 (in Amendment 5), including increasing the sample size in each treatment group by 1 patient (76 instead of 75 patients in each dalbavancin group, and 26 instead of 25 patients in the comparator arm) and adding planned recruitment of 10 patients aged < 3 months
- Change of Cohort 5 recruitment initiation parameters, including:
    - removal of specification of starting dosing recommendation parameters
    - removal of specification of staggered recruitment design based on age clarification that recruitment for Cohort 5 will be initiated based on review of initial results from patients > 28 days to < 3 months in study DAL-PK-02 (DUR001-107)
- Removal of statement describing expected enrollment numbers for patients with MRSA infections
- Update to audiologic testing patient disposition specifications:
    - removal of lower age range
    - reduction in the minimal threshold for number of children <2 years
    - removal of statement regarding number of children who should receive dalbavancin
    - removal of statement that all patients in Cohort 5 will have audiologic testing
- For Cohort 5: addition of wording defining rescue therapy, and how rescue therapy use is classified in terms of clinical response outcome

8.1.2 Study Results - DUR001-306

Compliance with Good Clinical Practices

The Applicant has provided attestation that the trial was conducted in compliance with Good Clinical Practices (GCPs).

Financial Disclosure

The Applicant certified that the clinical investigators had not entered into any financial arrangements whereby the value of the compensation could affect the outcome of the trial (see Appendix 14.2). None of the investigators had a proprietary interest in the product, had significant equity in the Applicant, or had received significant payments of other sorts as defined in 21 CFR part 54.

Patient Disposition

One hundred ninety-six (196) patients were screened, of which 5 were screen failures. These patients were screened at thirty sites, with 6 in the US, 4 in Latin America, 15 in Eastern Europe, 3 in Western Europe, and 2 in South Africa. Overall, 191 patients were enrolled and completed the baseline period, 188 (98.4%) completed study intervention, 187 (97.9%) completed the treatment period and also completed the follow-up period. Patient disposition is presented in Table 4 and a summary of the analysis populations are presented in Table 5. Note, there were five patients in the dalbavancin single-dose group enrolled with ABSSSI/neonatal sepsis suspected to be caused by a Gram-positive pathogen, that was later confirmed to be caused by a Gram-negative pathogen. These 5 patients were excluded from the mITT population.

Table 4: Patient Disposition (ITT)- Birth to <18 years of age

Phase / Disposition	Dalbavancin Single-Dose (N=83) n (%)	Dalbavancin Two-Dose (N=78) n (%)	Comparator (N=30) n (%)	Total (N=191) n (%)
Baseline Period	83 (100)	78 (100)	30 (100)	191 (100)
Completed	83 (100)	78 (100)	30 (100)	191 (100)
Study Drug				
Completed	83 (100)	75 (96.2)	30 (100)	188 (98.4)
Prematurely Discontinued	0 (0)	3 (3.8)	0 (0)	3 (1.6)
Reason for Premature Discontinuation				
Withdrawal of consent	0 (0)	2 (2.6)	0 (0)	2 (1)
Other	0 (0)	1 (1.3)	0 (0)	1 (0.5)
Treatment Period				
Completed	83 (100)	74 (94.9)	30 (100)	187 (97.9)
Prematurely Discontinued	0 (0)	4 (5.1)	0 (0)	4 (2.1)
Reason for Premature Discontinuation				
Withdrawal of consent	0 (0)	2 (2.6)	0 (0)	2 (1)
Lost to Follow-up	0 (0)	1 (1.3)	0 (0)	1 (0.5)
Other	0 (0)	1 (1.3)	0 (0)	1 (0.5)
Follow-up Period				
Completed	83 (100)	74 (94.9)	30 (100)	187 (97.9)

Prematurely Discontinued	0	(0)	0	(0)	0	(0)	0	(0)

Source: CSR, Table 10-1

Table 5: Analysis Populations- Birth to <18 years of age

Population	Dalbavancin Single-Dose	Dalbavancin Two-Dose	Comparator	Total
ITT	83	78	30	191
mITT	78	78	30	186
Safety	83	78	30	191
CE-48-72H	77	75	30	182
CE-EOT	76	72	30	178
CE-TOC	76	72	30	178
CE-Follow-up	75	71	30	176
microITT	51	55	18	124
ME-48-72H	50	52	18	120
ME-EOT	49	50	18	117
ME-TOC	49	50	18	117
ME-Follow-up	48	49	18	115

*Cohort 5 (Birth to <3 month of age), patients were all enrolled in the dalbavancin single-dose arm, and included in the table above. There were 5 Safety, 5 ITT, 3 MITT, 3 CE 48-72 hours, 3 CE at EOT, 3 CE at TOC, 3 CE at Follow-up, 1 MicroITT, 1 ME 48-72 hours, 1 ME at EOT, 1 ME at TOC, 1 ME at Follow-up in this Cohort.
Source: CSR, Table 10-2

Protocol Violations/Deviations

The incidence of significant protocol deviations is summarized in Table **6**. The majority of protocol violations were related to study procedures. None were related to dosing issues in the dalbavancin treatments arms, however, few dosing violations occurred in the comparator arm.

Table 6: Significant Protocol Deviations (ITT)- Birth to <18 years of age

	Dalbavancin Single-Dose (N=83)	Dalbavancin Two-Dose (N=78)	Comparator (N=30)	Total (N=191)
Number of Patients with at Least One Significant Protocol Deviations n (%)	30 (36.1)	15 (19.2)	19 (63.3)	64 (33.5)
Study Procedure	21 (25.3)	11 (14.1)	9 (30.0)	41 (21.5)
Informed Consent (ICH)	3 (3.6)	3 (3.8)	2 (6.7)	8 (4.2)
Inclusion Criteria (ICH)	6 (7.2)	2 (2.6)	0 (0.0)	8 (4.2)
IP dosing Non-compliance (ICH)	0 (0.0)	0 (0.0)	7 (23.3)	7 (3.7)
Wrong IP Dose (ICH)	1 (1.2)	1 (1.3)	3 (10.0)	5 (2.6)
Exclusion Criteria (ICH)	4 (4.8)	1 (1.3)	0 (0.0)	5 (2.6)

3 out of 5 patients in Cohort 5, who were in the dalbavancin single-dose group, and were qualified for mITT population had at least 1 significant protocol violation (exclusion criteria violation in 2 patients [subject# (b) (6) and study procedure related violation in 1 patient (Subject # (b) (6)
Abbreviations: IP= Investigational product; ICH= International Council for Harmonisation of technical equirements

for pharmaceuticals for human use
Source: CSR Erratum 01, Table 14.1-1.3

Table of Demographic Characteristics

In the ITT population, more males (62.3%) were randomized than females (37.7%). The majority of the patients were in the older age cohorts. The 12 to 17 year old cohort had 64 patients (33.5%); the 6 to < 12 year old cohort had 60 patients (31.4%); the 2 to < 6 year old cohort had 45 patients (23.6%); the 3 month to <2 year cohort had 12 patients (8.9%); and the birth to < 3 month cohort had 5 patients (2.6%). The vast majority of the patients were White (89%) and were not Hispanic or Latino (93.7%). Only 3.7% of the patients were from the United States, with the vast majority from Eastern Europe (83.2%). (Table **7**)

Table 7: Demographic characteristics of the primary efficacy analysis (SafetyITT)-Birth to <18 years of age

Demographic Parameters	Dalbavancin Single-Dose (N=83) n (%)	Dalbavancin Two-Dose (N=78) n (%)	Active Comparator (N=30) n (%)
Sex			
Male	48 (57.8)	53 (67.9)	18 (60.0)
Female	35 (42.2)	25 (32.1)	12 (40.0)
Age			
Mean years (SD)	8.279 (5.2378)	8.898 (4.9271)	6.775 (4.2048)
Median (years)	8.000	9.000	7.000
Min, max (years)	0.04, 17.00	0.25, 17.00	0.75, 15.00
Age Group			
Cohort 5: Birth to < 3 months	5 (6.0)	0 (0.0)	0 (0.0)
Birth to <= 28 days	3 (3.6)	0 (0.0)	0 (0.0)
> 28 days to < 3 mths	2 (2.4)	0 (0.0)	0 (0.0)
Cohort 4: 3 months to < 2 years old	6 (7.2)	8 (10.3)	3 (10.0)
Cohort 3: 2 years to < 6 years old	18 (21.7)	17 (21.8)	10 (33.3)
Cohort 2: 6 years to < 12 years old	25 (30.1)	24 (30.8)	11 (36.7)
Cohort 1: 12 years to 17 years old	29 (34.9)	29 (37.2)	6 (20.0)
Race			
White	72 (86.7)	69 (88.5)	29 (96.7)
Black or African American	4 (4.8)	6 (7.7)	0 (0.0)
Asian	1 (1.2)	1 (1.3)	0 (0.0)
American Indian or Alaska Native	3 (3.6)	1 (1.3)	1 (3.3)
Multiple [1]	3 (3.6)	1 (1.3)	0 (0.0)
Region			
United States	2 (2.4)	5 (6.4)	0 (0)
Rest of the World	81 (97.6)	73 (93.6)	30 (100)

Latin America	3 (3.6)	5 (6.4)	1 (3.3)
Eastern Europe	69 (83.1)	62 (79.5)	28 (93.3)
Western Europe	3 (3.6)	2 (2.6)	1 (3.3)
South Africa	6 (7.2)	4 (5.1)	0 (0)

[1] Patients who reported >=2 races, including patients who report White and >=1 other race.
For 5 patients in Cohort 5: There were 2 females and 3 males; 5 whites, 5 Not Hispanics or Latinos, 4 from sites in Eastern Europe and 1 from a US site
Source: Reviewer table modified from CSR, Table 10-3, CSR Listing 16.1.4-1, and CSR Listing 16.1.3.1

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

For mITT patients 3 months to less than 18 years of age, the ABSSSI infection types observed in the trial were major cutaneous abscess (53.6%), cellulitis (28.4%), and surgical site/traumatic wound infection (18.0), see Table 8 for more information.

Table 8: ABSSSI Infection Type (mITT patients 3 months to less than 18 years of age)

Infection Type	Dalbavancin Single-Dose N=75 n (%)	Dalbavancin Two-Dose N=78 n (%)	Comparator N=30 n (%)	Total N=183 n (%)
Cellulitis	21 (28.0)	19 (24.4)	12 (40.0)	52 (28.4)
Major Cutaneous Abscess	39 (52.0)	45 (57.7)	14 (46.7)	98 (53.6)
Surgical Site/Traumatic Wound Infection	15 (20.0)	14 (17.9)	4 (13.3)	33 (18.0)

In Cohort 5 (birth to <3 months of age) 3 patients qualified for mITT (2 patients had the diagnosis of ABSSSI [1 with cellulitis, 1 with major cutaneous abscess], and 1 patient had diagnosis of *S. aureus* sepsis).
Source: modified from CSR, Table 10-5

The most common pathogens isolated in the microITT population (N=124) were oxacillin-susceptible (MSSA) *Staphylococcus aureus* (N=104, 83.9%), *Streptococcus pyogenes* (N=12, 9.7%), oxacillin-resistant (MRSA) *Staphylococcus aureus* (N=6, 4.8%), *Enterococcus faecalis* (N=4, 3.2%), and *Streptococcus mitis/Streptococcus oralis* (N=3, 2.4%).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Seven participants (Dalbavancin single-dose: 5 [6.0%]; Dalbavancin two-dose: 2 [2.6%]; and Comparator: 0 [0%]) received at least 1 concomitant antibacterial drug, including three patients in the dalbavancin treatment arms who received concomitant vancomycin**.** Please refer to Table 9 for details.

Table 9: Concomitant Antibacterial Medications (Safety Population)

	Dalbavancin Single-Dose N=83 n (%)	Dalbavancin Two-Dose N=78 n (%)	Comparator N=30 n (%)	Total N=191 n (%)
Number of Patients with at Least One Preferred Term	5 (6.0)	2 (2.6)	0 (0.0)	7 (3.7)
RIFAMPICIN	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.5)

MEROPENEM TRIHYDRATE	1 (1.2)	0 (0.0)	0 (0.0)	1 (0.5)
AMOXICILLIN W/CLAVULANATE POTASSIUM	1 (1.2)	0 (0.0)	0 (0.0)	1 (0.5)
CEFALEXIN	1 (1.2)	0 (0.0)	0 (0.0)	1 (0.5)
VANCOMYCIN	2 (2.4)	1 (1.3)	0 (0.0)	3 (1.6)
METRONIDAZOLE	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.5)
CLINDAMYCIN	2 (2.4)	0 (0.0)	0 (0.0)	2 (1.0)
MUPIROCIN	1 (1.2)	0 (0.0)	0 (0.0)	1 (0.5)
CEFTRIAXONE	1 (1.2)	0 (0.0)	0 (0.0)	1 (0.5)

Source: CSR, Table 14.1-5.1.2

Efficacy Results – Primary Endpoint

The primary objective of the trial was to determine the safety of dalbavancin for the treatment of ABSSSI infections in children, from birth to 17 years (inclusive), known or suspected to be caused by susceptible Gram-positive organisms, including methicillin-resistant strains of *Staphylococcus aureus.* Thus, the primary endpoints were safety-related and are not discussed here.

Data Quality and Integrity

The data quality and integrity were adequate.

Efficacy Results – Secondary and other relevant endpoints

Table 10 contains the results for clinical response at 48-72 hours in the mITT population. The Applicant concluded that the clinical responder rates at 48 – 72 hours in the mITT population were similar across the three treatment groups. We do not recommend pooling across the five age cohorts, because the youngest age cohort, birth to <3 months of age, only enrolled patients in the dalbavancin single-dose treatment group and also included patients with both ABSSSI and neonatal sepsis. The table contains results by age cohort and by Cohorts 1 – 4 combined. Across the four oldest age cohorts, i.e., 3 months to less than 18 years of age, the clinical responder rates were relatively consistent. Given this consistency in rates across the four older age cohorts, we pooled data for patients 3 months to less than 18 years of age and found that the clinical responder rates at 48 – 72 hours in the mITT population were similar across the three treatment groups (dalbavancin single-dose: 97.3%, dalbavancin two-dose: 93.6%, and comparator: 86.7%). The difference in responder rates between the dalbavancin single-dose and comparator groups was 10.7%, with an exact 97.5% confidence interval (CI) of (-1.7%, 31.6%). The difference in responder rates between the dalbavancin two-dose and comparator groups was 6.9%, with an exact 97.5% CI of (-6.4%, 27.7%).

Table 10: Clinical Response* at 48 – 72 hours (mITT patients 3 month to less than 18 years)

	Dalbavancin Single-Dose (N=75) n (%)	Dalbavancin Two-Dose (N=78) n (%)	Comparator (N=30) n (%)
Age Cohort: 3 months to 17 years old	(N=75)	(N=78)	(N=30)

Clinical Responder	73 (97.3)	73 (93.6)	26 (86.7)
Clinical Non-Responder	2 (2.7)	1 (1.3)	3 (10.0)
Missing	0 (0)	4 (5.1)	1 (3.3)
Age Cohort 4: 3 months to < 2 years old	(N=6)	(N=8)	(N=3)
Clinical Responder	6 (100.0)	8 (100)	3 (100.0)
Clinical Non-Responder	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0)	0 (0)
Age Cohort 3: 2 years to < 6 years old	(N=18)	(N=17)	(N=10)
Clinical Responder	18 (100.0)	16 (94.1)	8 (80.0)
Clinical Non-Responder	0 (0.0)	0 (0.0)	2 (20.0)
Missing	0	1 (5.9)	0 (0)
Age Cohort 2: 6 years to < 12 years old	(N=25)	(N=24)	(N=11)
Clinical Responder	24 (96.0)	21 (87.5)	9 (81.8)
Clinical Non-Responder	1 (4.0)	1 (4.2)	1 (9.1)
Missing	0	2 (8.3)	1 (9.1)
Age Cohort 1: 12 years to 17 years old	(N=26)	(N=29)	(N=6)
Clinical Responder	25 (96.2)	28 (96.6)	6 (100.0)
Clinical Non-Responder	1 (3.8)	0 (0.0)	0 (0)
Missing	0 (0)	1 (3.4)	0 (0)

* Determined by the Applicant

** In Cohort 5, 3 of 5 patients qualified to be in mITT population (1 patient was diagnosed with cellulitis, 1 patient with major cutaneous abscess, and 1 patient with *S. aureus* sepsis.)

In Cohort 5, 2 patients were clinical responders at 48 – 72 hours and 1 patient was considered a non-responder because they received glycopeptide antibacterial, vancomycin prior to and during the treatment period.

Source: modified from CSR, Tables 11-1

Table 11 contains similar information as Table 10 but for the endpoint clinical response (Cure + Improvement) at the EOT visit. The clinical response rates at the EOT visit in the mITT population for patients 3 months to 17 years were similar for all three treatment groups (dalbavancin single-dose: 97.3%, dalbavancin two-dose: 92.3%, and comparator: 100.0%. The difference in cure rates between the dalbavancin single-dose and comparator groups was -2.7%, with an exact 97.5% CI of (-11.3%, 12.9%). The difference in cure rates between the dalbavancin two-dose and comparator groups was -7.7%, with an exact 97.5% CI of (-17.9%, 8.3%). Note that the numerically higher response rates with the dalbavancin arms seen at the 48-72 time point are no longer seen.

Table 11: Clinical Response* at the EOT Visit (mITT patients 3 month to less than 18 years)

	Dalbavancin Single-Dose (N=75) n (%)	Dalbavancin Two-Dose (N=78) n (%)	Comparator (N=30) n (%)
Age Cohort: 3 months to 17 years old	(N=75)	(N=78)	(N=30)
Clinical Cure	70 (93.3)	68 (87.2)	30 (100.0)
Clinical Improvement	3 (4.0)	4 (5.1)	0 (0)
Clinical Failure	1 (1.3)	2 (2.6)	0 (0)
Missing or Unknown	1 (1.3)	4 (5.1)	0 (0)

Age Cohort: 3 months to < 2 years old	(N=6)	(N=8)	(N=3)
Clinical Cure	4 (66.7)	5 (62.5)	3 (100.0)
Clinical Improvement	1 (16.7)	1 (12.5)	0 (0)
Clinical Failure	1 (16.7)	1 (12.5)	0 (0)
Missing or Unknown	0 (0)	1 (12.5)	0 (0)
Age Cohort: 2 years to < 6 years old	(N=18)	(N=17)	(N=10)
Clinical Cure	17 (94.4)	14 (82.4)	10 (100.0)
Clinical Improvement	0	1 (5.9)	0 (0)
Clinical Failure	0	0 (0)	0 (0)
Missing or Unknown	1 (5.6)	2 (11.8)	0 (0)
Age Cohort: 6 years to < 12 years old	(N=25)	(N=24)	(N=11)
Clinical Cure	25 (100.0)	22 (91.7)	11 (100.0)
Clinical Improvement	0 (0)	1 (4.2)	0 (0)
Clinical Failure	0 (0)	0 (0)	0 (0)
Missing or Unknown	0 (0)	1 (4.2)	0 (0)
Age Cohort: 12 years to 17 years old	(N=26)	(N=29)	(N=6)
Clinical Cure	24 (92.3)	27 (93.1)	6 (100.0)
Clinical Improvement	2 (7.7)	1 (3.4)	0 (0)
Clinical Failure	0 (0)	1 (3.4)	0 (0)
Missing or Unknown	0 (0)	0 (0)	0 (0)

* Determined by the Applicant: Clinical Response = Cure + Improvement
In Cohort 5, 2 patients were a clinical cure at EOT, and 1 patient was considered a Clinical Failure because they received vancomycin prior to and during the treatment period.
Source: modified from CSR, Tables 11-2 and 14.2-2.2

Table 12 contains similar information as Table 10 but for the endpoint clinical cure at the TOC visit. The clinical cure rates at the TOC visit in the mITT population were high for all three treatment groups (dalbavancin single-dose: 94.7%, dalbavancin two-dose: 92.3%, and comparator: 100.0%. The difference in cure rates between the dalbavancin single-dose and comparator groups was -5.3%, with an exact 97.5% CI of (-15.1%, 10.5%). The difference in cure rates between the dalbavancin two-dose and comparator groups was -7.7%, with an exact 97.5% CI of (-17.9%, 8.3%). Note that the numerically higher response rates with the dalbavancin arms seen at the 48-72 time point are no longer seen.

Table 12: Clinical Response at the TOC Visit (mITT patients 3 month to less than 18 years)

	Dalbavancin Single-Dose (N=75) n (%)	Dalbavancin Two-Dose (N=78) n (%)	Comparator (N=30) n (%)
Age Cohort: 3 months to 17 years old	(N=75)	(N=78)	(N=30)
Clinical Cure	71 (94.7)	72 (92.3)	30 (100.0)
Clinical Failure	1 (1.3)	2 (2.6)	0 (0)
Missing or Unknown	3 (4.0)	4 (5.1)	0 (0)
Age Cohort: 3 months to < 2 years old	(N=6)	(N=8)	(N=3)
Clinical Cure	4 (66.7)	6 (75.0)	3 (100)
Clinical Failure	1 (16.7)	1 (12.5)	0 (0)

Missing or Unknown	1 (16.7)	1 (12.5)	0 (0)
Age Cohort: 2 years to < 6 years old	(N=18)	(N=17)	(N=10)
Clinical Responder	18 (100)	15 (88.2)	10 (100.0)
Clinical Non-Responder	0 (0)	0 (0)	0 (0)
Missing or Unknown	0 (0)	2 (11.8)	0 (0)
Age Cohort: 6 years to < 12 years old	(N=25)	(N=24)	(N=11)
Clinical Cure	24 (96.0)	23 (95.8)	11 (100)
Clinical Failure	0 (0.0)	0 (0.0)	0 (0)
Missing or Unknown	1 (4.0)	1 (4.2)	0 (0)
Age Cohort: 12 years to 17 years old	(N=26)	(N=29)	(N=6)
Clinical Cure	25 (96.2)	28 (96.6)	6 (100.0)
Clinical Failure	0 (0.0)	1 (3.5)	0 (0)
Missing or Unknown	1 (3.9)	0 (0.0)	0 (0)

* Determined by the Applicant

In Cohort 5, 1 patient was a clinical cure at TOC, 1 patient was considered a Clinical Failure because they received vancomycin prior to and during the treatment period, and 1 patient had a missing assessment

Source: modified from CSR, Tables 11-3 and 14.2-3.2

Table 13 contains similar information as Table 10 but for the endpoint clinical cure at the follow-up visit. The clinical cure rates at the follow-up visit in the mITT population were similar for all three treatment groups (dalbavancin single dose: 96.0%, dalbavancin two-dose: 91.0%, and comparator: 100.0%). The difference in cure rates between the dalbavancin single-dose and comparator groups was -4.0%, with an exact 97.5% CI of (-13.1%, 11.6%). The difference in cure rates between the dalbavancin two-dose and comparator groups was -9.0%, with an exact 97.5% CI of (-19.3%, 7.1%). Note that the numerically higher response rates with the Dalbavancin arms seen at the 48-72 time point are no longer seen.

Table 13: Clinical Response* at the Follow-Up Visit (mITT patients 3 month to less than 18 years)

	Dalbavancin Single-Dose (N=75) n (%)	Dalbavancin Two-Dose (N=78) n (%)	Comparator (N=30) n (%)
Age Cohort: 3 months to 17 years old	(N=75)	(N=78)	(N=30)
Clinical Cure	72 (96.0)	71 (91.0)	30 (100)
Clinical Failure	1 (1.3)	2 (2.6)	0 (0)
Missing or Unknown	2 (2.7)	5 (6.4)	0 (0)
Age Cohort: 3 months to < 2 years old	(N=6)	(N=8)	(N=3)
Clinical Cure	5 (83.3)	6 (75.0)	3 (100)
Clinical Failure	1 (16.7)	1 (12.5)	0 (0)
Missing or Unknown	0 (0)	1 (12.5)	0 (0)
Age Cohort: 2 years to < 6 years old	(N=18)	(N=17)	(N=10)
Clinical Cure	18 (100)	16 (94.1)	10 100)
Clinical Failure	0 (0)	0 (0)	0 (0)
Missing or Unknown	0 (0)	1 (5.9)	0 (0)

Age Cohort: 6 years to < 12 years old	(N=25)	(N=24)	(N=11)
Clinical Cure	24 (96.0)	22 (91.7)	11 (100)
Clinical Failure	0 (0.0)	0 (0.0)	0 (0)
Missing or Unknown	1 (4.0)	2 (8.3)	0 (0)
Age Cohort: 12 years to 17 years old	(N=26)	(N=29)	(N=6)
Clinical Cure	25 (96.2)	27 (93.1)	6 (100)
Clinical Failure	0	1 (3.4)	0 (0)
Missing or Unknown	2 (3.8)	1 (3.4)	0 (0)

* Determined by the Applicant
In Cohort 5, 2 patients were a clinical cure at the Follow-up visit and 1 patient was considered a Clinical Failure because they received vancomycin prior to and during the treatment period.
Source: modified from CSR, Tables 11-4 and 14.2-4.2

The microbiologic response rates (see Table 14) for a favorable (i.e., eradication or presumed eradication) were greater than 90% for all treatment groups and time points, with the exception of the dalbavancin two-dose group at follow-up, where the microbiologic rate for favorable outcome was slightly below 90%, specifically 89.1% (49/55).

Table 14: Microbiologic Response (microITT patients 3 months to less than 18 years)

Assessment Visit	Dalbavancin Single-Dose (N=50) n (%)	Dalbavancin Two-Dose (N=55) n (%)	Comparator (N=18) n (%)
48 – 72 hours			
Favorable			
Eradication	0 (0)	1 (1.8)	0 (0)
Presumed Eradication	49 (98.0)	51 (92.7)	16 (88.9)
Unfavorable			
Persistence	0 (0)	1 (1.8)	0 (0)
Presumed persistence	1 (2.0)	1 (1.8)	1 (5.6)
Indeterminate	0 (0)	0 (0)	1 (5.6)
Missing	0 (0)	1 (1.8)	0 (0)
EOT			
Favorable			
Eradication	0	1 (1.8)	0 (0)
Presumed Eradication	48 (96.0)	50 (90.9)	18 (100)
Unfavorable			
Persistence	0 (0)	1 (1.8)	0 (0)
Presumed persistence	1 (2.0)	1 (1.8)	0 (0)
Indeterminate	1 (2.0)	1 (1.8)	0 (0)
Missing	0 (0)	1 (1.8)	0 (0)
TOC			
Favorable			
Eradication	0 (0)	1 (1.8)	0 (0)

Presumed Eradication	46 (92.0)	50 (90.0)	18 (100)
Unfavorable			
Persistence	0 (0)	0 (0)	0 (0)
Presumed persistence	1 (2.0)	2 (3.6)	0 (0)
Indeterminate	3 (6.0)	1 (1.8)	0 (0)
Missing	0 (0)	1 (1.8)	0 (0)
Follow-up			
Favorable			
Eradication	0 (0)	1 (1.8)	0 (0)
Presumed Eradication	47 (94.0)	48 (87.3)	18 (100)
Unfavorable			
Persistence	0 (0)	0 (0)	0 (0)
Presumed persistence	1 (2.0)	2 (3.6)	0 (0)
Indeterminate	2 (4.0)	3 (5.5)	0 (0)
Missing	0 (0)	1 (1.8)	0 (0)

For Cohort 5, there was 1 patient in the microITT population, and they had a microbiologic response of Presumed Eradication at all assessments
Source: modified from CSR, Tables 11-8 –11.11

Dose/Dose Response

The single-dose dalbavancin regimen for patients 3 months to < 6 years old was 22.5 mg/kg (maximum 1500 mg) on Day 1 and for patients ≥ 6 years to 17 years old (inclusive) the dose was 18 mg/kg (maximum 1500 mg) on Day 1. The two-dose dalbavancin regimen for patients 3 months to < 6 years old was 15 mg/kg (maximum 1000 mg) on Day 1, and 7.5 mg/kg (maximum 500 mg) on Day 8, and for patients ≥ 6 years to 17 years old (inclusive) the dose was 12 mg/kg (maximum 1000 mg) on Day 1 and 6 mg/kg (maximum 500 mg) on Day 8.

The clinical response and cure rates at the 48 – 72 hours, EOT, TOC, and Follow-Up visits were similar for both the dalbavancin single-dose and two-dose treatment groups (see Table 10 through Table 13. However, the results should be interpreted carefully because of the sample sizes in the trial.

Durability of Response

In all three treatment groups, the durability of response was demonstrated by the proportion of patients who sustained their positive clinical responses across the 48 – 72 hours, EOT, and TOC visits for mITT patients 3 months age to less than 18 years of age. The proportion of patients who were early clinical responders (48 – 72 hours) and subsequently were clinical responders at EOT was 97.3% (71/73) in the single-dose dalbavancin group, 93.2% (68/73) in the two-dose dalbavancin group, and 100% (26/26) in the comparator group. Similar rates were found in the proportion of responders at EOT who were subsequently clinical cures at TOC (single-dose dalbavancin: 95.9% (70/73); two-dose dalbavancin: 100% (72/72); and comparator: 100% (30/30)).

8.1.3 Integrated Assessment of Effectiveness

Efficacy of dalbavancin for the treatment of ABSSSI in pediatric patients was extrapolated from adults. Study DUR-306 was the only study supporting efficacy and safety of dalbavancin in the treatment of ABSSSI in pediatric population.

Three Phase 3 ABSSSI studies in adults (DUR001-301, -302 and -303) have been previously reviewed. In Studies DUR001-301 and DUR001-302, a two-dose regimen of dalbavancin was compared to the comparator for the treatment of adults with ABSSSI. Treatment differences in clinical responder/success rates were similar between the two studies in adult patients which demonstrated noninferiority to the comparator (vancomycin with possible switch to linezolid). For Study DUR001-301, the early clinical responder rates were 83.3% for the two-dose dalbavancin group and 81.8% for the comparator group. In study DUR001-302, the early clinical responder rates were 76.8% for the two-dose dalbavancin group and 78.3% for the comparator group. Study DUR001-303 compared a single-dose dalbavancin to a two-dose dalbavancin regimen. Early clinical response rates were 81.4% for the single-dose dalbavancin and 84.2% for the two-dose dalbavancin groups. Clinical cures rates were 84.5% for the single-dose dalbavancin group and 85.1% for the two-dose dalbavancin group. Of note, there were some differences in the definition of clinical response and clinical cure in the adult trials as compared to the pediatric trial. The adult trials required that patients to be afebrile to be considered an early clinical responder, which pediatric study (DUR-306) did not require.

In pediatric Study DUR-306, the efficacy results were analyzed descriptively. In general, the rates of favorable clinical response/cure and microbiological response were high for the two dalbavancin treatment groups and the comparator group across various analysis populations and study visits. No numerical trends were found that would point to any specific efficacy concern for either of the dalbavancin treatment groups.

At the early clinical response assessment (48 –72 hour), in patients 3 months to less than 18 years of age, clinical responder rates were 97.3% in the dalbavancin single-dose group, 93.6% in the dalbavancin two-dose group, and 86.7% in the comparator group. At the TOC assessment (28 ±2 days), in patients 3 months to less than 18 years of age, clinical cure rates were 94.7%, in the dalbavancin single-dose group, 92.3% in the dalbavancin two-dose group, and 100.0% in the comparator group.

In patients younger than 3 months of age, there were 5 patients enrolled in the trial and they were all enrolled in the dalbavancin single-dose group. However only 3 patients qualified for efficacy analysis. The clinical responder rate at 48 – 72 hours was 66.7% (2/3) and the clinical cure rate at TOC was 33.3% (1/3).

Overall, the efficacy results in this trial provide supportive evidence to expand the adult indication of ABSSSI to the pediatric population (birth to less than 18 years). Similarly to adults, in this pediatric study clinical responses were comparable across the dalbavancin dose regimens and age cohorts, and similar to comparator treatments.

8.2 Review of Safety

8.2.1 Safety Review Approach

This safety review is based on a single Phase 3, open-label, randomized, multicenter, comparator-controlled trial (Study DUR001-306) of pediatric patients from birth to less than 18 years of age with ABSSSI, known or suspected to be caused by Gram-positive pathogens.

Studies A8841004, DUR001-106, and DAL-PK-02 were Phase 1 single-dose PK studies in the pediatric population to determine dosing in this population. They were reviewed for supplemental safety information and will not be considered in the presentation of safety analyses here.

8.2.2 Review of the Safety Database

Overall Exposure

In the Phase 3 trial (Study DUR001-306), 161 pediatric patients were exposed to dalbavancin (83 in the single-dose arm and 78 in the 2-dose arm). A total of 30 patients received the comparator drug: either IV vancomycin (for methicillin-resistant Gram-positive infections) or IV oxacillin or flucloxacillin (for methicillin-sensitive Gram-positive infections) for 10-14 days. There were more patients in the older age groups in the study, as demonstrated in Table 15. The median age of dalbavancin-exposed patients was 8 years in the single-dose group, 9 years in the 2-dose group, and 7 years in the comparator groupn the 2-dose group (including both IV and oral antibiotic therapy).

Table 15: Exposure to dalbavancin by age group (Safety Population)

Patients exposed to dalbavancin (N=161)			
Age cohort	**Single dose**	**2 doses**	**Total**
Cohort 1: 12 to 17 years	29	29	58
Cohort 2: 6 to <12 years	25	24	49
Cohort 3: 2 to <6 years	18	17	35
Cohort 4: 3 months to <2 years	6	8	14
Cohort 5: Birth to <3 months (including preterm* neonates with gestational age ≥ 32 weeks)	5**	0	5
Total	83	78	161

Source: Reviewer generated, CSR

* There was 1 patient who was preterm

** 5 were assigned to this arm and received single dose of dalbavancin. All 5 were included in safety analysis. However , in mITT efficacy analysis, 2 patients were excluded due to infections caused solely by Gram-negative pathogen.

An additional 8 participants were enrolled in the PK study (Study DAL-PK-02) and received a dalbavancin single dose of 22.5 mg/kg dalbavancin as a 30-minute IV infusion. Six (6) participants in Cohort 1 (young infants aged > 28 days to < 3 months), and one (1) participant each in Cohort 2 (term neonates [defined as gestational age ≥ 37 weeks] aged ≤ 28 days) and Cohort 3 (preterm neonates [defined as gestational age ≥ 32 to < 37 weeks] aged ≤ 28 days).

Relevant characteristics of the safety population

In Study DUR001-306, 161 patients received any dose of dalbavancin and 30 participants received a comparator drug. The mean/range age of patients who received a single dose of dalbavancin, 2 doses of dalbavancin, or a comparator was 8 years (0.04 - 17.0), 9 years (0.25 - 17.0), and 7 years (0.75 to 15.0), respectively.

The majority of patients were male (62.3%) and white (89.0%). BMI ranged from 9.3 to 31.6 kg/m^2 and creatinine clearance was ≥ 30 mL/min/1.73m2 in all patients where it was measured. The reader is referred to Table **7** , Section 8.1.2 for demographic information and baseline characteristics.

In terms of ABSSSI infection types, the majority of patients enrolled had major cutaneous abscess (n=99, 53.2%), followed by cellulitis (n=53, 28.5%), and surgical site/traumatic wound infection (n=33, 17.7%). Overall, the most frequent anatomical site of infection was extremities (n=60, 36.5%), followed by central face (n=40, 21.5%).

Clinical signs and symptoms at baseline included erythema, purulent discharge, swelling/induration, fluctuance, pain/tenderness to palpation, and localized warmth.

A summary of adverse events in Study DUR-306 is presented in Table 16. In this pediatric study, 6 (7.2%) participants in the dalbavancin single-dose arm, 8 (10.3%) in the dalbavancin two-dose arm, and 1 (3.3%) in the comparator arm experienced treatment emergent adverse event (TEAE).

Table 16: Overview of Adverse Events – Study DUR306 (Safety Population)

Adverse event category	Dalbavancin Single-dose (N = 83) n (%)	Dalbavancin 2-dose (N = 78) n (%)	Comparator (N = 30) n (%)
Any AE	6 (7.2)	8 (10.3)	1 (3.3)
Treatment-emergent AEs (TEAEs)	6 (7.2)	7 (9.0)	1 (3.3)
Treatment-related TEAEs	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-emergent serious AEs	3 (3.6)	0 (0.0)	0 (0.0)
Treatment-related treatment-	0 (0.0)	0 (0.0)	0 (0.0)
AEs leading to study treatment	0 (0.0)	0 (0.0)	0 (0.0)
AEs leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-emergent SAEs leading to	0 (0.0)	0 (0.0)	0 (0.0)

Source: Table 14.3.1-1.1 of the DUR001-306 CSR;

Adequacy of the safety database

The safety population consisted of all randomized patients who received at least 1 dose of study drug (dalbavancin or comparator). The safety population was used for summaries of demographic and baseline characteristics and all safety and tolerability-related analyses. Overall, the study arms were balanced in terms of baseline demographic characteristics. However, no patients were enrolled with renal impairment , therefore, safety was not evaluated in this patient population.

Safety assessments included analyses of the incidence of all adverse events (AEs), including treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), deaths, adverse events leading to premature discontinuation of study treatment, changes in vital signs, body weight, hematology, and blood chemistry parameters. Descriptive statistics are used to describe the observed findings.

Additionally, to evaluate ototoxicity, audiologic testing was conducted at selected centers in 17 children less than 17 years old, both at baseline and at Day 28 (+/- 2 days). All patients evaluated had normal audiology testing at baseline. The Applicant also evaluated the impact of dalbavancin on bowel flora in all participants from birth to <2 years by performing PCR for *Clostridioides difficile* and stool culture or rectal swab for VRE at baseline and at Day 28 (+/- 2 days). This bowel flora testing was done in both the dalbavancin arm and the comparator arm.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no issues identified with the integrity or quality of the data for this study. The data were submitted in standardized formats for review.

Categorization of Adverse Events

The evaluation of safety and tolerability of dalbavancin in pediatric patients was based upon assessment of patient deaths, adverse events, serious adverse events, laboratory assessments, and vital sign measurements. Adverse events were coded using Medical Dictionary for Regulatory Affairs (MedDRA) version 17.0, and categorized by a System Organ Class (SOC) and Preferred Term (PT). A TEAE was defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of the study (dalbavancin or comparator) drug.

Routine Clinical Tests

Clinical tests for safety evaluations consisted of vital sign monitoring (including blood pressure, respiratory rate, heart rate, and temperature); physical examination including targeted exam of the infection site; and laboratory studies (including hematology, serum chemistry, high sensitivity C-reactive protein [hsCRP]).

8.2.4 Safety Results

8.2.4.1 Deaths

There were no deaths reported in Study DUR001-306 or any of the pediatric pharmacokinetic studies.

8.2.4.2 Serious Adverse Events

There were 3 serious adverse events (SAEs) in total, all of which were reported in the dalbavancin single-dose arm (Table 17).

Table 17: Serious Adverse Events (SAEs) in Study DUR001-306- Safety Population

	Treatment group: IV dalbavancin (n=161)		**Comparator (n=30)** n (%)
Preferred Term	Single-dose (n = 83) n (%)	Two-dose (n = 78) n (%)	
Skin Abscess, bacterial	1 (1.2)	0 (0.0)	0 (0.0)
Febrile convulsion	1 (1.2)	0 (0.0)	0 (0.0)
Osteomyelitis, bacterial	1 (1.2)	0 (0.0)	0 (0.0)

Source: CSR DUR-306; Modified by reviewer

Narratives of patients with SAEs

1. Bacterial abscess in Cohort 5 (birth to <3 months)

This patient was a 20-day-old female who was enrolled in the study with a diagnosis of major cutaneous abscess of left groin/labial area. Patient was randomized to the dalbavancin single-dose arm and received the dose on Day 1. The next day, the patient underwent incision and drainage (I&D) of the abscess with Gram stain showing Gram-positive bacilli, however, later cultures were reported growing *E. coli,* which was negative for beta-lactamase production. Blood culture showed no growth. The patient received a concomitant antibacterial for Gram-positive coverage, clindamycin IV on Day 2. On Day 4, examination showed mild induration of the labial abscess and patient was afebrile.

Over the next few days, the patient's clinical course was complicated by worsening of the lesion with progressive swelling, induration, warmth, and drainage of the abscess. The patient was transitioned to another antibacterial medication, oral cephalexin on Day 8. On Day 15, patient continued to have a mild purulent drainage which, grew *E. coli* and *Klebsiella pneumoniae*. Patient showed some improvement for next few days. On Day 41, the patient became febrile again, with increased drainage, swelling, and erythema and was hospitalized to receive IV ceftriaxone and clindamycin. She underwent a second I&D on Day 43 and was discharged on amoxicillin-clavulanate for 8 days until Day 51. The abscess ultimately resolved by Day 57. The patient was correctly classified as clinical failure in efficacy analysis. The SAE was considered unrelated to study drug by the Investigator.

Reviewer comment: Despite I&D to achieve source control of this abscess and the initial clinical improvement, this patient experienced clinical worsening of the abscess requiring a second I&D after receiving dalbavancin. It is not unexpected that her abscess continued to worsen on dalbavancin because it was found to grow Gram-negative organisms, against which dalbavancin does not demonstrate activity.

2. Febrile convulsion in Cohort 4 (3 months to <2 years)

This patient was a 13-month-old female who had right neck cellulitis with abscess, was randomized to the dalbavancin single-dose arm, and received the dose on Day 1. On study Day 6, the patient had a fever to 39°C and had a tonic-clonic seizure lasting 1-2 minutes. She received an antipyretic, an antiepileptic, steroids, mannitol, andintravenous vancomycin due to concern of worsening infection. The event resolved, and she completed the study with the last visit on Day 54. This SAE was considered unrelated to the study drug by the Investigator.

Reviewer comment: Pediatric patients between 6 months and 6 years of age can have simple or complex febrile seizures. Being 13 months old, this patient was within the age range during which febrile seizures may be expected without an underlying neurological condition.

3. Bacterial osteomyelitis in Cohort 1 (12 to 17 years)

This patient was a 13-year-old male with a history of left tibia & fibula fractures who underwent open reduction and internal fixation (ORIF) with hardware placement 4 months prior to enrollment. The patient subsequently developed a cutaneous abscess of the surgical site 11 days prior to enrollment which gradually became purulent. The patient was randomized to the dalbavancin single-dose arm, and received the dose on Day 1. Culture of the lesion grew *Staphylococcus epidermidis*. Blood culture showed no growth. During the study period the patient required multiple surgical washout procedures with cultures showing growth of polymicrobial organisms. On study Day 18, a bone scan confirmed diagnosis of osteomyelitis of the proximal tibia. Specimen from bone biopsy cultures grew *Acinetobacter haemolyticus* and *Stenotrophomonas maltophilia.* Blood cultures showed no growth. After a final surgical washout procedure on Day 31 the patient had resolution of osteomyelitis, and completed the study on Day 54. The investigator considered the serious adverse event of Gram-negative polymicrobial osteomyelitis as not related to the study treatment.

Reviewer comment: This patient had a significant bone injury prior to this study with indwelling hardware, which represented a potential nidus for ongoing/recurrent infection. The development of osteomyelitis during the study period may represent a natural progression of his illness. Additionally, given the growth of multiple Gram-negative organisms on wound cultures, it is not unexpected that his disease progressed despite dalbavancin as it is not effective against Gram-negative organisms.

8.2.4.3 Dropouts and/or Discontinuations Due to Adverse Effects

There were no dropouts or discontinuations of study drug due to AEs in this study.

8.2.4.4 Significant Adverse Events

In the Phase 3 pediatric trial, there were no patients with TEAEs that fell into one of the special adverse events of interest categories, including hypersensitivity reactions such as anaphylaxis or skin reactions; infusion-related reactions including "Red-Man Syndrome"; or liver test abnormalities. There were no TEAEs leading to treatment discontinuation.

In adult studies, more participants treated with dalbavancin than the comparator drug who had normal alanine amino transferase (ALT) at baseline experienced a rise in ALT greater than three times the upper limit of normal during the study. However, in this pediatric study no participants had ALT values that rose to this level or met criteria for Hy's law.

8.2.4.5 Treatment Emergent Adverse Events and Adverse Reactions

A summary of Treatment emergent adverse events is presented in Table 18.

Table 18: Summary of Treatment Emergent Adverse Events in Study DUR001-306 (Safety Population)

System Organ Class/ MedDRA Preferred Term	**Dalbavancin single-dose (N = 83)** n (%)	**Dalbavancin 2-dose (N = 78)** n (%)	**Comparator (N = 30)** n (%)
Patients with at least one preferred term	**6 (7.2)**	**7 (9.0)**	**1 (3.3)**
Gastrointestinal disorders	0 (0.0)	3 (3.8)	0 (0.0)
Constipation	0 (0.0)	1 (1.3)	0 (0.0)
Diarrhea	0 (0.0)	1 (1.3)	0 (0.0)
Vomiting	0 (0.0)	1 (1.3)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	3 (3.8)	0 (0.0)
Pyrexia	0 (0.0)	2 (2.6)	0 (0.0)
Infusion site extravasation	0 (0.0)	1 (1.3)	0 (0.0)

Immune system disorders: Drug hypersensitivity	1 (1.2)	0 (0.0)	0 (0.0)
Infections and infestations	4 (4.8)	1 (1.3)	1 (3.3)
Abscess, bacterial	1 (1.2)	0 (0.0)	0 (0.0)
Bronchitis	1 (1.2)	0 (0.0)	0 (0.0)
Nasopharyngitis	0 (0.0)	0 (0.0)	1 (3.3)
Osteomyelitis, bacterial	1 (1.2)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	1 (1.2)	0 (0.0)	0 (0.0)
Varicella	0 (0.0)	1 (1.3)	0 (0.0)
Injury, poisoning, procedural complications: Anemia, postoperative	0 (0.0)	1 (1.3)	1 (3.3)
Investigations: Blood bilirubin increased	1 (1.2)	0 (0.0)	0 (0.0)
Nervous system disorders	1 (1.2)	1 (1.3)	0 (0.0)
Dizziness	0 (0.0)	1 (1.3)	0 (0.0)
Febrile convulsion	1 (1.2)	0 (0.0)	0 (0.0)
Respiratory, thoracic, mediastinal disorders	0 (0.0)	4 (5.1)	0 (0.0)
Cough	0 (0.0)	2 (2.6)	0 (0.0)
Epistaxis	0 (0.0)	1 (1.3)	0 (0.0)
Nasal congestion	0 (0.0)	1 (1.3)	0 (0.0)
Rhinorrhea	0 (0.0)	1 (1.3)	0 (0.0)
Skin and subcutaneous tissue disorders	2 (2.4)	1 (1.3)	0 (0.0)
Acne, infantile	1 (1.2)	0 (0.0)	0 (0.0)
Pruritus	1 (1.2)	0 (0.0)	0 (0.0)
Skin exfoliation	0 (0.0)	1 (1.3)	0 (0.0)

Source: adapted from Applicant table 12-3 in DUR001-306 Clinical Study Report

The most common TEAEs which occurred in more than 1 patient were pyrexia and cough. Pyrexia occurred in 2 patients in the two-dose arm (1.2% of all dalbavancin recipients). Cough also occurred in 2 patients in the two-dose arm (1.2% of all dalbavancin recipients). None of these TEAEs were considered related to study drug by the Investigator. Overall, common TEAEs in the dalbavancin pediatric study was similar to those observed in adults, except that TEAEs occurred at slightly higher frequency in adult studies. Across both treatment groups in both the pediatric and adult studies, the majority of TEAEs were mild or moderate in intensity and most of the events were assessed as not related to study drug.

8.2.4.6 Laboratory Findings

In the adult trials, the incidence of patients with leukopenia during the study was slightly higher in the dalbavancin group as compared to the comparator. Similar trends were noted in the pediatric study, with decreases in mean white blood cell counts and neutrophils, however, these were consistent with the resolution of infection-related leucocytosis. There were no clinically significant changes in other hematology or chemistry parameters. No cases met Hy's Law criteria, and no patients had ALT levels which rose to the level of $\geq$3x ULN in any patients.

Vital Signs

Vital signs were analyzed separately for each age cohort, which is appropriate given the variation in normal vital sign ranges among pediatric age groups. Mean pulse rate, respiratory rate, and temperature were decreased from baseline at all visits across the age cohorts. There were no reported cardiac adverse events. Descriptive statistics were provided by the Applicant and showed baseline vitals and change from baseline at each visit for each cohort. Review of temperature, heart rate, respiratory rate and systolic and diastolic blood pressures in all cohorts did not reveal clinically significant changes throughout treatment.

Electrocardiograms (ECGs)

Electrocardiograms (ECGs) were not performed in this pediatric study. In a thorough QT (TQT) study in adults dalbavancin at IV doses up to 1500 mg did not prolong the QTc interval and had no effect on the heart rate, PR, or QRS intervals.

8.2.5 Analysis of Submission-Specific Safety Issues

Dalbavancin is structurally related to glycopeptide antibacterials. Safety concerns associated with this class of antibacterial drugs include infusion-related events including phlebitis and flushing of the upper body during rapid infusion, nephrotoxicity, ototoxicity, neutropenia, and thrombocytopenia.There were no patients with AEs that fell into one of the special interest categories. There were no hypersensitivity reactions such as anaphylaxis or skin reactions; no infusion-related reactions and no hepatic effects seen. Additional safety analyses were performed to assess for ototoxicity, gastrointestinal dysbiosis, as well as an examination of patients with bacteremia:

Ototoxicity
Audiologic testing was conducted at selected centers in 17 children < 17 years old (n=6 in the 2-year to < 6-year cohort; n=4 in the 6-year to < 12-year cohort; n=7 in the 12-year to 17-year cohort). Audiology parameters were reviewed at baseline and at Day 28 in all tested participants. All participants had normal findings at baseline and at Day 28. There were no evident signals of ototoxicity from clinical examination or audiologic test results.

Impact of dalbavancin on *Clostridioides difficile* or Vancomycin-resistant Enterococci (VRE) occurence
The Applicant also evaluated the impact of dalbavancin on *C. difficile* and VRE occurence in all participants from birth to <2 years by performing PCR for *Clostridioides difficile* at baseline and at Day 28 (+/- 2 days). This testing was done in both the dalbavancin arms and the comparator arm. In this study, 5 patients tested positive for *C. difficile* at baseline in the dalbavancin arm. At the TOC visit, 2 tested negative and 3 had missing values. There was 1 participant who tested positive for VRE at baseline in the dalbavancin treatment arm and remained positive at TOC visit. No conclusions could be drawn from this evaluation.

Bacteremia
The efficacy of dalbavancin in clearance of Gram-positive bacteremia could not be evaluated in the pediatric study.

In adult dalbavancin two-dose trials (Study DUR-301, and DUR-302), the number of patients with bacteremia due to Gram-positive pathogens was 28 (4.2%) in the dalbavancin arms. A total of 22 out of 28 (78.5%) dalbavancin patients had documented clearance of bacteremia. In Study DUR-306, 12 patients in the single dose dalbavancin arm and 10 patients in two dose dalbavancin arm had bacteremia with Gram-positive pathogens at baseline. All patients had clearance of bacteremia by EOT visit.

In the pediatric study, 2 out of 191 patients presented with Gram-positive bacteremia at baseline: 1 each in dalbavancin single-dose and two-dose arms. Both of these patients received rescue therapy with IV vancomycin.

One patient who was randomized to the dalbavancin two-dose arm was a 13-month old male with cutaneous abscess of the right scalp which developed 3 days prior to enrollment. This patient had a positive blood culture growing *Staphylococcus aureus* (MSSA) and a wound culture which grew MRSA at baseline. The patient received the 1st dose of dalbavancin on Day 1. On study Day 3, the patient developed fever, blood cultures were sent and he was started on rescue treatment with IV vancomycin and rifampin. Blood cultures from Day 3 grew *S. epidermidis*.The patient was discontinued from the study treatment on Day 3 by the investigator due to the possibility of therapeutic failure. This patient did not receive the second dose of dalbavancin as planned on Day 8, as he was discontinued from the study. Culture from Day 5 showed no growth, however patient was started on vancomycin since Day 3, therefore, it was confounding efficacy assessment for dalbavancin in clearance of bacteremia.

Another patient with bacteremia was randomized to the dalbavancin single-dose arm. The patient was a 13-month-old female with right neck cellulitis, who had a positive blood culture growing MSSA and *Streptococcus pyogenes* at baseline. This patient also had an SAE of febrile convulsions on Study Day 6 with high fevers, for which she received rescue therapy with IV vancomycin along with anti-epileptic drugs and other supportive measures. Follow-up blood cultures were performed on Day 47 and showed no growth.

8.2.6 Safety Analyses by Demographic Subgroups

The number of patients in this study was relatively small, therefore no specific safety analyses were done by subgroup, but no obvious patterns emerged on review of the data. As mention earlier in this review, the majority of patients in this pediatric study were male (62.3%), and the vast majority were White (89%). Very few patients were from the United States (3.7%) with the

vast majority from Eastern Europe (83.2%). It is, therefore, not possible to comment on any potential differences in the safety profile of dalbavancin by racial backgrounds.

Safety information in patients from birth to less than 3 months of age in pharmacokinetic study (DAL-PK-02)

In addition to safety information from 5 patients aged birth to less than 3 months age from pediatric Phase 3 trial (Study DUR-306), safety was also evaluated in 8 patients enrolled in a PK study, Study DAL-PK-02, which was a pharmacokinetic study of a single-dose of dalbavancin in neonates to infants ages < 3 months of age with suspected or confirmed bacterial infection. Safety assessments included AEs, audiology testing, clinical laboratory values, vital signs (including weight and temperature) and physical examination findings.

The study enrolled a total of 8 patients, which included preterm neonates (gestational age ≥ 32 to < 37 weeks, aged ≤ 28 days; n=1), term neonates (gestational age ≥ 37 weeks, aged ≤ 28 days; n=1) and young infants (aged 28 days to < 3 months; n=6), who were receiving at least 24 hours of non-investigational intravenous anti-infective treatment with non-glycopeptide antibacterial drugs for known or suspected bacterial infections. The patients received a single intravenous infusion of 22.5 mg/kg dalbavancin over 30 minutes on Day 1.

All 8 (100%) patients completed the study as planned and no patient prematurely discontinued from the study. The mean age was 40.6 days (range: 6 to 65 days) across all 3 cohorts with a mean gestational age of 36.1 weeks (range: 28 to 41 weeks). Six (6) patients were female and two (2) were male. Seven patients were white and 1 patient was of multiple races. Overall participant weight (SD) and height (SD) was 3.49 (0.772) kg (range: 2.6 to 4.5 kg) and 51.06 (4.460) cm (range: 44.5 to 57.0 cm), respectively.

There were no deaths or discontinuations due to AEs. One patient in age group 28 days to <3 months reported a serious adverse events of necrotizing enterocolitis and hydrocephalus. The necrotizing enterocolitis resolved. Both events were considered unrelated to dalbavancin as the patient had a history of pneumatosis intestinalis on abdominal ultrasound prior to drug administration. The hydrocephalus was ongoing at the time of final report, and was reported to be not related to dalbavancin, but the underlying condition of ventriculomegaly and severe meningitis/ventriculitis.

The most commonly reported TEAEs were pyrexia (3/8 [37.5%] patients) and procedural pain (2/8 [25.0%] patients); all in the > 28 days age group. A total of 2 patients in this age group also reported non-serious TEAEs during the study which included vomiting in 1 patient, and liver function test increased (ALT > 3 × ULN and direct bilirubin > 2.5 × ULN). This event was transient and resolved without any sequelae. This case was not considered as a Hy's Law case because the patient was receiving other concomitant medications and had comorbid conditions that could explain the abnormal ALT and direct bilirubin.

8.2.7 Additional Safety Explorations

Pediatrics and Assessment of Effects on Growth

The patients were not followed long-term to determine effects of the drug on growth or other developmental parameters as dalbavancin is not intended for long-term use.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Dalbavancin and its components are not known to be associated with abuse, withdrawal, or rebound effects. It is also administered intravenously in a monitored setting, making the possibility of overdose less likely.

8.2.8 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The adverse drug reactions identified post approval in adults, based on postmarketing experience include hypersensitivity (including angioedema), anaphylactic reaction, and back pain as a symptom of infusion-related reactions. This information has already been added to the dalbavancin USPI.

A search of the published literature did not reveal any additional safety information in pediatric patients. A query of the FDA adverse events reporting system was performed by this reviewer for off-label use of dalbavancin in the pediatric population. The results were restricted to cases in patients <18 years of age in which dalbavancin was listed as the primary suspect for the event. Five cases were reported in patients treated for osteomyelitis. The most frequently reported adverse event was “off-label use” in three of the patients, followed by “urticaria” in two patients. No new safety signals were identified from these data.

8.2.9 Integrated Assessment of Safety

The safety of dalbavancin for injection for the treatment of ABSSSI was evaluated in 161 pediatric patients from birth to less than 18 years of age with ABSSSI (n=83 patients treated with a single-dose and n=78 patients treated with a two-dose regimen). The median age of the patients was 9 years, ranging from 13 days to 17 years. The majority of patients were male (62.3%) and White (89.0%).

There were no deaths or treatment discontinuations due to adverse reactions in this study. Serious adverse events occurred in 3 patients treated with the dalbavancin and were unrelated to the study drug. The most common treatment-emergent adverse event occuring in more than 1% patients was pyrexia (2/161 [1.2%]). Other less common adverse drug events that occured in 1 patient each in this study were diarrhea, dizziness, and pruritus. The majority of adverse events were mild to moderate in severity.

Additionally, there were no cases of infusion-related events including phlebitis, flushing, and no cases of nephrotoxicity, ototoxicity, neutropenia, or thrombocytopenia, as reported in other members of the glycopeptide antibacterial class. Overall, the safety findings in pediatric patients were similar to those observed in adults.

8.3 Statistical Issues

Because of the relatively small size of the trial, the efficacy analyses should be interpreted cautiously. There is a fair amount of variability in the estimates, as evidenced by the wide confidence intervals due to the small sample size.

8.4 Conclusions and Recommendations

Results from this pediatric Phase 3 trial support the extention of the indication of ABSSSI to pediatric patients from birth to less than 18 years of age. The efficacy of dalbavancin in pediatric patients is extrapolated from adults as comparable drug exposure between pediatric patients receiving the proposed dosage and adult patients receiving the approved dosage allows for extrapolation of effectiveness. The Phase 3 pediatric trial provides additional supportive efficacy data.

No safety concerns related to the use of dalbavancin in pediatric patients for the treatment of ABSSSI have been identified. Similar to adult studies, the safety and efficacy of the dalbavancin single-dose and two-dose regimens were similar in pediatric patients. Although, both single- and two-dose regimens were safe and well-tolerated in pediatric patients with ABSSSI, the Applicant proposes the single-dose regimen for pediatric age group for ease of administration and to avoid discomfort of multiple administrations in pediatric patients.

One important limitation of the available data is the lack of information to support the safety and effectiveness of dalbavancin in pediatric patients with renal impairment as patients with renal impairment were excluded in the pediatric study.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee was not convened and there were no external consultations.

10 Pediatrics

This sNDA was submitted to provide safety and efficacy information with regards to the use of dalbavancin in pediatric patients aged from birth to less than 18 years of age with ABSSSI. This NDA supplement is intended to fulfill the following Pediatric Research Equity Act (PREA) post-marketing requirements (PMRs):

PMR 2145-2: Conduct a single dose pharmacokinetic (PK) study in neonates/infants from 0 to less than 3 months of age;

PMR 2145-3: Conduct a Phase 3, randomized, comparator-controlled study of dalbavancin in children from 3 months to 17 years of age with ABSSSI.

PMR 2145-4: Conduct a Phase 3, randomized, comparator-controlled study of dalbavancin in neonates/infants from birth to less than 3 months of age with ABSSSI.

Of note, on June 19, 2017, the Applicant was released from PMRs 2145-3 and 2145-4, as they elected to modify the study and combine the age group to be studied from "less than 3 months" to "birth to 18 years of age" in a single PMR. For additional details, please refer to 'Section 3 Regulatory Background' of this review. At the time of release, PMR 2145-10 was issued to incorporate the age group modification as follows:

PMR 2145-10: Conduct a Phase 3, randomized, comparator-controlled study of dalbavancin in children from birth to 18 years of age with ABSSSI.

PMR 2145-2 is fulfilled by study DAL-PK-02 and PMR 2145-10 is fulfilled by Study DUR001-306. To note, PMR 2145-1 was fulfilled by study DUR001-106 in March 28, 2016.

This submission was discussed with the Pediatric Review Committee (PeRC) on May 25, 2021. PeRC agrees that PMR 2145-2 and PMR 2145-10 should be considered fulfilled.

11 Labeling Recommendations

11.1 Prescription Drug Labeling

Labeling negotiations were ongoing at the time of completion of this review. Key changes to the Applicant's proposed labeling are discussed in this section. The numbers indicate the corresponding sections of the USPI.

1. Indications and Usage

The Applicant proposed to expand the ABSSSI indications to include the pediatric population from birth to less than 18 years of age, which is acceptable. The Applicant also proposed to include (b) (4) This was not granted for the following reasons:

(b) (4)

2. Dosage and Administration

The Applicant's proposal for pediatric dosage and administration was revised with minor editorial changes and the following key modifications:

- CrCl greater than (b) (4) was revised to read as CLcr 30mL/min/1.73m^2 and above This was because CLcr was calculated using the modified or bedside Schwartz formula in clinical studies/trial. Therefore, CLcr is normalized by body surface area.
- (b) (4) information was incorporated into the existing text as appropriate.
- The regulatory required verbatim statement for parenterals "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit" was added according to the labeling requirements in 21 CFR 201.57 (c)(2).

The following pediatric dosage labeling language was added to the to the Dosage and Administration section of the United States Prescribing Information (USPI) after the revisions were made:

The recommended dosage regimen of DALVANCE in pediatric patients with CLcr 30 mL/min/1.73m^2 and above is a single dose regimen based on the age and weight of the pediatric patient (Table 1 of USPI). Administer DALVANCE over 30 minutes by intravenous infusion.

There is insufficient information to recommend dosage adjustment for pediatric patients younger than 18 years with CLcr less than 30 mL/min/1.73m^2 *[see Use in Specific Populations (8.4) and Clinical Pharmacology (12.3)]*.

Table 1. Dosage of DALVANCE in Pediatric Patients with CLcr* 30 mL/min/1.73m^2 and above

Age Range	**Dosage (Single Dose Regimen)**
Birth to less than 6 years	22.5 mg/kg (maximum 1500 mg)
6 to less than 18 years	18 mg/kg (maximum 1500 mg)

6. ADVERSE REACTIONS

Key modifications to the applicant's proposal for the clinical trials experience in pediatric patients infromation added to section 6 were as follows:

- Removal of the statement [redacted] (b) (4) description based on the same rationale provided in section 1 (Indications and Usage) above and also to avoid suggesting or implying an indication or use that is not included in the INDICATIONS AND USAGE section of the USPI as per 21 CFR 201.57 (c)(2).
- Revision of the incidence rate for the most common adverse reactions from [redacted] (b) (4) to "1% with one adverse reaction of pyrexia reported."
- Incidence rate under the "Other Adverse Reactions" heading was changed from [redacted] (b) (4) to "1%" but no adverse reactions were added or removed from the Applicant's proposed list of adverse reactions.
- The applicant's proposal to retain the statement [redacted] (b) (4) was not acceptable due to the following reasons:
    - It minimizes the adverse reactions, and
    - Per the glossary of the guidance on the Adverse Reactions Section of Labeling (final guidance), the definition for Adverse Reaction notes that: "…This definition does not include all adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event."

Section 6 of the USPI was updated with the addition of safety findings observed in pediatric studies and updated as as follows:

Clinical Trials Experience in Pediatric Patients

Adverse reactions were evaluated in one Phase 3 pediatric clinical trial which included 161 pediatric patients from birth to less than 18 years of age with ABSSSI treated with DALVANCE (83 patients treated with a single dose of DALVANCE and 78 patients treated with a two-dose regimen of DALVANCE) and 30 patients treated with comparator agents for a treatment period

up to 14 days. The median age of pediatric patients treated with DALVANCE was 9 years, ranging from birth to <18 years.The majority of patients were male (62.3%) and White (89.0%). The safety findings of DALVANCE in pediatric patients were similar to those observed in adults.

Serious Adverse Reactions and Adverse Reactions Leading to Discontinuation
Serious adverse reactions (SARs) occurred in 3/161 (1.9%) of patients treated with DALVANCE, all in the single-dose arm. There were no adverse reactions leading to DALVANCE discontinuation.

Most Common Adverse Reactions
Most common adverse reaction occuring in more than 1% of pediatric patients 2/161 (1.2%) was pyrexia.

Other Adverse Reactions
The following selected adverse reactions were reported in DALVANCE-treated patients at a rate of less than 1% in this pediatric clinical trial:
Gastrointestinal disorders: diarrhea
Nervous system disorders: dizziness
Skin and subcutaneous tissue disorders: pruritus

8. USE IN SPECIFIC POPULATIONS
The 'Pediatric use' subsection was updated based on the labeling recommendations in the Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling[6] as follows:

8.4 Pediatric Use
Key modifications made to the Applicant's proposal are as follows:
Revision of the statement (b) (4) o read as
"The safety and effectiveness of DALVANCE for the treatment of ABSSSI has been established in pediatric patients aged birth to less than 18 years."
The rationale for this modification is provided in section 1 (Indications and Usage) above.

8.6 Renal Impairment
Key modifications made to the Applicant's proposal are as follows:
Removal of (b) (4) from the applicant's proposed statement "There is insufficient information to recommend dosage adjustment for pediatric patients with ABSSSI and (b) (4) (CLcr less than 30 mL/min/1.73m^2) *[see Dosage and Administration (2.2)].*

[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/labeling-human-prescription-drug-and-biological-products-implementing-plr-content-and-format

(b) (4)

he glomerular filtration rate of a full term neonate is approximately 30 mL/min/1.73^2. [7]

12. CLINICAL PHARMACOLOGY

The information under the 'Specific Population' subheading was revised to present key study details and study findings based on the FDA clininal pharmacology team review as follows:

12.3 Specific Population

Pediatric Patients

The pharmacokinetics of dalbavancin has been evaluated in 211 individual pediatric patients [4 days to 17.9 years of age, including a preterm neonate (gestational age 36 weeks; n=1) and term neonates (gestational age 37 to 40 weeks; n=4)] with CLcr 30 mL/min/1.73 m^2 and above. There is insufficient information to assess the exposure of DALVANCE in the pediatric patients with CLcr less than 30 mL/min/1.73 m^2. No clinically important differences in drug exposure between pediatric age groups (including preterm neonates) and adults are expected following administration of the age-dependent recommended single dose of DALVANCE. The median plasma AUC from 0 to 120 hours ($AUC_{0\text{-}120h}$) of dalbavancin in pediatric patient age groups from term neonates at birth to less than 18 years is expected to be comparable to that in adult patients ($AUC_{0\text{-}120h}$, 10400 mg*h/L). The expected median plasma $AUC_{0\text{-}120h}$ of dalbavancin in preterm neonates at birth (gestational age 26 weeks to <37 weeks) was approximately 62% of that in adult patients. The expected median maximum plasma concentrations (C_{max}) of dalbavancin for pediatric patient age groups ranged between approximately 53% to 73% of that in adult patients (C_{max}, 412 mg/L). However, in all pediatric age groups, the percentage of patients attaining PK/PD targets related to in vivo drug activity were above 90% or higher for MICs up to 0.25 mg/L.

14 CLINICAL STUDIES

This section was updated to include the results of the Phase 3 trial in pediatric patients with from birth to less than 18 years of age with ABSSSI, Study DUR-306.

Key modifications made to the Applicant's proposal are as follows:

- Retained statement "83% were from Eastern Europe" under the Clinical Study of DALVANCE in Pediatric Patients with Acute Bacterial Skin and Skin Structure Infections heading in section 14 of the PI.
- The Applicant's proposal to (b) (4) was not acceptable. (b) (4)

[7] Baum M. Neonatal Nephrology. Curr Opin Pediatr. 2016 Apr; 28(2): 170–172.

- [redacted] (b) (4)
- The Applicant's proposal to add a statement [redacted] (b) (4) was not acceptable [redacted] (b) (4)

In addition, there were editorial changes throughout the USPI. Please refer to final prescribing information that will be published at the time of approval.

12 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

13 Postmarketing Requirements and Commitment

None

14 Appendices

14.1 References

Ambrose, B. R. (2007). Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore. *Clinical Infectious Diseases*, 79-86.

Andes, D., & Craig, W. A. (2007). In Vivo Pharmacodynamic Activity of the Glycopeptide Dalbavancin. *Antimicrobial Agents and Chemotherapy*, 1633-1642.

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Schmidt, S., Röck, K., Sahre, M., Burkhardt, O., Brunner, M., Lobmeyer, M., & Derendorf, H. (2008). Effect of protein binding on the pharmacological activity of highly bound antibiotics. *Antimicrobial Agents and Chemotherapy*, 3994-4000.

Zeitlinger, M., Derendorf, H., Mouton, J., Cars, O., Craig, W., Andes, D., & Theuretzbacher, U. (2011). Protein binding: do we ever learn? *Antimicrobial Agents and Chemotherapy*, 3067-3074.

14.2 Financial Disclosure

Disclosure of financial interests of the investigators who conducted the clinical trials supporting this NDA, including statements of due diligence in cases where the applicant was unable to obtain a signed form from the investigator, was submitted in the FDA form 3454. These disclosures were certified by David Bharucha, MD, PhD, Vice President of Clinical Development, Global Clinical Development of Clinical Operations, Allergan Sales LLC.

Covered Clinical Study (Name and/or Number): Study DUR-306

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: Principal Investigators: n= 32 Sub-Investigators: n= 114		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and		

<table>
<tr><td colspan="3">(f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____

Significant payments of other sorts: _____

Proprietary interest in the product tested held by investigator: _____

Significant equity interest held by investigator in S

Sponsor of covered study: _____</td></tr>
<tr><td>Is an attachment provided with details of the disclosable financial interests/arrangements:</td><td>Yes ☐</td><td>No ☐ (Request details from Applicant)</td></tr>
<tr><td>Is a description of the steps taken to minimize potential bias provided:</td><td>Yes ☐</td><td>No ☐ (Request information from Applicant)</td></tr>
<tr><td colspan="3">Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____</td></tr>
<tr><td>Is an attachment provided with the reason:</td><td>Yes ☐</td><td>No ☐ (Request explanation from Applicant)</td></tr>
</table>

14.3 Tabulated Summary of Patients in Age group birth to <3 months age (DUR-306)

SubjID	Age/Sex/ Race	Study Dx	Micro	MH	Outcome Early	Outcome TOC	AE	CONCOMITANT MEDICATION/Comment
(b) (6)	29days /F/White	Sepsis	None	Erythroblastosis fetalis, neonatal exchange transfusion, neonatal hyperbilirubinemia, rhesus incompatibility, bile duct obstruction, electrolyte abnormalities and staphylococcal sepsis prior to enrollment; was receiving meropenem (started 5 days before continued 8 D post enrollment) and vancomycin (started 8 days before ad continued 4 days post enrolment). Patient was enrolled in the study with diagnosis of 'sepsis'. Had generalized erythema at the time of enrolment. Patient was not bacteremic at time of enrolment.	Responder? **Considered Failure due to receipt of rescue Tx with vancomycin*	Cure?	Bilirubin Increased	VANCOMYCIN -8 TO 5 -Pt had protocol violations related to study procedures
(b) (6)	20days /M/White	Cellulitis	None	Gastrostomy, esophageal atresia, Trisomy 21,	Responder	Missing	None	Pt had protocol violation "Exclusion" criteria
(b) (6)	13days /M/White	Major Cutaneous Abscess	MSSA-wound	Neonatal hyperbilirubinemia, limb abscess,	Responder	Cure	None	Pt had protocol violation "Exclusion" criteria

Patients included in Safety but not in MITT population								
(b) (6)	20days /F/White	Major Cutaneous Abscess	E. Coli-wound	20-day-old female with was enrolled with Dx of left groin abscess one day prior to enrollment. She underwent I&D of the abscess with culture growing *E. coli*. Blood culture showed no growth. She received dalbavancin and clindamycin. Over the next few days, she had progressive swelling, induration, warmth, and drainage of the abscess but was afebrile. She transitioned to oral cephalexin for 14 days on Day 8. On Day 15 she had mild purulent drainage which grew *E. coli* and *Klebsiella pneumoniae*. On Day 41, she became febrile with increased drainage, swelling, and erythema and was hospitalized for IV ceftriaxone and clindamycin. She underwent a second I&D on Day 43 and was discharged on amoxicillin-clavulanate for 8 days until Day 51, which was discontinued due to an allergic rash. The abscess resolved and she completed the study on Day 57.	Responder	Failure	Abscess	
(b) (6)	40days /M/White	Surgical Site/Traumatic Wound Infection	Gm Stain Wound Scraping: *S. salivarius* Surgical Tissue: Klebsiella Pneumonia	Ileal atresia and stenosis, ileus, underwent exploratory laparotomy, had wound infection with S. aureus post operatively. No organism at BL.	Responder	Cure	None	

14.4 SSTI-Convenience Questionnaire

SSTI-Convenience Questionnaire

CONVENIENCE QUESTIONNAIRE - GENERAL

Patient Identification No.:		***Visit Description:***
|___|___| |___|___|___| |___|___|___|		***Day 14 (± 2 days)***

Date Questionnaire Administered: |__|__| |__|__|__| |__|__|__|__|

dd mmm yyyy

FEELINGS RELATED TO THE OVERALL ANTIBIOTIC TREATMENT				
1. How often were you (or your child) concerned about receiving the antibiotic treatment?				
None of the time ***1 □***	***A little of the time*** ***2 □***	***Some of the time*** ***3 □***	***Most of the time*** ***4 □***	***All of the time*** ***5 □***

OUTPATIENT TREATMENT CONVENIENCE

Are you (or your child) currently hospitalized?

1 □ Yes ' Please go directly to question 4

0 □ No ' Please answer all remaining questions.

2. Did receiving the antibiotic treatment interfere with your (or your child's) usual daily activities?

Significantly	***Moderately***	***Slightly***	***Not at all***
1 □	***2 □***	***3 □***	***4 □***

3. Were you (or your child) easily able to modify your schedule to take the antibiotic treatment?

Yes	***No***
1 □	***2 □***

TREATMENT REGIMEN SATISFACTION AND PREFERENCE				
4. Overall, how satisfied were you (or your child) with the antibiotic treatment?				
Extremely satisfied ***1 □***	***Very satisfied*** ***2 □***	***Moderately satisfied*** ***3 □***	***Slightly satisfied*** ***4 □***	***Not at all satisfied*** ***5 □***
5. In terms of your experience with your (or your child's) antibiotic treatment, would you recommend for yourself (or your child) or others the same antibiotic treatment again?				
Definitely Yes ***1 □***	***Probably*** ***2 □***	***Maybe*** ***3 □***	***Probably No*** ***4 □***	***Definitely Not*** ***5 □***
6. If you had the choice between the following antibiotic treatments for yourself (or your child), which one would you prefer?				
One 30-minute infusion once ***1 □***	***One 3-hour infusion once*** ***2 □***	***One 30-minute infusion once a week for two weeks*** ***3 □***	***Two 1-hour infusions per day for a whole week*** ***4 □***	***A few days of two 60-minute infusions per day and then 1 pill 3-4 times per day the rest of the week*** ***5 □***
FEELINGS RELATED TO THE OVERALL ANTIBIOTIC TREATMENT				
7. Overall, how satisfied were you with the care you (or your child) received?				
Very satisfied ***1 □***	***Neutral*** ***2 □***	***Very or quite dissatisfied*** ***3 □***		
8. Were you satisfied with the effect of the IV antibiotic on your (or your child's) infection?				
Very satisfied ***1 □***	***Neutral*** ***2 □***	***Very or quite dissatisfied*** ***3 □***		
9. Overall how satisfied are you (or your child) with the location of care received (hospital, outpatient or both)?				
Very satisfied ***1 □***	***Neutral*** ***2 □***	***Very or quite dissatisfied*** ***3 □***		

10. Where do you think it is preferable to receive the kind of care provided (for yourself or your child)?		
In the hospital *1* □	***In the community (as an outpatient)*** *2* □	***No preference*** *3* □

14.5 Nonclinical Pharmacology/Toxicology

[Insert carci data as needed. Limit to 2 pages]

14.6 OCP Appendices (Technical documents supporting OCP recommendations)

14.6.1 Nonclinical Studies

14.6.1.1 Protein Binding

In vitro plasma protein binding of dalbavancin in mice, rats, dogs, and humans has been estimated in five studies. Equilibrium dialysis and serum antimicrobial potency methods have been employed to quantify in vitro plasma protein binding (PPB).

Reviewer Conclusions:

The fraction of dalbavancin (DAL) bound to human plasma protein is approximately 0.93 and was approximately constant across concentrations expected in the clinic. Comparable (species independent) plasma protein binding of dalbavancin is reported when evaluating two or more species in the same study using equilibrium dialysis methods. To determine the degree of PPB, free fraction measurement methods such as equilibrium dialysis are the standard. PPB estimates and comparisons between species based on antimicrobial potency changes do not meet this standard and are viewed as secondary data.

Murine In Vitro PPB (Study VER001-MI-013)

The impact of drug binding to serum and serum proteins was investigated by comparing the MIC of dalbavancin for two strains of Staphylococcus aureus (*S. aureus*) in broth, infected mouse serum, human serum (Table 22). Based upon the MIC difference between broth and 95% mouse serum, the fraction of DAL binding to mouse serum is estimated to be 99.6%. Alternatively, based upon the MIC difference between 95% mouse serum ultrafiltrate and 95% mouse serum, the fraction of DAL binding to mouse serum is estimated to be 98.4%. Based upon the MIC difference between broth and 95% human serum, the fraction of DAL binding to human serum is estimated to be 98.5% (Applicant states 96%). No MIC is reported for human 95% ultrafiltrate. A murine DAL PPB value of 98.4% was used in subsequent murine PK-PD analyses (Andes & Craig, 2007) (Lepak, Marchillo, VanHecker, & Andes, 2015) and target attainment analysis (DAL-MS-02).

Table 19: Impact of Serum, Serum Ultrafiltrate on the In Vitro Activity of DAL Against Selected *S. aureus* Strains

S. aureus strain	MIC Broth	MIC 95% Mouse Serum	MIC 95% Mouse Serum Ultrafiltrate	MIC 95% Human Serum
ATCC 25923	0.12	32	0.5	8
MRSA	0.12	32	0.5	8

Equation: (the minimum inhibitory concentration (MIC) in 95% serum – MIC in serum ultrafiltrate) / MIC in 95% serum
Source: Study Report VER001-MI-013, Table 5, pg. 10 with slight modifications for readability

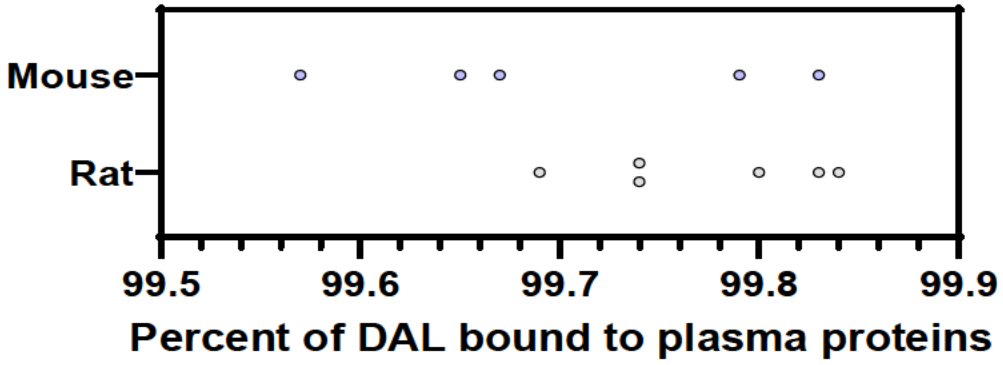
A variety of factors preclude the use of antimicrobial potency data (especially highly protein bound drugs) to quantify the degree of PPB or to make comparisons across species (Zeitlinger, et al., 2011; Beer, Wagner, & Zeitlinger, 2009; Schmidt, et al., 2008).

Murine and Rat In Vitro PPB (Study XBL 12687-02878)

DAL PPB in mouse (ICR/Swiss) and rat (Sprague-Dawley) was estimated under the same experimental conditions and method (equilibrium dialysis and LC/MS/MS)(Table 23).

Table 20: Summary of DAL binding to mouse and rat plasma proteins

Concentration (µg/mL)	Mouse Plasma % Bound	Rat Plasma % Bound
100	99.81	99.82
200	99.63	99.72
Average	99.72	99.77



Recoveries from all samples were acceptable.
Source: Study Report XBL12687-02878, Table 1, pg. 16 with slight modifications for readability

Plasma protein binding was constant across species.

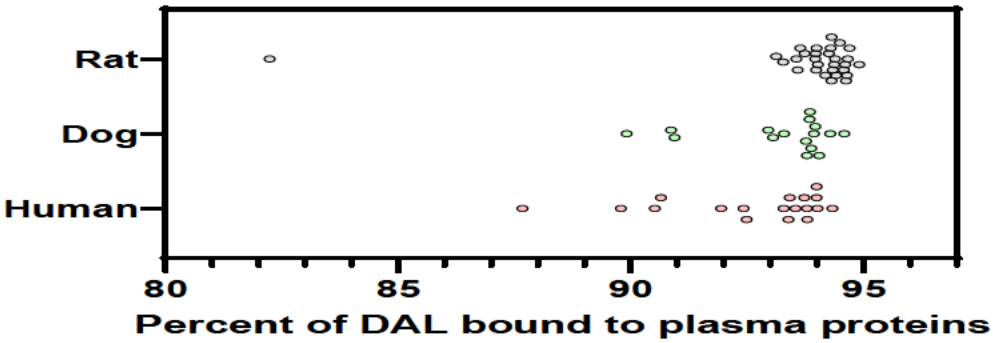
Human, Dog, and Rat In Vitro PPB (Study XBL 04052)

Human, dog, and rat plasma protein binding of DAL was estimated under the same experimental condition and method (equilibrium dialysis of ^{14}C-dalbavancin) (Table 24).

Table 21: Summary of DAL binding to rat, dog and human plasma proteins

Concentration (µg/mL)	Rat Plasma % Bound	Dog Plasma % Bound	Human Plasma % Bound
0.182	94.42	94.07	90.27
1.82	94.40	90.39	91.63
18.2	94.56	93.7	94.04
90.8	94.19	92.95	NA
136.3	94.30	NA	93.9
181.7	94.61	93.67	NA
227.1	93.99	NA	92.37
299.8	93.36	93.56	93.36

363.3	93.65	NA	NA
454.2	94.09	NA	NA
Average	94.16	93.06	92.6



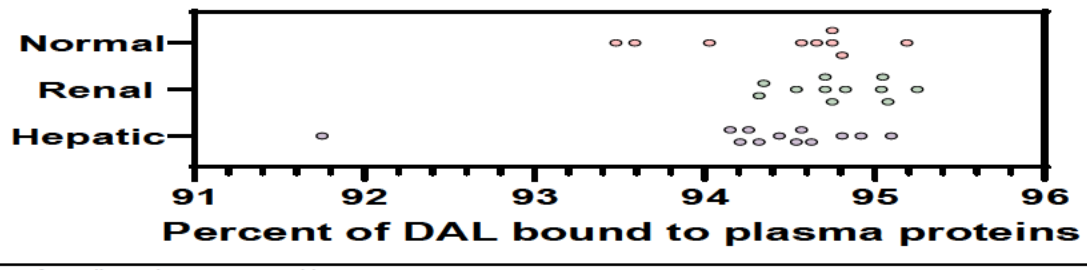
Recoveries from all samples were acceptable
Source: Study Report XBL04052, Table 1, pg. 17 with slight modifications for readability

Human In Vitro PPB (Study XBL 04057)

Human plasma protein binding of DAL was estimated under the same experimental condition and method (equilibrium dialysis of ^{14}C-dalbavancin) using plasma from adults with normal organ function, severe renal, or severe hepatic impairment (Table 25).

Table 22: Summary of DAL binding to human plasma proteins from different groups

	Human Plasma (% Bound)		
Concentration (µg/mL)	Normal	Renal Impairment	Hepatic Impairment
1.82	94.2	94.7	93.4
18.2	94.7	95	94.7
90.8	93.8	94.4	94.3
454.2	95	95	94.9
Average	94.4	94.8	94.3



Recoveries from all samples were acceptable
Source: Study Report XBL04057, Table 1, pg. 18 with modifications

The DAL PPB values are higher in this study compared to Study 04052 but considered comparable. Collectively, for PTA analyese, it would be reasonable to use the same DAL PPB value between *mice and* humans. The Applicant originally used 98.4% DAL PPB in mice to determine the *f*AUC/MIC target values and 93% DAL PPB in humans to estimate the *f*AUC in patients, which resulted in higher PTAs than that predicted with the same DAL PPB between mice and humans. We requested the Applicant re-conduct PTA analyese with the same DAL PPB between mice and humans. See Section 14.6.3.3 for the results of the reconducted PTA analyses.

14.6.2 Clinical Pharmacokinetic Studies

14.6.2.1 Pediatric Clinical Trial with Single Dose

DUR001-106

This was a phase 1, open-label study to investigate the pharmacokinetics (PK), safety, and tolerability of a single intravenous (IV) dose of dalbavancin (DAL) infused over 30 min in hospitalized children of age 3 mo. to 11 yr. receiving standard IV anti-infective treatment for bacterial infections.

	Cohort 1 3 mo. to 2 yr. (n=11)	Cohort 2 2 to 6 yr. (n=12)	Cohort 3 6 to 11 yr. (n=11)
Dose	15 mg/kg	25 mg/kg[b]	10 mg/kg[a]

[a]max dose of 1000 mg
[b]One patient received 15 mg/kg

Six plasma DAL PK samples per individual were collected from K_2EDTA anticoagulated whole blood; pre-dose, 30-minutes after end of infusion, and out to 648 hrs post-start of infusion. PK data was combined with adolescent data collected from prior Study A8841004 and a preliminary pediatric population PK analysis (Report ICPD 00348-02) and final pop PK analysis (DAL-MS-02) performed. Participant baseline characteristics and DAL PK from noncompartmental analysis are summarized in Table 26, respectively.

Table 23: Baseline Anthropomorphic Characteristics and Demographics of PK Evaluated Individuals

	Cohort 1 3 mo. to 2 yr. (n=11)	Cohort 2 2 to 6 yr. (n=11[a])	Cohort 3 6 to 11 yr. (n=11)
Age (years)	0.9 [0.57, 1.3] (0.25, 1.7)	3 [2.45, 4.2] (2.2, 5.9)	9 [8.1, 10.8] (6.7, 11.7)
Weight (kg)	9.6 [8.3, 11] (5.7, 13)	15.7 [13.5, 16.4] (10.7, 18.9)	31.4 [25.4, 42.7] (19.8, 92)
BMI (kg/m^2)	18.4 [17.5, 19] (16.8, 38.5)	15.5 [14.2, 17.0] (11.4, 20.3)	18.1 [14.7, 22.4] (13.5, 35.9)
Albumin (mg/dL)	3.4 [3.2, 4] (2.9, 4.5)	3.6 [3.1, 3.85] (2.2, 4.5)	4.1 [3.55, 4.15] (3.4, 4.4)
Creatinine (mg/dL)	0.4 [0.3, 0.46] (0.17, 0.48[b])	0.27 [0.23, 0.3] (0.1, 0.4[c])	0.44 [0.38, 0.52] (0.25, 0.72)
CL_{cr} (mL/min/1.73 m^2)	77 [66.5, 110.5] (49, 208)	202 [177, 219] (128, 275)	169 [145, 203] (122, 215)
Gender (% male)	81.8	54.5	81.8
Race (% Black)	45.5	9.1	0
Ethnicity (% Hispanic)	0	27.3	72.7

[a] Loss of 1 patient due to thawing during transit to assay lab
[b] One individual ≤ 0.2 mg/dL
[c] Three individuals ≤ 0.2 mg/dL
[d] Applicant estimated creatinine clearance using the modified Schwartz method (Children < 1 year: k =0.45; Children ≥ 1 to 13 years of age: k= 0.55)
[ǂ] Data presented as median [interquartile 1, interquartile 3] (min, max) unless stated otherwise
Assumed creatinine methods recalibrated to be traceable to IDMS
Sources: dur001-106 tabulation legacy lb.xpt and dm.xpt and analysis advs.xpt datasets

Table 24: DAL Exposure and PK parameters Following a Single mg/kg IV DAL Dose Infused Over 30 min

	Cohort 1 3 mo. to 2 yr. (n=11)	Cohort 2 2 to 6 yr. (n=11[a])	Cohort 3 6 to 11 yr. (n=11)
C_{max} (µg/mL)	123 [116.5, 132.5]	287 [283, 321.5]	222 [193.5, 238]
AUC_{0-120} (h·µg/mL)	5036.7 [4,482.4, 5,456.7]	12,579.2 [11,144.2, 14,875.3]	9,087.4 [8,335.8, 11,179.3]
AUC_{0-inf} (h·µg/mL)	8,569 [8,090.1, 9,229][a]	22,878 [17,910, 26,389.6][a]	19,115.5 [15,409.6, 22,748.4][a]
$T_{1/2}$ (h)	113.5 [106.1, 120.4][a]	120.7 [116.2, 122.3][a]	132.3 [119.9,139.2][a]
CL (mL/h)	11.4 [8.5, 14.2][a]	16.3 [14.7, 17.5][a]	27 [23.4, 30.1][a]
C_{max}/Dose	1.33 [1.04, 1.67]	0.8 [0.73, 0.9]	0.43 [0.37, 0.52]
AUC_{0-inf}/Dose	88.5 [70.8, 117.43]	62.7 [57.2, 69.5]	37.1 [33.2, 42.9]

[a] Loss of 1 patient due to thawing during transit to assay lab
[a] n=10, 1 participant excluded due to AUC% extrapolated > 20
[¥] Data presented as median [interquartile 1, interquartile 3]
AUC_{0-120} = area under the plasma concentration-time curve from time 0 to 120; AUC_{0-inf} = area under the plasma concentration-time curve from time 0 to infinity; CL = clearance; C_{max} = maximum concentration; $T_{1/2}$= terminal half-life;
Reviewer's Analysis with actual sampling times
Sources: Dur001-106 tabulation legacy ex.xpt and pc xpt datasets.

Study DAL-PK-02

This was a phase 1, multi-center, randomized, open-label, single IV dose of DAL infused over 30 min in hospitalized neonates to infant ages < 3 months with suspected or confirmed bacterial infection receiving standard IV anti-infective treatment.

	Cohort 1 Young infant >28 days to < 3 mo. (n=6)	Cohort 2 Term neonate ≤ 28 days (n=1)	Cohort 3 Preterm neonate ≤ 28 days (n=1)
Dose		22.5 mg/kg	

Six plasma DAL PK samples per individual were collected from K_2EDTA anticoagulated whole blood; pre-dose, 30-minutes after end of infusion, and out to 672 hrs post-start of infusion. PK data was included in the final pediatric population PK analysis performed (DAL-MS-02). Participant baseline characteristics and DAL PK from noncompartmental analysis are summarized in Table 28 and Table 29, respectively.

Table 25: Baseline Anthropomorphic Characteristics and Demographics of PK Evaluated Individuals

	Cohort 1 Young infant >28 days to < 3 mo. (n=6)	Cohort 2 Term neonate ≤ 28 days (n=1)	Cohort 3 Preterm neonate ≤ 28 days (n=1)
Age (days)	52 [35, 62] (30, 65)	6	23
Gestational Age (weeks)	38 [29, 40] (28, 41)	39	36
Weight (kg)	3.9 [2.9, 4.4] (2.6, 4.5)	2.9	2.8
BMI (kg/m^2)	14 [13.5, 14.6] (12.3, 14.6)	11.6	11.2

Albumin (mg/dL)	2.9 [2.7, 3.1] (2.6, 3.2)	3.5	2.7
Creatinine (mg/dL)	0.3 [0.26, 0.3] (0.2, 0.3[a])	0.6	0.29
CL_{cr} (mL/min/1.73 m^2)[b]	78.8 [66.3, 99] (49, 128.3)	34	70.7
Gender (% male)	33.3	0	0
Race (% Multiple[c])	16.7	0	0
Ethnicity (% Hispanic)	16.7	0	0

[a] Two individuals < 0.3 mg/dL
[b] Applicant estimated creatinine clearance using the modified Schwartz method (premature infants: k = 0.33; term infants: k = 0.45; Children ≥ 1 to 13 years of age: k= 0.55)
[c] Multiple races selected by participants
[¥] Data presented as median [interquartile 1, interquartile 3], (min, max) unless stated otherwise
Assumed creatinine methods recalibrated to be traceable to IDMS
Reviewer's noncompartmental analysis with actual sampling times
Sources: dal-pk-02 tabulation lb.xpt and dm.xpt and analysis advs.xpt dataset

Table 26: DAL Exposure and PK parameters Following a Single 22.5 mg/kg IV DAL Dose Infused Over 30 min

	Cohort 1 Young infant >28 days to < 3 mo. (n=6)	Cohort 2 Term neonate ≤ 28 days (n=1)	Cohort 3 Preterm neonate ≤ 28 days (n=1)
C_{max} (µg/mL)	197.4 [172.6, 217.8]	250.85	198.66
$AUC_{0\text{-}120}$ (h·µg/mL)	5,699.7 [5,069.4, 7,199]	7,758.40	6,512.44
$AUC_{0\text{-}inf}$ (h·µg/mL)	9,435.6 [8,205.1, 12,963.4][a]	13,380.93	10,536.28
$T_{1/2}$ (h)	107.2 [99.4, 109.4][a]	122.89	111.20
CL (mL/h)	7.3 [6.9, 7.5][a]	5.04	5.77
C_{max} / Dose	2.44 [2.09, 2.9]	3.7	3.3
$AUC_{0\text{-}inf}$ / Dose	136.5 [125.7, 151.9]	198.2	173.4

[a] n=5, 1 participant excluded due to AUC% extrapolated > 20
[¥] Data presented as median [interquartile 1, interquartile 3]
$AUC_{0\text{-}120}$ = area under the plasma concentration-time curve from time 0 to 120; $AUC_{0\text{-}inf}$ = area under the plasma concentration-time curve from time 0 to infinity; CL = clearance; C_{max} = maximum concentration; $T_{1/2}$= terminal half-life;
Reviewer's noncompartmental analysis with actual sampling times
Source: DAL-PK-02 analysis dataset adpc.xpt and tabulation dataset ex.xpt

14.6.2.2 Pediatric clinical trial with single or two-dose regimen

DUR001-306

This was a Phase 3, multicenter, open-label, randomized, comparator-controlled trial evaluating the safety and efficacy of a single dose of IV dalbavancin and a 2-dose regimen of once weekly IV dalbavancin (for a total of 14 days of coverage) for the treatment of ABSSSI known or suspected to be due to susceptible Gram-positive organisms in children. In order to support enrollment of participants < 3 months of age, Cohort 5 recruited participants with either ABSSSI or neonatal sepsis. The comparators (Cohorts 1 to 4 only) were either IV vancomycin (for methicillin-resistant Gram-positive infections) or IV oxacillin or flucloxacillin (for methicillin-susceptible Gram-positive infections) for 10-14 days.

Participants were allocated to 1 of 5 cohorts based on age and doses were based on age and weight of the participant (Table 30):

Table 27: DUR001-306 Cohorts and Doses

Cohorts	Single Dose[a] N=83	Two Dose[b] N=78 Day1/Day 8
12 yr to 17 yr, inclusive	18 mg/kg (n=29)	12 / 6 mg/kg (n=29)
6 yr to <12 yr	18 mg/kg (n=25)	12 / 6 mg/kg (n=24)
2 yr to <6 yr	22.5 mg/kg (n=18)	15 / 7.5 mg/kg (n=17)
3 mo to <2 yr	22.5 mg/kg (n=6)	15 / 7.5 mg/kg (n=8)
Birth to <3 mo	22.5 mg/kg (n=5[c])	NA

[a] Maximum dose of 1500 mg
[b] Maximum dose of 1000 mg Day 1 and 500 mg Day 8
[c] 3 out of the 5 were between birth to ≤ 28 days and none were preterm neonates (gestational age ≥ 32 but <37 weeks) were enrolled
$AUC_{0\text{-}120}$ = area under the plasma concentration-time curve from time 0 to 120; $AUC_{0\text{-}inf}$ = area under the plasma concentration-time curve from time 0 to infinity; CL = clearance; C_{max} = maximum concentration; $T_{1/2}$= terminal half-life;
Reviewer's noncompartmental analysis with actual sampling times – Phoenix 8.3.0.5
Source: DAL-PK-02 analysis dataset adpc.xpt and tabulation dataset ex.xpt

For the DAL participants in the safety population, most were white (88%) and male (62%). Overall, the average age and weight was approximately 8.6 yr of age (range: 0.04 to 17) and 34 kg (range: 3.2 to 85) respectively. Creatinine clearance was approximately 124 mL/min/1.73 m^2 (range: 42 to 486).

PK samples (5 per participant) were collected from each participant over 14 days in the DAL groups and plasma DAL concentration data from this study were included in the final pediatric population PK analysis (See Section 14.6.3.1).

14.6.3 Pharmacometrics

14.6.3.1 Population Pharmacokinetics (PK) Analysis

Review Summary

The Applicant's final population pharmacokinetic (PopPK) model for subjects aged from birth to less than 18 years is adequate in: 1) describing the PK data, 2) supporting simulation of exposure metrics (0-120 hour AUC), and 3) using simulated exposures to conduct probability of target attainment (PTA) analysis and to support proposed doing regimen for pediatric population. The applicant's analyses were verified by the reviewer and no significant discordance was identified.

Introduction

The applicant sought to optimize dalbavancin dose levels (exposure matching and PK-PD assessment via probability of target attainment) across the pediatric population from birth to less than 18 years of age. The primary objectives of applicant's analysis were as follows:

- Characterize the PopPK profile of dalbavancin as a function of dose and time
- Evaluate the impact of covariates on the PK of dalbavancin

- Perform pharmacodynamic target attainment as a function of dalbavancin simulated exposure by evaluation of proposed dosing regimen across pediatric age range with respect to the established adult efficacy and safety metrics

Model Development

Data

A total of 4 studies were included to conduct the PopPK analysis: A8841004, DUR001-106, DUR001-107 (DAL-PK-02), DUR001-306 (DAL-MD-02). The pediatric subgroup ranges were broken down to 12 to 17 years, < 12 years of age, birth to 3 months of age, and birth to 17 years of age, respectively.

Table 31 describes the subjects providing the PK data by dosages and studies, as well as observation counts by studies and BLQ status. Table 32 provides summary statistics for baseline demographics of pediatric subjects in the analysis. Overall, 211 pediatric subjects with age ranging from 4 days to 17 years contributed 1124 non-BLQ dalbavancin PK observations to the final PopPK analysis.

Table 28: Summary of Patients (%) in PopPK Analysis Dataset by Dosages and Studies

Study	A8841004	DUR001-106	DUR001-107	DUR001-306	All
	(N=10)	(N=33)	(N=8)	(N=160)	(N=211)
Dose					
10 mg/kg		11 (33.3%)			11 (5.2%)
12 mg/kg				53 (33.1%)	53 (25.1%)
15 mg/kg	10 (100.0%)	12 (36.4%)		22 (13.8%)	44 (20.9%)
18 mg/kg				54 (33.8%)	54 (25.6%)
22.5 mg/kg			8 (100.0%)	31 (19.4%)	39 (18.5%)
25 mg/kg		10 (30.3%)			10 (4.7%)
PK observation records					
Number of pre-dose BQL observations	10	0	0	0	10
Number of post-dose BQL observations	1 (0.8%)	0 (0%)	1 (2.1%)	16 (2%)	18 (1.6%)
Number of post-dose non-BQL observations	119	192	47	766	1124

Source: Applicant's PopPK Report, Table 2, page 24

Table 29: Summary of Baseline Demographics for Included Subjects

Study	A8841004	DUR001-106	DUR001-107	DUR001-306	All
	(N=10)	(N=33)	(N=8)	(N=160)	(N=211)
Gender					
Female	3 (30.0%)	9 (27.3%)	6 (75.0%)	59 (36.9%)	77 (36.5%)
Male	7 (70.0%)	24 (72.7%)	2 (25.0%)	101 (63.1%)	134 (63.5%)
Race					
AI or AN				4 (2.5%)	4 (1.9%)
Asian				2 (1.2%)	2 (0.9%)
Black	5 (50.0%)	6 (18.2%)		10 (6.2%)	21 (10.0%)
Other			1 (12.5%)	4 (2.5%)	5 (2.4%)
White	5 (50.0%)	27 (81.8%)	7 (87.5%)	140 (87.5%)	179 (84.8%)
Age (yr)					
Mean (SD)	15.1 (1.6)	4.59 (3.8)	0.104 (0.056)	9.08 (5.1)	8.32 (5.4)
Median (range)	15.7 (12.4 - 17)	3.01 (0.249 - 11.8)	0.0986 (0.011 - 0.172)	9.29 (0.0356 - 17.9)	8.5 (0.011 - 17.9)
Height (cm)					
Mean (SD)	164 (7.2)	102 (30)	51.1 (4.5)	130 (32)	124 (36)
Median (range)	165 (148 - 171)	100 (47 - 160)	50.5 (44.5 - 57)	132 (51 - 182)	128 (44.5 - 182)
Weight (kg)					
Mean (SD)	66 (20)	21 (17)	3.49 (0.77)	34.2 (20)	32.5 (22)
Median (range)	60.4 (47.9 - 105)	15.7 (5.7 - 92)	3.35 (2.6 - 4.5)	30 (3.2 - 85)	26.4 (2.6 - 105)
Body Mass Index (kg/m2)					
Mean (SD)	24.6 (7.4)	18.4 (5.6)	13.2 (1.4)	18.2 (4.3)	18.3 (4.9)
Median (range)	21.7 (18.2 - 41.1)	17.3 (11.4 - 38.5)	13.6 (11.2 - 14.6)	17.2 (9.26 - 31.6)	17.2 (9.26 - 41.1)
Body Surface Area (m2)					
Mean (SD)	1.7 (0.22)	0.741 (0.38)	0.211 (0.032)	1.09 (0.46)	1.03 (0.5)
Median (range)	1.69 (1.4 - 2.07)	0.645 (0.286 - 1.95)	0.206 (0.173 - 0.253)	1.04 (0.212 - 2.05)	0.978 (0.173 - 2.07)
Serum Albumin (g/dL)					
Mean (SD)	3.2 (0.88)	3.64 (0.56)	2.95 (0.31)	4.47 (0.37)	4.22 (0.63)
Median (range)	2.95 (1.9 - 4.6)	3.7 (2.2 - 4.5)	2.9 (2.6 - 3.5)	4.5 (3.3 - 5.3)	4.4 (1.9 - 5.3)
Serum Creatinine (mg/dL)					
Mean (SD)	0.736 (0.27)	0.369 (0.13)	0.316 (0.12)	0.573 (0.19)	0.539 (0.2)
Median (range)	0.67 (0.5 - 1.29)	0.37 (0.16 - 0.72)	0.3 (0.2 - 0.6)	0.555 (0.13 - 1.11)	0.52 (0.13 - 1.29)

AI, American Indian; AN: Alaska Native
Source: Applicant's PopPK Report, Table 2, page 25

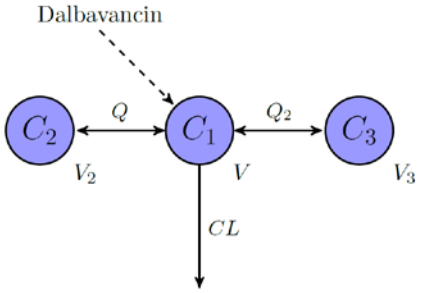
Base model

The base model was a three-compartment PopPK model parameterized with zero-order drug input (intravenous infusion) into the central volume of distribution (V) and first-order elimination (CL) from V. The two distribution compartments (V2, V3) were parameterized with Q, as defined by the product of respective inter-compartmental transfer constants (k12, k21, k13, k31) and volume of distribution compartments (V, V2, V3).

In the base model, fixed allometric exponents of 0.75 and 1 were utilized for subject body weight on CL and V, respectively, with body weight centered on 70 kg. Inter-individual variability (IIV) was included on CL, V, and V2. The proportional error model was utilized to describe residual error. The proportional residual error was estimated for DUR001-306 separately.

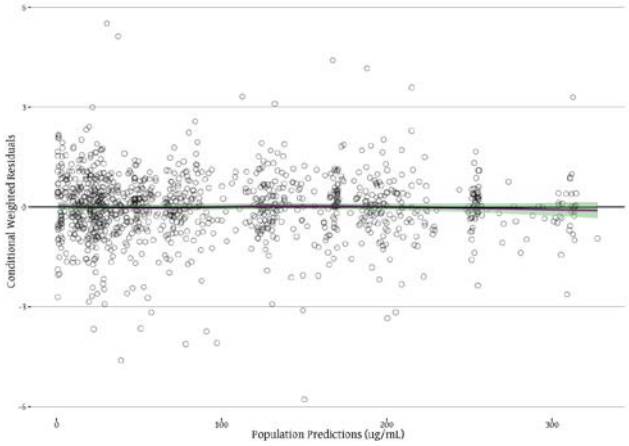
A schematic of the structural model is depicted in Figure 1. Base model diagnostics, such as goodness-of-fits (GoF) plots, are described in Figures 2-6. Table 33 lists the parameter estimates from the base model.

Figure 1: Scheme of Base Model Structure



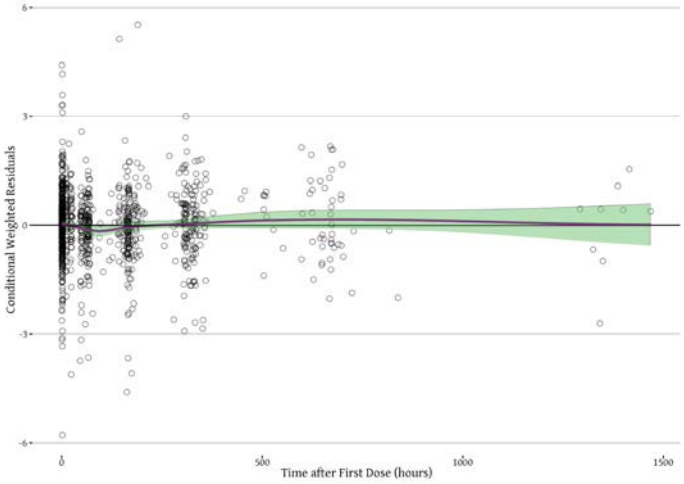
Source: Applicant's PopPK Report, Figure 9, page 45

Figure 2: CWRES vs Predictions in the Base Model



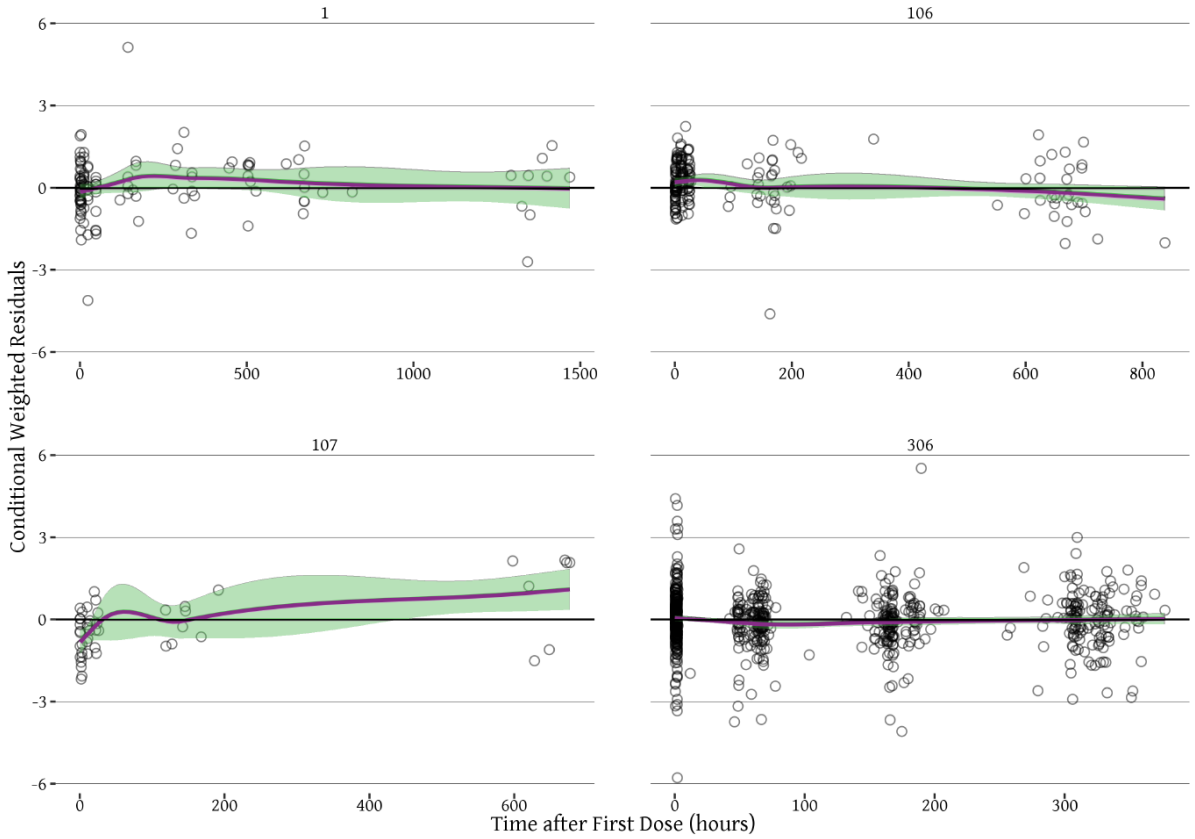
CWRES, conditional weighted residuals; solid line, LOESS; shaded area, 95% CI of LOESS curve
Source: Applicant's PopPK Report, Figure 10, page 47

Figure 3: CWRES vs Time after First Dose (hours) in the Base Model



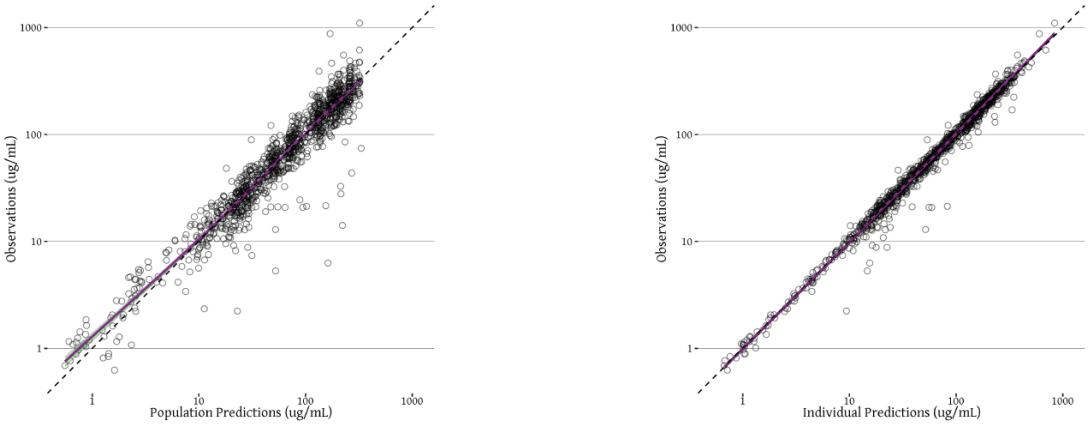
Solid line, LOESS; shaded area, 95% CI of LOESS curve
Source: Applicant's PopPK Report, Figure 11, page 47

Figure 4: CWRES vs Time after 1st Dose Stratified by Study in the Base Model



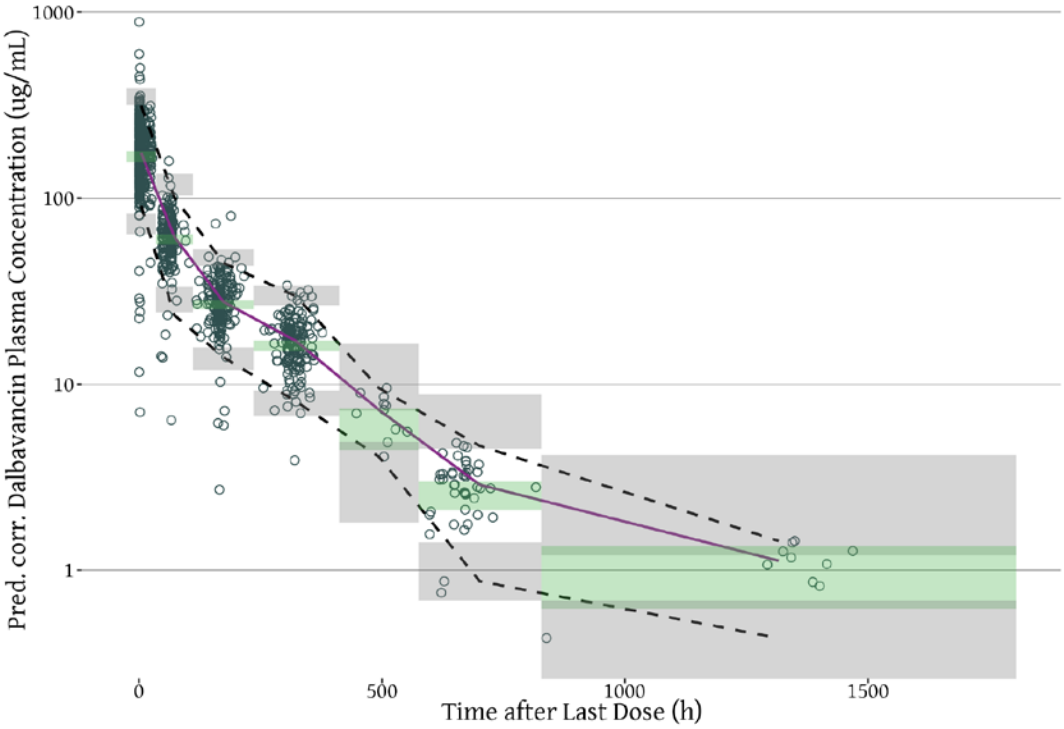
CWRES, conditional weighted residuals
Source: Applicant's PopPK Report, Figure A.5.4, page 132

Figure 5: Observed vs. Predicted Dalbavancin Concentrations in the Base Model



Solid line, LOESS; shaded area, 95% CI of LOESS curve; dashed line, line of identity
Source: Applicant's PopPK Report, Figure A.5.2, page 131

Figure 6: Prediction-corrected Visual Predictive Check in the Base Model



Circles: Observations, **Solid Blue Line**: Median of the observed dalbavancin concentrations, **Dashed Lines**: 2.5^{th} and 97.5^{th} percentiles of the observed dalbavancin concentrations, **Shaded Area**: The shaded areas indicate the 95% CI around the prediction-corrected median (green area), and 2.5^{th} and 97.5^{th} percentiles of the simulated concentrations (grey areas). All observations and predictions are adjusted using prediction correction as described in Bergstrand et al. (Bergstrand et al., 2011).

Source: Applicant's PopPK Report, Figure A.5.8, page 135

Table 30: Parameter estimates of the Base PopPK Model (Based on Reference Weight = 70 kg)

Parameter	Description	Units	Estimate	95% CI
θ_1	CL	L/h	0.0579	(0.0553 - 0.0606)
θ_2	V	L	4.71	(4.42 - 5.02)
θ_3	V2	L	6.25	(5.78 - 6.76)
θ_4	Q	L/h	0.821	(0.732 - 0.922)
θ_5	Q2	L/h	0.0107	(0.00974 - 0.0118)
θ_6	V3	L	6.6	(5.14 - 8.46)
$\omega_{1.1}$	IIV,CL	sd (CV%)	0.314 (32.2)	(0.0595 - 0.137)
$\omega_{2.1}$	Corr,CL-V	-	0.825	-
$\omega_{2.2}$	IIV,V	sd (CV%)	0.459 (48.5)	(0.0944 - 0.328)
$\omega_{3.1}$	Corr,CL-V2	-	0.851	-
$\omega_{3.2}$	Corr,V-V2	-	0.742	-
$\omega_{3.3}$	IIV,V2	sd (CV%)	0.332 (34.1)	(0.0559 - 0.163)
$\sigma_{1.1}$	PropErr	sd	0.127	(0.00803 - 0.0241)
$\sigma_{3.3}$	PropErr-PhIII	sd	0.175	(0.0196 - 0.0418)

Note: The standardized reference weight of 70 kg was used in the allometric scaling of all disposition parameters, with fixed exponents of 0.75 for all clearances and 1 for all volumes. ω_X: variance of the IIV of parameter X, IIV as a %CV was derived from variance according to $\sqrt{e^{\omega_X} - 1} \cdot 100$. Covariances are reported as a correlations.

Note: when reference weight was modified to 26.4 kg (median weight of pooled pediatric population), the typical parameter estimates were: CL (0.0279 L/h), V (1.77 L), Q (0.395 L/h), V2 (2.36 L/h), Q2 (0.00517 L/h) and V3 (2.49 L).
Source: Applicant's PopPK Report, Table 13, page 46

Reviewer's comments: In general, the Applicant's base model provided acceptable agreement between observed and predicted concentrations. This was demonstrated through the GoF plots:

1) *the CWRES plots showing randomly scattered data points without abnormal trends and all data points are centered around y=0 over population predictions and over time (Figure 2 and Figure 3)*
2) *the observed vs. predicted plots have no obvious bias and show generally acceptable agreement between observed data and predictions (Figure 5).*

Yet, the reviewer had the following observations when the CWRES vs time plot was stratified by study.

1) *As shown in Figure 4, an under-prediction was observed between hours 600-800 for study 106; however, the deviation from y=0 was minor*
2) *In contrast, an over-prediction (but CWRES <3) was noted starting around hour 200 through hour 600 for study 107; however, study 107 was limited by sample size (n=10), as well as PK samples around that time period. This was apparent in the available data at around 600 hours that could affect the LOESS fit (deviation from y=0).*

Overall, the base model describes the observed, pooled data adequately across time for the 2.5th and 97.5th percentiles of the observed dalbavancin concentrations (Figure 6). The base model parameter estimates were generally precise with the highest RSE of 30.1% for Q (theta 4) while RSEs for other base model PK parameters were between 0.8-6.7%. The reviewer was able to reproduce the PK parameter results, as well as the IIV on CL, V, and V2. Shrinkages of random

effects were acceptable (3.9%-13%). In addition, the reviewer modified the reference weight to the median pediatric body weight of 26.4 kg in the base model and was able to reproduce the results (data not shown here). Numeric shift of the reference weight value did not affect the random effects (IIV) estimates.

Covariate Analysis

Prior dalbavancin population PK in adult patients were considered when evaluating renal function and albumin (ALB) level in the pediatric PopPK model. ALB was parameterized via F (fixed to 1) and renal function (as described by the Rhodin and bedside Schwartz equations for subjects <2 years of age and those ≥2 years, respectively) was included on CL (for details regarding renal function calculation, refer to Applicant's PopPK Report, Appendix A.1, Model Analysis Plan). The final base model (with *a priori* inclusion of body weight, ALB, and renal function) underwent formal stepwise covariate testing (forward inclusion and backwards elimination) for the covariate-parameter relationships for age, race, and sex (Table 34). No additional significant covariates were identified fromTable 34

Table 31: Covariate-parameter Relationship Tested from the Final Base Model

PK Model Parameter	Covariates
CL	AGE, RACE, SEX
V_1, V_2, V_3, Q_2, Q_3	AGE, RACE, SEX

Source: Applicant's PopPK Report, Table 8, page 33

Reviewer's comments: Considering that dalbavancin is highly protein bound (~93% in human) and approximately 33% is excreted renally, the Applicant's approaches in:

1) incorporation of ALB to a fixed bioavailability (F=1) to model the effects of ALB on dalbavancin PK

2) using validated equations for describing renal function in age-specific groups (incorporation of renal function maturation for those below 2 years of age)

were acceptable in describing the PK data and generating estimated exposures (e.g., cumulative AUCs from 0-120 hours) for the probability of target attainment analysis.

Regarding the approach for estimation of renal function using either the Rhodin or bedside Schwartz equations, the follow key points should be considered:

1) *While both methodologies are widely accepted to estimate renal function in pediatric patients (age dependent), all study subjects (n=211) included in the final PopPK dataset were enrolled based on renal function estimated only by the bedside Schwartz equation (< 30mL/min as an exclusion criterion for all clinical study protocols).*
2) *For the final PopPK analysis dataset, renal function was estimated for a total of 37 subjects (11, 8 and 18 subjects with median post-menstrual age of 83, 40, and 89 weeks from studies DUR001-106, DUR001-107, and DUR001-306, respectively) using the Rhodin equation (based on Rhodin et al. derived mean parameter values based on normal fat mass and theoretical allometry on body weight).*
3) *Given renal function maturation from birth to 2 years of age (approximately 98% of mature renal function), the Rhodin equation with fixed Hill coefficient may provide more*

accurate theoretical estimated glomerular filtration rates (EGFR) in pediatric patients under 2 years old when compared to bedside Schwartz equation.

As such, the reviewer performed sensitivity analysis by replacing the piece-wise function of renal function (Rhodin vs. Schwartz) on CL in the Applicant's final PopPK model to assess the impact of renal function descriptor on CL, using bedside Schwartz equation alone as per clinical study protocol.

Final Model

The final PopPK model was a 3-compartment model with first-order elimination, a proportional error model (aligned with base model where proportional error was estimated for the Phase 3 study, DUR001-306, separately). IIV was modeled for CL, V, and V2. For covariates, body weight was modeled on PK parameters with fixed allometric scalers of 0.75 or 1 for drug clearance or volume of distribution related terms, respectively. ALB was modeled on bioavailability (F) and renal function [as described by Rhodin equation (EGFR) or bedside Schwartz equation (CLCRN)] was on CL.

The parameter estimates for the final PopPK model are listed in Table 35. Figures 7-12 are relevant diagnostic plots.

Table 32: Parameter Estimates of the Final PopPK Model (Based on Reference Weight = 70 kg)

Parameter	Description	Units	Estimate	Bootstrap 95% CI
θ_1	CL	L/h	0.0578	(0.0549 - 0.0609)
θ_2	V	L	4.58	(4.27 - 4.92)
θ_3	V2	L	6.1	(5.59 - 6.55)
θ_4	Q	L/h	0.794	(0.702 - 0.887)
θ_5	Q2	L/h	0.00996	(0.00909 - 0.0113)
θ_6	V3	L	5.57	(4.5 - 7.25)
θ_8	F1,ALB	-	0.385	(0.151 - 0.578)
θ_9	CL,EGFR	-	0.167	(0.0406 - 0.27)
θ_{10}	CL,CLCRN	-	0.0681	(-0.0396 - 0.175)
$\omega_{1.1}$	IIV,CL	sd (CV%)	0.319 (32.8)	(0.257 - 0.397)
$\omega_{2.1}$	Corr,CL-V	-	0.821	-
$\omega_{2.2}$	IIV,V	sd (CV%)	0.454 (47.8)	(0.305 - 0.588)
$\omega_{3.1}$	Corr,CL-V2	-	0.854	-
$\omega_{3.2}$	Corr,V-V2	-	0.683	-
$\omega_{3.3}$	IIV,V2	sd (CV%)	0.321 (32.9)	(0.248 - 0.416)
$\sigma_{1.1}$	PropErr	sd	0.123	(0.0925 - 0.156)
$\sigma_{3.3}$	PropErr-PhIII	sd	0.173	(0.142 - 0.2)

Note: The standardized reference weight of 70kg was used in the allometric scaling of all disposition parameters, with fixed exponents of 0.75 for all clearances and 1 for all volumes. ω_X: variance of the IIV of parameter X, IIV as a %CV was derived from variance according to $\sqrt{e^{\omega_X} - 1} \cdot 100$. Covariances are reported as correlations between the indicated parameters. Median and 95%CI calculated from a 1000-sample bootstrap, with 952 successful minimizations.

Note: when reference weight was modified to 26.4 kg (median weight of pooled population), the following typical parameters were: CL (0.0278 L/h), V (1.73 L), Q (0.382 L/h), V2 (2.3 L/h), Q2 (0.00479 L/h) and V3 (2.1 L).
Source: Applicant's PopPK Report, Table 16, page 55

Reviewer's comments: The results of the final PopPK model were verified and reproduced by the reviewer using a reference weight of 70 kg. In general, the PK parameters were precise (under 31% RSE); however, the parameter-covariate relationship for CLCRN and CL was relatively weak and resulted in a moderately high RSE at 76.4%, presumably from the between-subject variability. Yet, the Applicant's approach to include CLRCN or EGFR as a piece-wise function on CL was appropriate based on dalbavancin route of elimination, prior PK characteristics and pediatric renal function maturation. IIV for CL, V and V2 were moderate (32.8-47.8%) and associated shrinkages were low to modest (3.7-14.4%).

For additional analyses with the final PopPK model, the reviewer modified the reference weight to the median body weight of 26.4 kg in the final model run and was able to reproduce the results (data not shown here). Numeric shift of the reference weight value did not affect the random effects estimates. In a separate analysis, the reviewer estimated the allometric scalers of body weight on CL and V related terms as appropriate and found the Applicant's approach to use fixed allometric exponents to be acceptable. The data-driven allometric scaler (RSE%) of body weight for CL and V related terms were 0.71 (4.3%) and 0.95 (3.7%), respectively, with the 95% CI containing the proposed fixed values in the final model (0.65-0.77 and 0.88-1.01, respectively).

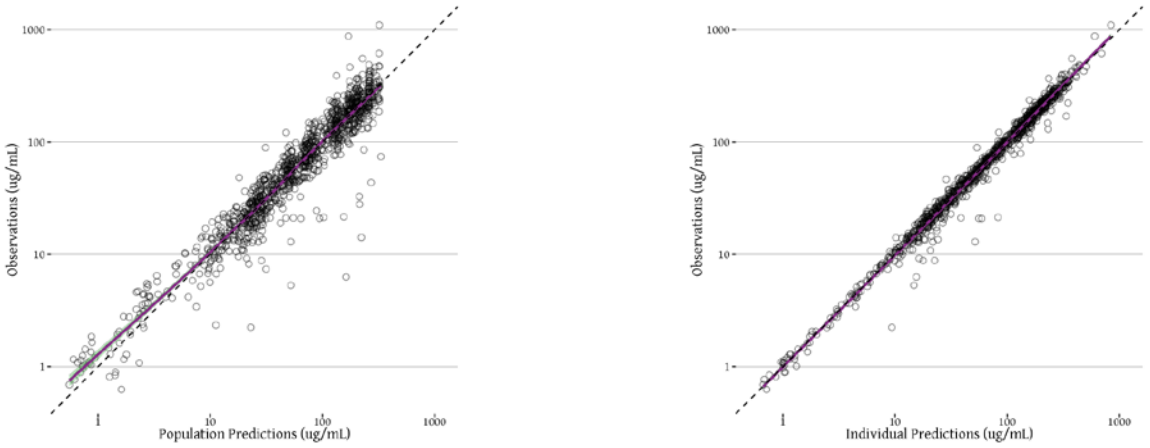
As described in the Covariate Analysis section above, the following model runs were performed by the reviewer to further support the final PopPK model results (and the utility of the model for estimating exposures via simulation). The following final PopPK model variants were run by the reviewer without modifications to the structural model, error model, nor IIV parameters:

1) *One theta with bedside Schwartz only; reference CLCRN at 100.88 mL/min/1.73m^2*
2) *Two thetas stratified by age at <2 or ≥2 years (Rhodin vs. bedside Schwartz, respectively) and reference median renal functions at 74.06 and 100.88 mL/min/1.73m^2, respectively*

The model variants demonstrated (results data not shown) that structural PK parameter point estimates aligned with the unmodified final PopPK model (Table 35) with less than 2.3% change. IIV changes ranged from 0 to 4.1%. No significant changes in objective function values were observed with the model variants.

Overall, the final PopPK model was acceptable in describing the pediatric PK data and in supporting exposure estimates for target attainment analysis.

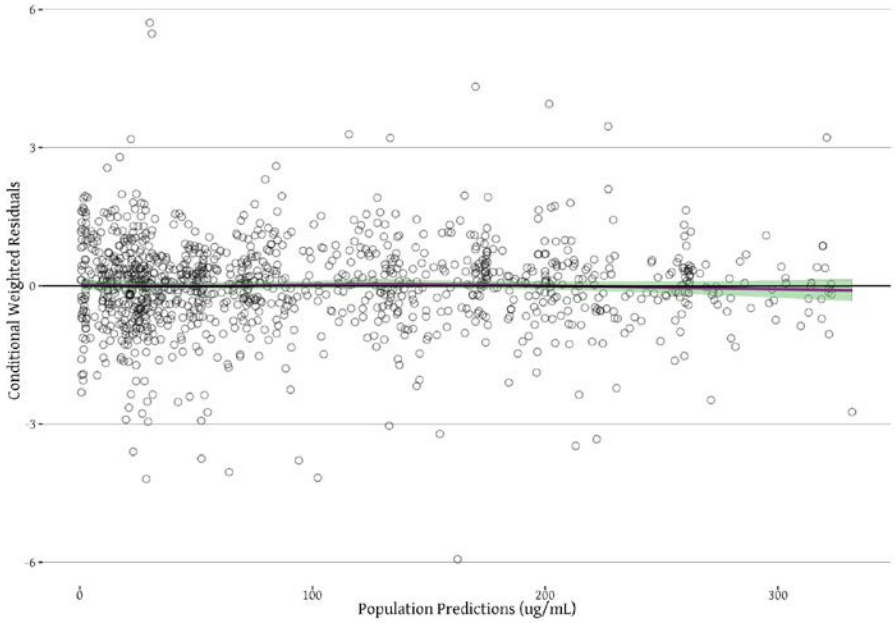
Figure 7: Observed vs. Predicted Dalbavancin Concentrations in the Final Model (Based on Reference Weight = 70 kg)



Solid line: LOESS smooth. **Shaded area:** 95% confidence interval of the LOESS smooth. **Dashed line:** Line of identity.

Source: Applicant's PopPK Report, Figure 18, page 56

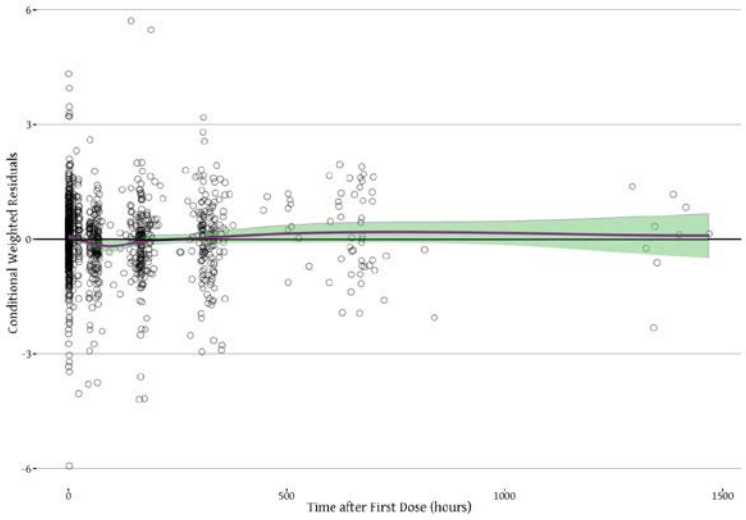
Figure 8: CWRES vs Predictions in the Final Model



Solid line: LOESS smooth. **Shaded area:** 95% confidence interval of the LOESS smooth.

Source: Applicant's PopPK Report, Figure 19, page 56

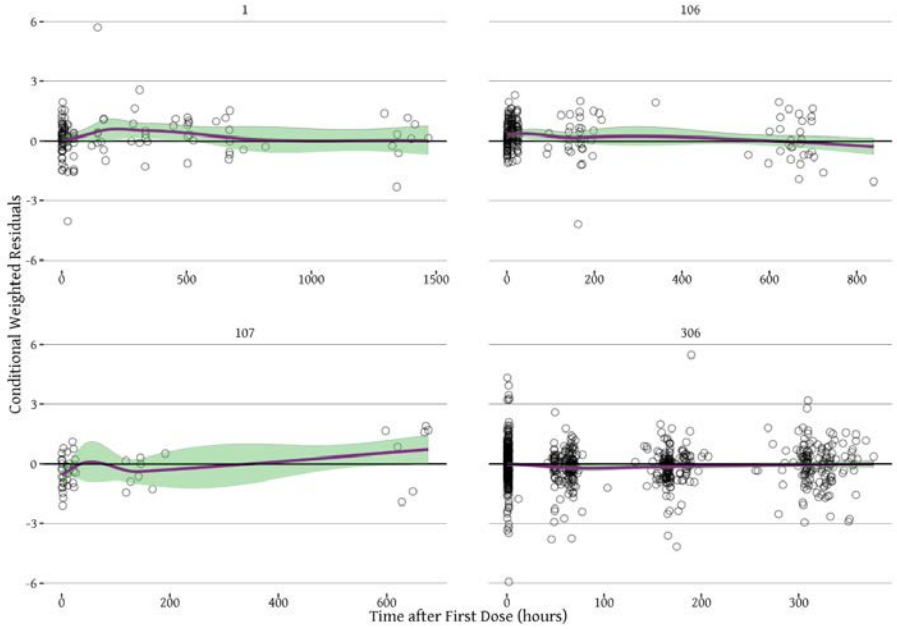
Figure 9: CWRES vs. Time after First Dose in the Final Model



Solid line: LOESS smooth. **Shaded area:** 95% confidence interval of the LOESS smooth.

Source: Applicant's PopPK Report, Figure 20, page 57

Figure 10 CWRES vs Time after 1st Dose Stratified by Study in the Final Model

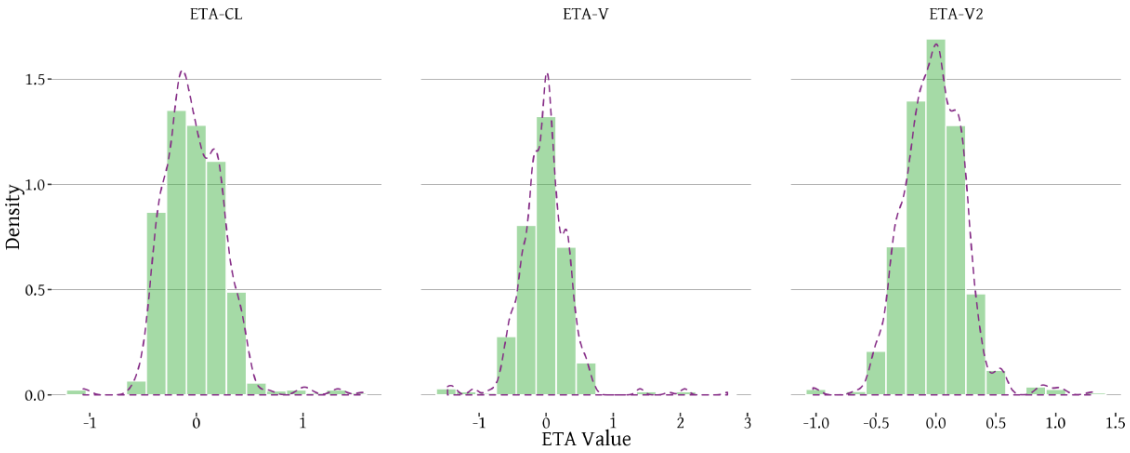


Solid line: LOESS smooth. **Shaded area:** 95% confidence interval of the LOESS smooth.

Source: Applicant's PopPK Report, Figure A.5.11, page 137

Reviewer's comments: The final PopPK model described the dalbavancin pooled PK data adequately. CWRES are generally randomly scattered around x=0 over population predictions and time (since first dose) without obvious trends. When stratifying CWRES vs Time plots by studies, the over-prediction in study 107 improved (i.e., more precise predictions). The slight under-prediction between 600-800 hours for study 106 persisted.

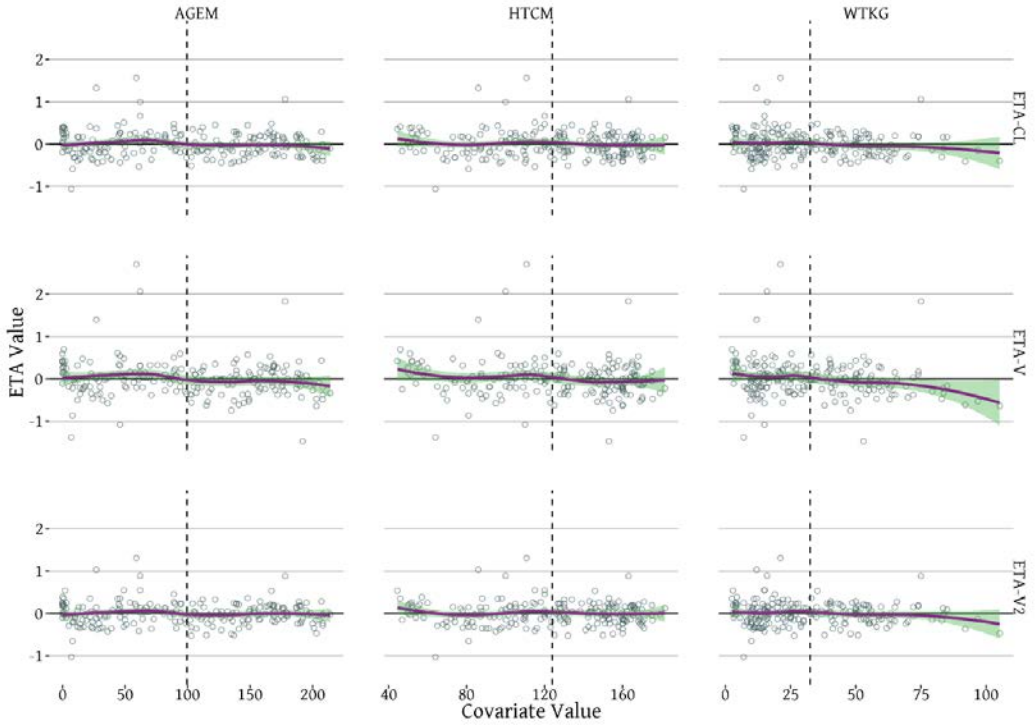
Figure 11: ETA Density Plot for the Final Model



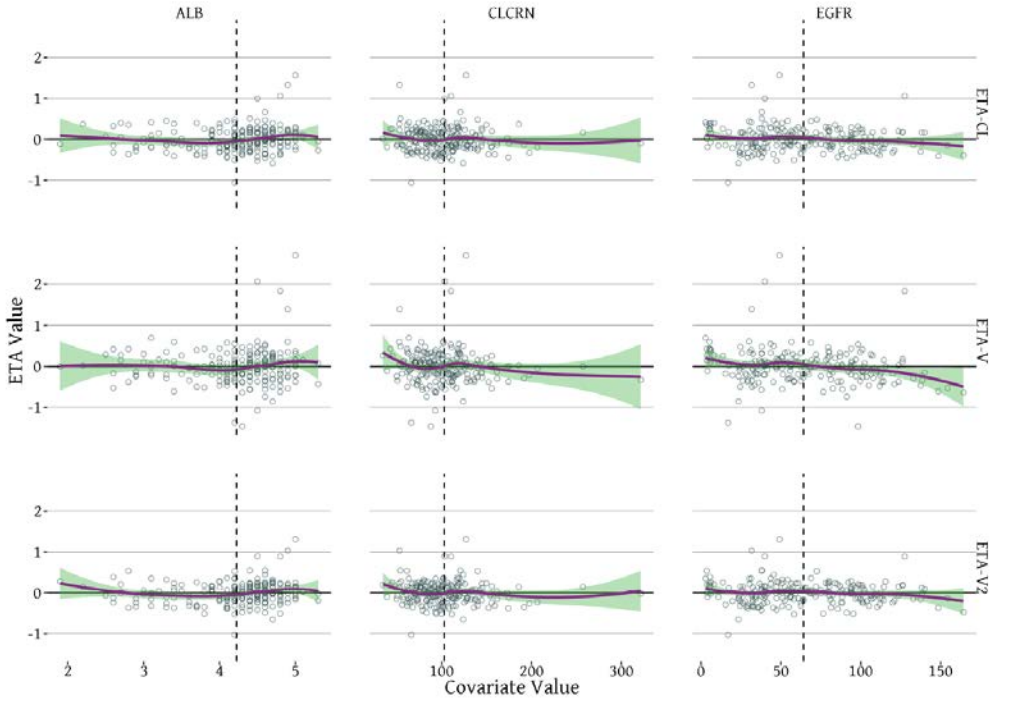
Source: Applicant's PopPK Report, Figure A.5.13, page 138

Reviewer's comments: The distributions of ETAs for CL, V and V2 in the final model showed adequate central tendency around zero with no obvious skewness, indicating acceptable capturing of random effects and final model fit to the PK data. In plots of distribution of ETAs vs. categorical (not shown, refer to Applicant's PopPK Report, Figure 21, page 58) or continuous covariates (Figure 12), no obvious trends or deviations from y=0 were identified.

Figure 12: Distribution of ETAs vs. Clinical Covariates in the Final Model



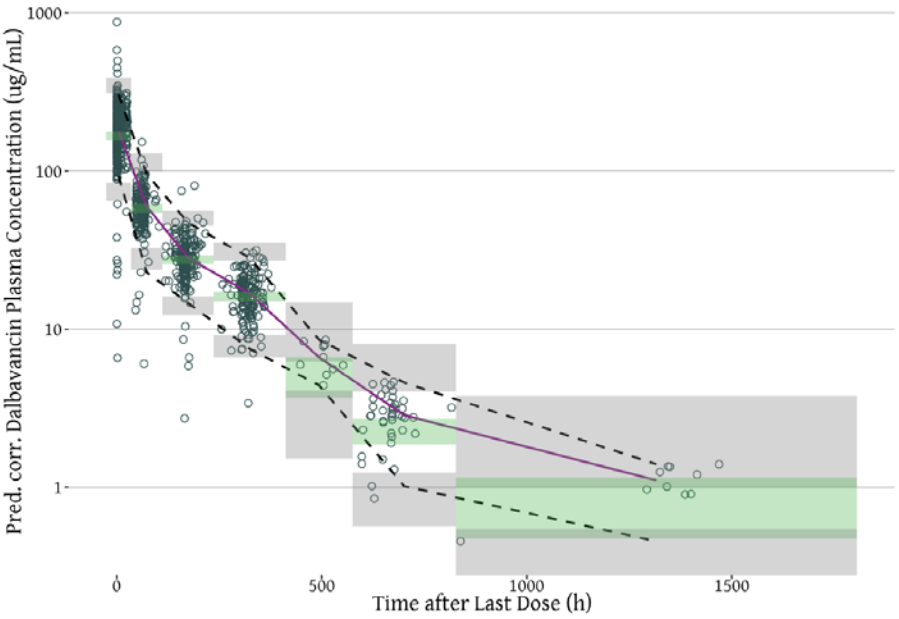
AGEM: Age in months. **HTCM:** Height in cm. **WTKG:** Weight in kg.



ALB: Serum albumin concentration in g/dL. **CLCRN:** Standardized Creatinine Clearance Rate (Schwartz equation) in mL/min/1.73m2. **EGFR:** Estimated Glomerular Filtration Rate (Rhodin equation) in mL/min.

Source: Applicant's PopPK Report, Figure 22-23, page 59-60

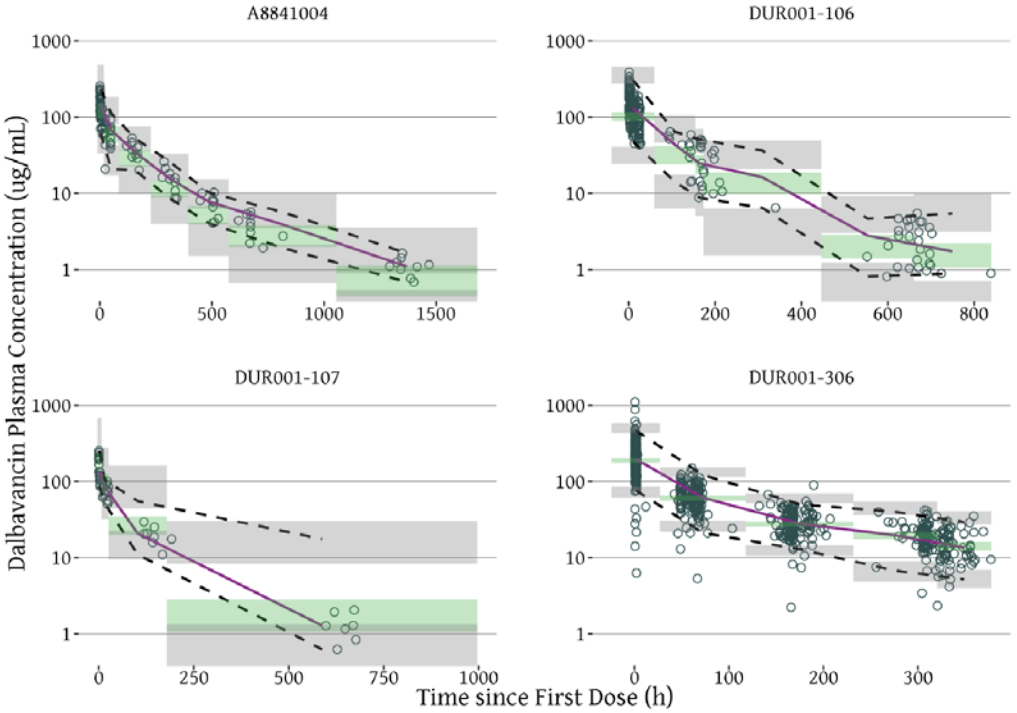
Figure 13: Prediction-corrected Visual Predictive Check in the Final Model



Circles: Observations, **Solid Blue Line**: Median of the observed dalbavancin concentrations, **Dashed Lines**: 2.5^{th} and 97.5^{th} percentiles of the observed dalbavancin concentrations, **Shaded Area**: The shaded areas indicate the 95% CI around the prediction-corrected median (green area), and 2.5^{th} and 97.5^{th} percentiles of the simulated concentrations (grey areas). All observations and predictions are adjusted using prediction correction as described in Bergstrand et al. (Bergstrand et al., 2011).

Source: Applicant's PopPK Report, Figure A.5.15, page 140

Figure 14: Visual Predictive Check by Study in the Final Model



Circles: Observations, **Solid Blue Line**: Median of the observed dalbavancin concentrations, **Dashed Lines**: 2.5^{th} and 97.5^{th} percentiles of the observed dalbavancin concentrations, **Shaded Area**: The shaded areas indicate the 95% CI around the simulated median (green area), and 2.5^{th} and 97.5^{th} percentiles of the simulated concentrations (grey areas).

Source: Applicant's PopPK Report, Figure 24, page 61

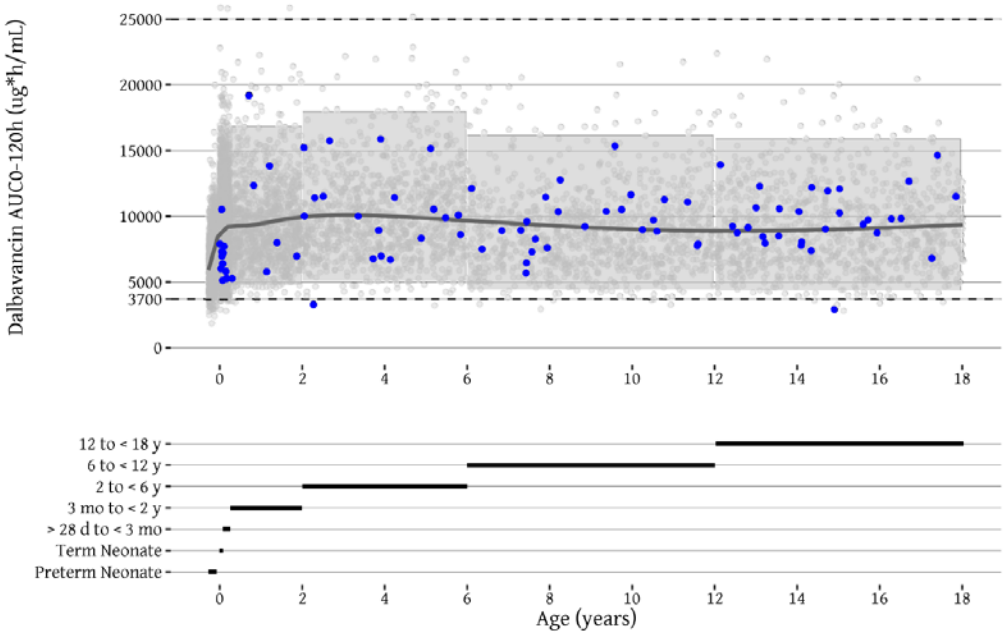
Reviewer's comments: While improvements based on CWRES plots were observed from the base model, the reviewer noticed that the VPC plots (without prediction corrections) stratified by study (Figure 14) showed slight under-predictions in 106 and 107 for both 2.5th and 97.5th percentiles. These under-predictions, however, likely will not impact on the exposure estimates used for the target attainment analysis as: 1) the slight under-predictions will be more conservative measures for the lower bound (2.5th percentile) of expected concentrations, and 2) the prediction-corrected VPC (Figure 13) demonstrated overall acceptable model fit with the pooled data (along with aforementioned diagnostic plots from the final model) for the purpose of simulating exposures. In general, the dalbavancin PopPK final model showed acceptable agreement between observed and predicted data, supporting estimation of exposures to conduct probability of target attainment analysis.

14.6.3.2 Pediatric PK Simulations

Simulation Approach

The final PopPK model was utilized to conduct simulations for dalbavancin plasma concentration at the following hours: 0.5, 1-120 (1-hr increments), 144, and 648. A total of 7000 virtual subjects were generated based on seven age groups with a 1 to 1 male to female ratio (refer to Applicant's PopPK Report, Table 6, page 26). The simulated, cumulative pediatric exposures from 0-120 hours ($AUC_{0\text{-}120h}$) after a single dose administration, stratified by age, weight, and serum ALB, were compared to the observed exposures ($AUC_{0\text{-}120h}$, 3500-25000 mg*h/L) of adult patients from Phase III Study (Figures 15-17). The daily, free dalbavancin exposure metric, $fAUC_{avg}$, was defined was AUC from 0-120 hours divided by 5 and multiplied by 0.07 (assuming 93% drug was bound to ALB). The *f*AUC/MIC (fraction of unbound drug exposure to MIC ratio) indices were 27.1, 53.3, and 111.11 hour for stasis, 1-log kill, and 2-log kill, respectively (refer to Applicant's PopPK Report, Section 4.2.2).

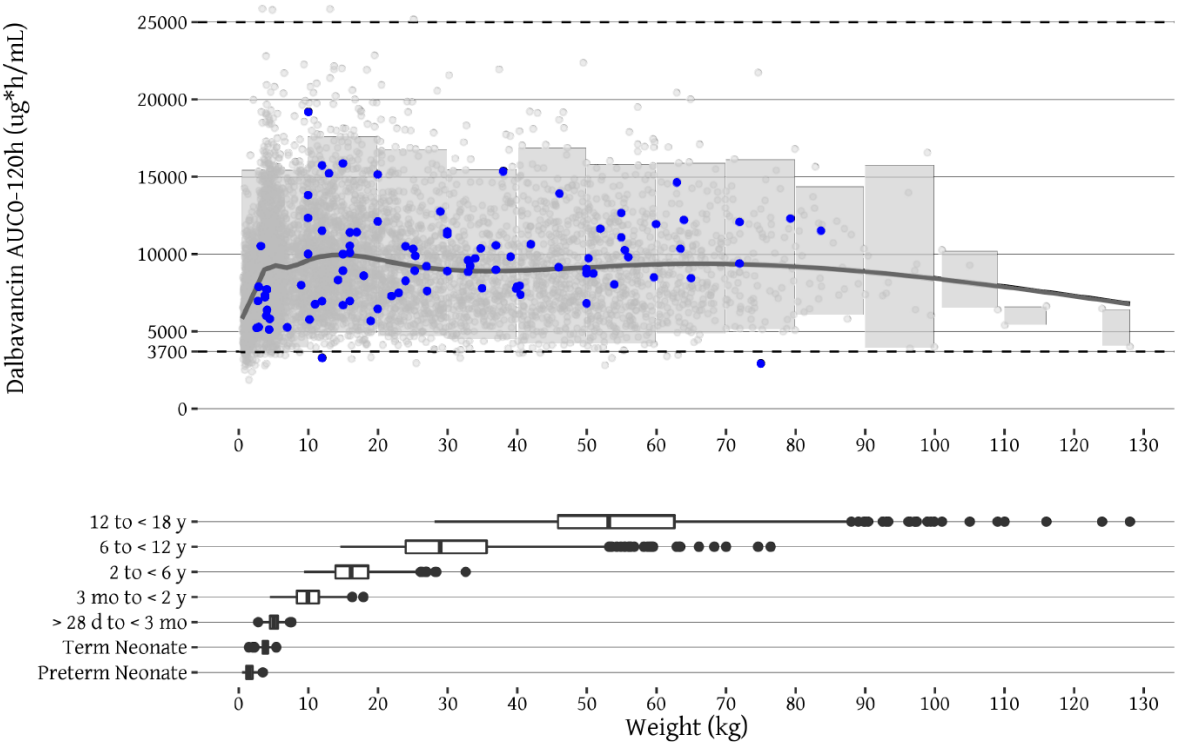
Figure 15: Simulated Pediatric Exposures: $AUC_{0\text{-}120h}$ vs. Age



Open circles: Simulated Individual Pediatric Exposures (AUC0-120h). **Shaded Bins:** 95% Prediction Intervals. **Dashed lines:** Adult Exposure (AUC0-120h) range observed in PhIII. **Blue circles:** Post-hoc exposure estimates of subjects in studies DUR001-107 and DUR001-306, treated with the simulated regimen. **Solid line:** LOESS smooth. **Line segments, bottom panel:** Uniformly sampled age range by age group.

Source: Applicant's PopPK Report, Figure 31, page 68

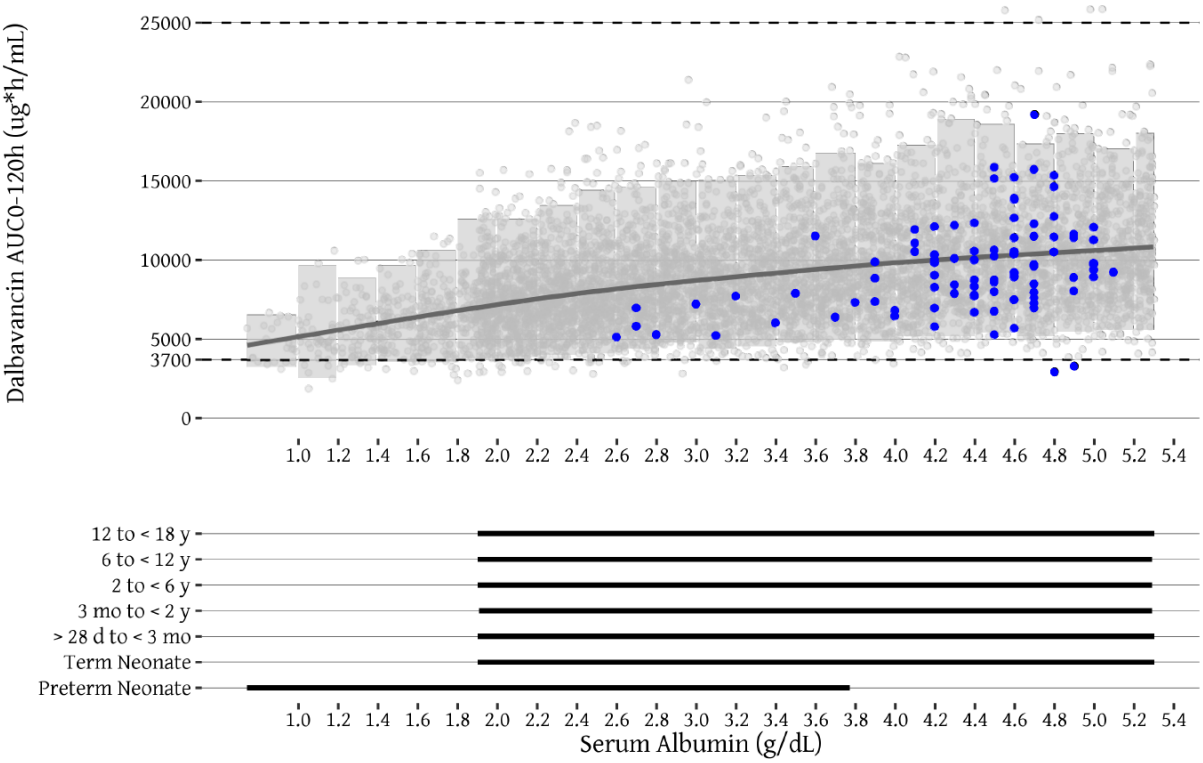
Figure 16: Simulated Pediatric Exposures: $AUC_{0\text{-}120h}$ vs. Body Weight



Open circles: Simulated Individual Pediatric Exposures (AUC0-120h). **Shaded Bins:** 95% Prediction Intervals. **Dashed lines:** Adult Exposure (AUC0-120h) range observed in PhIII. **Blue circles:** Post-hoc exposure estimates of subjects in studies DUR001-107 and DUR001-306, treated with the simulated regimen. **Solid line:** LOESS smooth. **Box plots, bottom panel:** WT distribution by age group.

Source: Applicant's PopPK Report, Figure 32, page 69

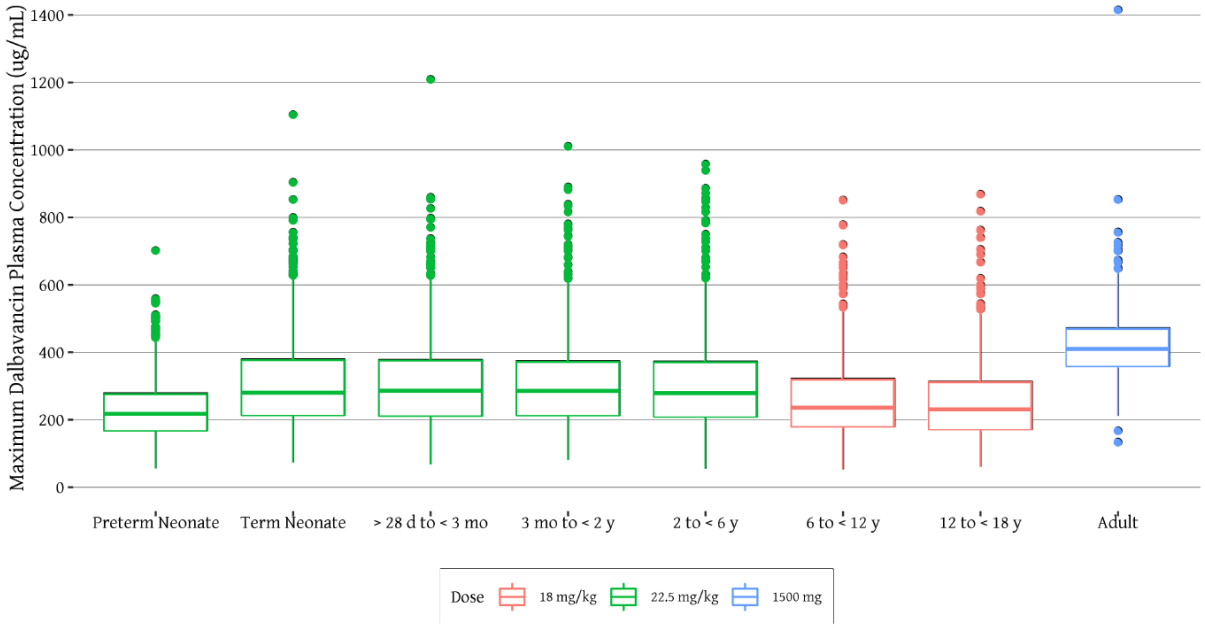
Figure 17: Simulated Pediatric Exposures: $AUC_{0\text{-}120h}$ vs. Baseline Serum ALB



Open circles: Simulated Individual Pediatric Exposures (AUC0-120h). **Shaded Bins:** 95% Prediction Intervals. **Dashed lines:** Adult Exposure (AUC0-120h) range observed in PhIII. **Blue circles:** Post-hoc exposure estimates of subjects in studies DUR001-107 and DUR001-306, treated with the simulated regimen. **Solid line:** LOESS smooth. **Line segments bottom panel:** Uniformly sampled ALB range by age group, with the exception of the preterm population for which ALB was simulated (with IIV and residual variability) from a sigmoidal relationship with GA

Source: Applicant's PopPK Report, Figure 33, page 70

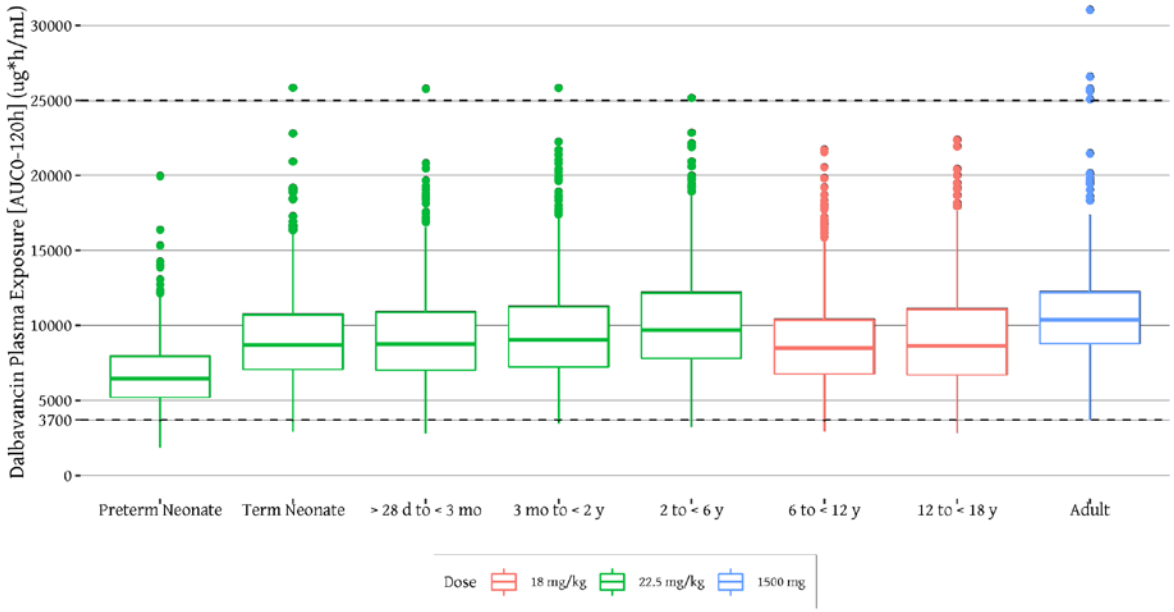
Figure 18: Simulated Pediatric vs. Adult Dalbavancin Cmax



Box and whisker plot: The central line is the sample median, the boxes denote the interquartile range, the whiskers extend to 1.5 times the interquartile range, and any dots represent data outside the whiskers.

Source: Applicant's PopPK Report, Figure 37, page 74

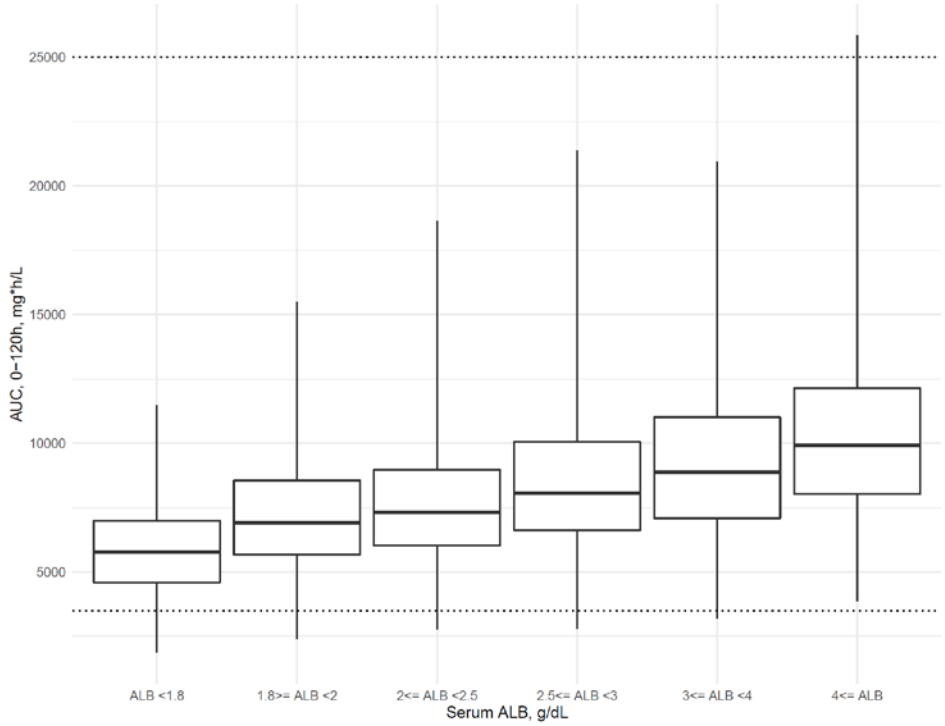
Figure 19: Simulated Pediatric vs. Adult Dalbavancin Exposure ($AUC_{0\text{-}120h}$)



Box and whisker plot: The central line is the sample median, the boxes denote the interquartile range, the whiskers extend to 1.5 times the interquartile range, and any dots represent data outside the whiskers. **Dashed lines**: Exposure (AUC0-120h) range observed in Ph3 in adults treated with a single 1500 mg dose.

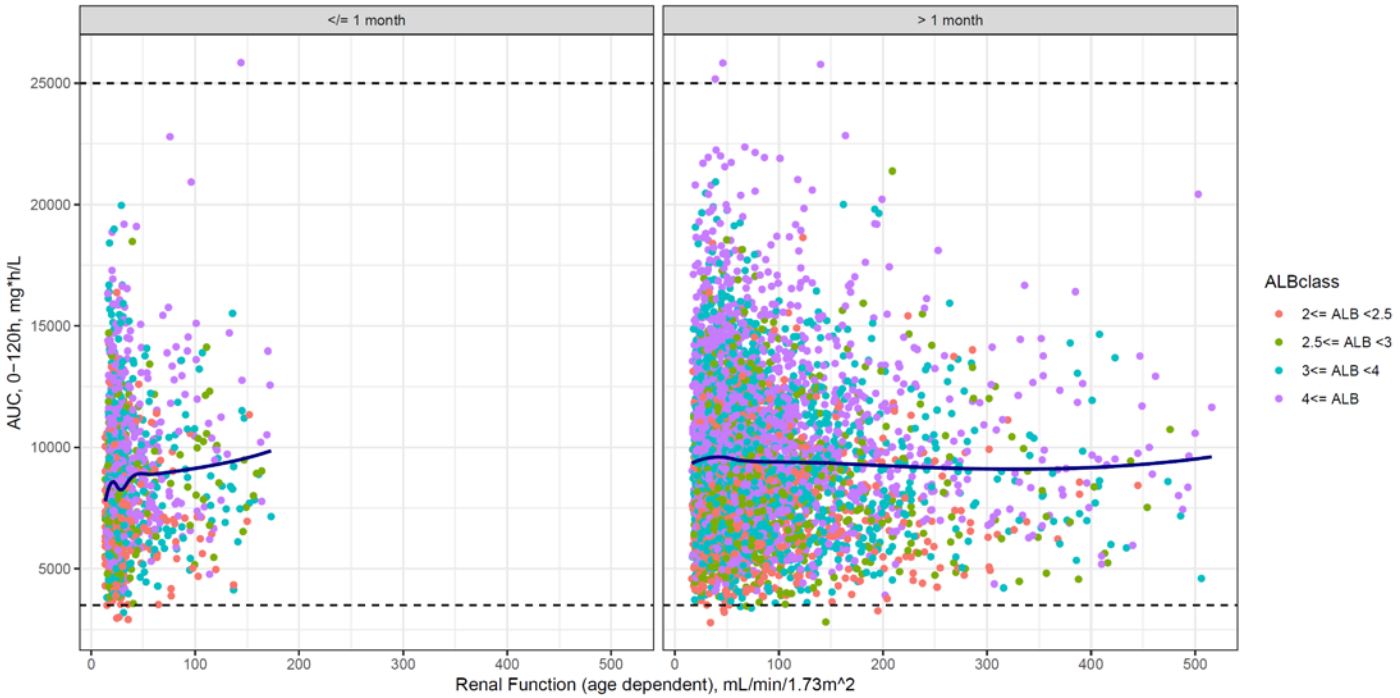
Source: Applicant's PopPK Report, Figure 38, page 75

Figure 20: Reviewer's Analysis: Boxplot of Simulated Pediatric Dalbavancin Exposures by Serum ALB Group



*Box and whisker denote median, IQR, and 1.5*IQR; dashed lines denote lower and upper bounds of observed adult exposures*

Figure 21: Reviewer's Analysis: Simulated Pediatric Dalbavancin Exposures by Age, Serum ALB, and Renal Function



Age group was defined by ≤ 1 month (preterm and term neonates) or >1 month of age; ALB group defines serum ALB groups after removing ALB <2 g/dL; renal function was based on age-appropriate estimated GFR from Rhodin or bedside Schwartz equations; blue lines represent LOESS fit; dashed lines denote lower and upper bounds of observed adult exposures

Reviewer's comments: Figures 15-19 demonstrated that, based on simulations, the expected exposures of pediatric subjects across clinical covariates (age, weight, and serum ALB) generally fall within the observed adult exposures.

The reviewer noted that when exposures were stratified by serum ALB groups (Figure 17 and Figure 20), the expected exposures were trending slightly downward as serum ALB was decreasing, despite remaining within the acceptable exposure range. The following points should be taken into consideration when interpreting exposures at the lower end of the serum ALB groups:

1) *In the pooled database of 211 pediatric subjects, only 2 (0.9%) subjects (from A8841004, DUR001-106) had observed baseline serum ALB below 2.5 g/dL. In the simulation database, there were 1809 (26%) virtual, simulated serum ALB levels below 2.5 g/dL (median, 2.1; 25th percentile, 1.9; 75th percentile, 2.3). Of note, the range of simulated serum ALB were 0.74 to 5.3 g/dL.*
2) *In a study conducted by Reading and Fleetwood (doi: 10.1016/0378-3782(90)90082-t.), serum ALB was found to rise from 2 g/dL in 28-week preterm neonates to 3 g/L in term neonates. In a recent prospective study by Torer et al. (doi: 10.1002/jcla.21949), the 50th percentile serum ALB levels (g/dL) were 2.7 and 3.3 for gestation age groups of ≤28 weeks and those >28 weeks, respectively.*
3) *Considering that the youngest pediatric subject in the dalbavancin database (n=211) was 36-week-old (based on post-menstrual age), a serum ALB level of ≥2 g/dL may be the more clinically relevant and conservative lower bound to consider when interpreting the current simulation results.*

As such, the reviewer assessed simulated exposures (0-120 h AUCs) when grouping by age, serum ALB (≥2 g/dL), and renal function. As depicted in simulation in Figure 21, most pediatric subjects are expected to achieve exposures within the reference adult exposure range across the grouping variables.

Regarding renal function, included pediatric subjects were enrolled in clinical trials based on exclusion criteria of estimated GFR <30 mL/min (bedside Schwartz equation). Given a lack of data for pediatric patients with renal function <30 mL/min and the unclear impact of such on dalbavancin exposure, there is insufficient information to inform dosage for pediatric patients with estimated GFR <30 mL/min.

Overall, the simulation results support the utility of simulated exposures to conduct percent target attainment analysis based on proposed dosage against microbiological characteristics of clinical isolates.

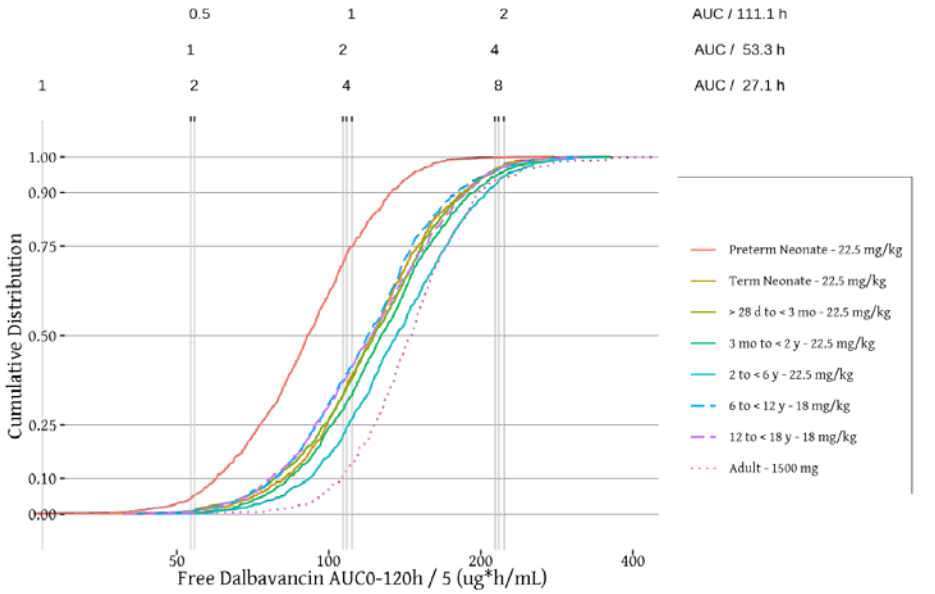
14.6.3.3 Probability of Target Attainment

Probability of Target Attainment (PTA) Analysis by Applicant

PTA was performed using the simulated exposures ($AUC_{0\text{-}120h}$ based on single dose regimen) based on the final PopPK model and the pre-clinical (*in vivo*) *f*AUC/MIC targets (fraction of unbound drug over MIC) that resulted in static, 1-log kill, and 2-log kill in bacterial load (27.1h, 53.3h, and 111.1h, respectively). Average dalbavancin exposure was defined as (*f*AUC0-120h divided by 5) and was evaluated across double dilutions of minimum inhibitory concentrations (MIC) of 0.5 to 8 µg/mL (*refer to the Applicant's PopPK Report, Section 5.2.2*).

Figure 22 depicts the cumulative distribution of free, average dalbavancin exposure (*f*AUC0-120h/5) with the pre-clinical stasis/kill targets. Figure 23 represents the PTA based on 2-log kill pre-clinical target. For the full PTA result across MICs of 0.12 to 8 µg/mL stratified by age groups and pre-clinical targets, refer to Applicant's PopPK Report (Table 21, on page 78-79).

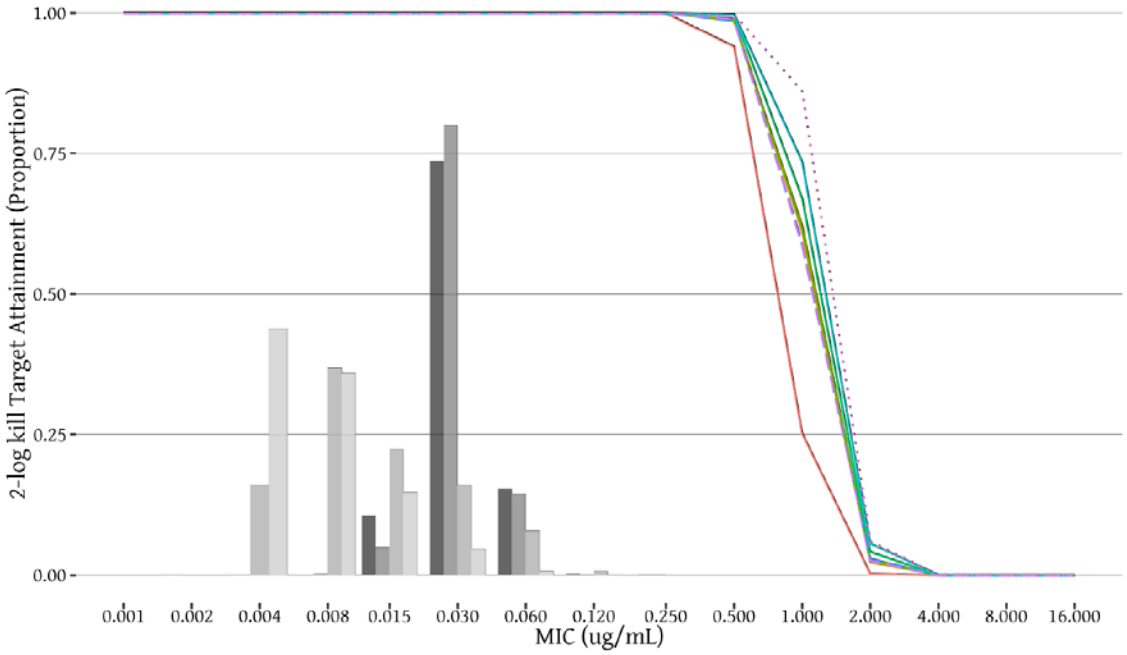
Figure 22: Statis, 1-log kill and 2-log kill Target Attainment by Age Groups Including Adults



Vertical Grey Lines: MIC value corresponding with fAUC over stasis (27.1h), 1-log kill (53.3h) or 2-log kill (111.1h) targets.

Source: Applicant's PopPK Report, Figure 34, page 71

Figure 23: Simulated Pediatric and Adult 2-log Kill Target Attainment in Relation to Surveillance MIC Distribution



Histogram: MIC distributions from 2017 surveillance data for the 4 most relevant species of pathogens. **Solid Lines:** Projected 2-log kill Target Attainment by age group-specific treatment regimen (1500 mg [adults], 18 mg/kg [adolescents, children] or 22.5 [other]). **MIC:** Minimal Inhibitory Concentration (μg/mL).

Source: Applicant's PopPK Report, Figure 39, page 77

Table 33: *f*AUC$_{0\text{-}120h}$/5 and MIC attained for 99% for Population by Target

Age Group	fAUCavg (ug·h/mL)	Stasis MIC (ug/mL)	1-Log kill MIC (ug/mL)	2-Log kill MIC (ug/mL)
Preterm Neonate	42.1	1.55	0.789	0.379
Term Neonate	55.2	2.04	1.040	0.497
> 28 d to < 3 mo	54.0	1.99	1.010	0.486
3 mo to < 2 y	59.2	2.19	1.110	0.533
2 to < 6 y	61.8	2.28	1.160	0.556
6 to < 12 y	54.6	2.01	1.020	0.491
12 to < 18 y	55.1	2.03	1.030	0.496

Source: Applicant's PopPK Report, Table 19, page 72

Reviewer's comments: The FDA-approved breakpoint is currently 0.25 µg/mL for dalbavancin against relevant Gram positive isolates (same breakpoint per CLSI M100-ED31 document). In the PTA analysis with 2-log kill (Figure 23), 111.1 h, as the PKPD target, the proposed dosage regimens, including that for preterm and term neonates, attained an MIC coverage from 0.001 µg/mL to 0.5 µg/mL (above 90% PTA). For 1-log kill target, all pediatric dosages attained >90% PTA for MICs up to 1 µg/mL (refer to Applicant's PopPK Report, Table 21, page 78-79). Furthermore, 99% of the simulated exposure achieved at least a 3-fold dilution from the breakpoint for 1-log kill and approximately 2-fold dilution for the 2-log kill, except for preterm with a 2-log kill MIC of 0.379 µg/mL, which remains above current breakpoint of 0.25 µg/mL.

Reviewer's Analysis of Target Attainment

During our review, we re-evaluated the nonclinical PK-PD relationship and target attainment analyses (TA) (Table 37) considering: **(i)** the same DAL PPB value for mice and humans should be used based on our interpretation of the PPB data (See Section 14.6.1.1) and **(ii)** pharmacodynamic (PD) variability, described by arithmetic mean ± standard deviation, in the free-drug plasma AUC$_{0\text{-}24}$:MIC target value associated with 1-log kill (53.29 ± 27.9) and 2-log kill (111.1 ± 51.8) of *S. aureus* (Lepak, Marchillo, VanHecker, & Andes, 2015).

Free-drug plasma AUC$_{0\text{-}24}$:MIC ratios were assessed to determine the percent probability of attaining median and randomly assigned free-drug plasma AUC:MIC targets associated with 1- and 2-log$_{10}$ CFU reductions from baseline by MIC value. When simulating log$_{10}$ normal data (for the random target[8]) the arithmetic mean (m) and standard deviation (sd) were used to derive the corresponding parameters for the underlying normal distribution of log$_{10}$ data. Consequently, the following formulas were used:

[8] PD target variability (i.e., AUC$_{0\text{-}24}$/MIC) incorporated by randomly estimating a target value based upon an observed mean and standard deviation (murine lung infection PKPD studies) and truncated (2 SD) log$_{10}$ normal distribution.

$$mu = \log\left(\frac{m^2}{\sqrt{sd^2 + m^2}}\right)$$

$$sigma = \sqrt{\log\left(1 + \left(\frac{sd^2}{m^2}\right)\right)}$$

Table 34: Reviewer's Target (free-drug plasma $AUC_{avg,\ 5\text{-}day}$ / MIC) Attainment Analysis by Age Group and by MIC for *S. aureus*

		1-log_{10} Kill[a] *S. aureus* MIC [mcg/mL]				2-log_{10} Kill[b] *S. aureus* MIC [mcg/mL]			
		0.12	0.25	0.5	1	0.12	0.25	0.5	1
Mean PD Target	Preterm Neonate	1	0.92	0.21	0	0.89	0.17	0	0
	Term Neonate	1	0.98	0.56	0.01	0.98	0.50	0.01	0
	> 28 day to <3 mo	1	0.98	0.56	0.02	0.97	0.52	0.01	0
	3 mo to <2yr	1	0.99	0.60	0.03	0.99	0.56	0.02	0
	2yr to <6 yr	1	1	0.69	0.04	0.99	0.64	0.03	0
	6 yr to <12 yr	1	0.98	0.53	0.02	0.98	0.48	0.01	0
	12 yr to <18 yr	1	0.98	0.54	0.02	0.98	0.50	0.01	0
	Adults	1	1	0.78	0.04	1	0.73	0.03	0
Random PD Target	Preterm Neonate	1	0.85	0.41	0.05	0.83	0.36	0.03	0
	Term Neonate	1	0.95	0.60	0.16	0.94	0.55	0.12	0
	> 28 day to <3 mo	1	0.94	0.62	0.18	0.94	0.58	0.14	0
	3 mo to <2yr	1	0.95	0.66	0.20	0.95	0.62	0.15	0
	2yr to <6 yr	1	0.96	0.71	0.24	0.96	0.68	0.19	0.01
	6 yr to <12 yr	1	0.94	0.59	0.16	0.94	0.55	0.10	0
	12 yr to <18 yr	1	0.94	0.59	0.17	0.94	0.55	0.13	0
	Adults	1	0.99	0.72	0.25	0.99	0.69	0.19	0

[a] Based on the assessment of arithmetic mean or random (arithmetic mean ± SD) free-drug plasma $AUC_{0\text{-}24}$:MIC ratio targets associated with a 1-log_{10} CFU reduction from baseline of 53.3 or 53.3 ± 27, respectively, for *S. aureus*.

[b] Based on the assessment of arithmetic mean or random (arithmetic mean ± SD) free-drug plasma $AUC_{0\text{-}24}$:MIC ratio targets associated with a 2-log_{10} CFU reduction from baseline of 111.1 or 111.1 ± 51.8, respectively, for *S. aureus*.

PPB was assumed linear and the unbound fraction fixed at 0.016. This value was chosen so that the murine *f*$AUC_{0\text{-}24}$/MIC target values could be used without a transformation step re-adjusting the PK/PD target with the same unbound DAL plasma fraction used in humans (0.07). This approach lowers human exposures by 4.35-fold.

The 5-day average plasma AUC of DAL in humans was calculated by simulating the DAL plasma $AUC_{0\text{-}120}$/5 and used as a conservative estimator of $AUC_{0\text{-}24}$

Blue box denotes current FDA approved Susceptibility Test Interpretive Criteria or "Breakpoint".

Gray box denotes PTA ≥0.9

MIC = minimum inhibitory concentration; PD = pharmacodynamic; $AUC_{0\text{-}24}$ = area under the concentration-time curve from 0 h to 24 h start of dosing; $AUC_{0\text{-}120}$ = area under the concentration-time curve from 0 h to 120 h start of dosing; SD = standard deviation; $AUC_{avg,\ 5\text{-}day}$ = $AUC_{0\text{-}120}$/ 5

Source: Pediatrics: Applicant's NONMEM simulation model (run104sim2.mod) and simulation dataset (nm-pediatric-sim-add.csv); Adults: Applicant's NONMEM model and estimated parameters (run109.lst) were used as the simulation model and simulation dataset (DAL-MS-01 Analysis Dataset NM_PK_ALLDATA_01.csv; only DUR-303 Phase 3 trial individuals). Like the Applicant we ran 1000 virtual patients per subgroup.

To confirm our results, we requested the Applicant re-conduct their TA analysis with the consideration that DAL PPB is similar between mice and humans. Results are consistent with our analysis (Table 38).

Table 35: Applicant's Target Attainment (free-drug plasma $AUC_{avg,\ 5\text{-}day}$ / MIC) Sensitivity Analysis by Age Group and by MIC for *S. aureus*

		1-log_{10} Kill[a] *S. aureus* MIC [mcg/mL]				2-log_{10} Kill[b] *S. aureus* MIC [mcg/mL]			
		0.12	**0.25**	**0.5**	**1**	**0.12**	**0.25**	**0.5**	**1**
Mean PD Target	Preterm Neonate	1	0.92	0.21	0	0.92	0.17	0.01	0
	Term Neonate	1	0.98	0.56	0.01	0.98	0.50	0.01	0
	> 28 day to <3 mo	1	0.98	0.56	0.02	0.98	0.52	0.01	0
	3 mo to <2yr	1	0.99	0.60	0.02	0.99	0.55	0.02	0
	2yr to <6 yr	1	1	0.69	0.04	1	0.64	0.03	0
	6 yr to <12 yr	1	0.98	0.53	0.02	0.98	0.48	0.01	0
	12 yr to <18 yr	1	0.98	0.54	0.02	0.98	0.5	0.01	0
	Adults	1	1	0.81	0.05	1	0.76	0.03	0

[a] Based on the assessment of arithmetic mean free-drug plasma $AUC_{0\text{-}24}$:MIC ratio targets associated with a 1-log_{10} CFU reduction from baseline of 233.1 for *S. aureus*.

[b] Based on the assessment of arithmetic mean free-drug plasma $AUC_{0\text{-}24}$:MIC ratio targets associated with a 2-log_{10} CFU reduction from baseline of 486.2 for *S. aureus*.

PPB was assumed linear and the unbound fraction fixed at 0.07. The Applicant had to transform the murine *f*$AUC_{0\text{-}24}$/MIC target values (adjusted to account for an unbound DAL fraction of 0.016) to re-adjust for the same unbound DAL plasma fraction in mice and humans (0.07). This approach increases the PK/PD target 4.375-fold. For example; 1-log kill target of 53.3 x (0.07/0.016) = 233.1

The 5-day average plasma AUC of DAL in humans was calculated by simulating the DAL plasma $AUC_{0\text{-}120}$/5 and used as a conservative estimator of $AUC_{0\text{-}24}$

Blue box denotes current FDA approved Susceptibility Test Interpretive Criteria or "Breakpoint".

Gray box denotes PTA ≥0.9

MIC = minimum inhibitory concentration; PD = pharmacodynamic; $AUC_{0\text{-}24}$ = area under the concentration-time curve from 0 h to 24 h start of dosing; $AUC_{0\text{-}120}$ = area under the concentration-time curve from 0 h to 120 h start of dosing; SD = standard deviation; $AUC_{avg,\ 5\text{-}day}$ = $AUC_{0\text{-}120}$/ 5

Source: DAL-MS-02: Population Pharmacokinetic & Target Attainment Analysis of Dalbavancin in Pediatric Subjects PKPD Target Sensitivity Analysis report; Table 4, pg. 11.

To determine the impact of using the plasma $AUC_{0\text{-}24}$ of DAL in humans rather than the 5-day average ($AUC_{0\text{-}120}$/5) on the target attainment rates, we re-conducted the target attainment analysis (Table 39). Note use of the plasma $AUC_{0\text{-}24}$ is consistent with how the PK/PD index in mice was determined.

Table 36: Reviewer's Target (free-drug plasma $AUC_{0\text{-}24}$ / MIC) Attainment Analysis by Age Group and by MIC for *S. aureus*

		1-log_{10} Kill[a] *S. aureus* MIC [mcg/mL]				2-log_{10} Kill[b] *S. aureus* MIC [mcg/mL]			
		0.12	0.25	0.5	1	0.12	0.25	0.5	1
Mean PD Target	Preterm Neonate	1	1	0.82	0.12	1	0.80	0.09	0
	Term Neonate	1	1	0.96	0.36	1	0.95	0.31	0.01
	> 28 day to <3 mo	1	1	0.95	0.38	1	0.93	0.33	0
	3 mo to <2yr	1	1	0.96	0.38	1	0.95	0.33	0.01
	2yr to <6 yr	1	1	0.97	0.41	1	0.96	0.36	0.01
	6 yr to <12 yr	1	1	0.92	0.22	1	0.90	0.18	0
	12 yr to <18 yr	1	1	0.91	0.26	1	0.89	0.21	0
	Adults	1	1	0.99	0.54	1	0.99	0.47	0.01
Random PD Target	Preterm Neonate	1	0.98	0.78	0.32	0.98	0.76	0.26	0.02
	Term Neonate	1	1	0.90	0.48	1	0.89	0.44	0.08
	> 28 day to <3 mo	1	0.99	0.90	0.49	0.99	0.89	0.45	0.08
	3 mo to <2yr	1	1	0.90	0.51	1	0.89	0.45	0.08
	2yr to <6 yr	1	1	0.91	0.53	1	0.91	0.48	0.10
	6 yr to <12 yr	1	1	0.85	0.43	1	0.83	0.38	0.03
	12 yr to <18 yr	1	0.99	0.83	0.42	0.99	0.82	0.37	0.04
	Adults	1	1	0.95	0.63	1	0.95	0.58	0.11

[a] Based on the assessment of the arithmetic mean free-drug plasma $AUC_{0\text{-}24}$:MIC ratio target associated with a 1-log_{10} CFU reduction from baseline of 53.3 for *S. aureus*.

[b] Based on the assessment of the arithmetic mean free-drug plasma $AUC_{0\text{-}24}$:MIC ratio target associated with a 1-log_{10} CFU reduction from baseline of 111.1 for *S. aureus*.

PPB was assumed linear and the unbound fraction fixed at 0.016. This value was chosen so that the murine *f*$AUC_{0\text{-}24}$/MIC target values could be used without a transformation step re-adjusting the PK/PD target with the same unbound DAL plasma fraction used in humans (0.07). This approach lowers human exposures by 4.35-fold.

The plasma $AUC_{0\text{-}24}$ of DAL in humans was calculated by numerical integration.

Blue box denotes current FDA approved Susceptibility Test Interpretive Criteria or "Breakpoint".

Gray box denotes PTA ≥0.9

MIC = minimum inhibitory concentration; PD = pharmacodynamic; $AUC_{0\text{-}24}$ = area under the concentration-time curve from 0 h to 24 h start of dosing; SD = standard deviation

Source: Pediatrics: Applicant's NONMEM simulation model (run104sim2.mod) and simulation dataset (nm-pediatric-sim-add.csv); Adults: Applicant's NONMEM model and estimated parameters (run109.lst) were used as the simulation model and simulation dataset (DAL-MS-01 Analysis Dataset NM_PK_ALLDATA_01.csv; only DUR-303 Phase 3 trial individuals). Like the Applicant we ran 1000 virtual patients per subgroup.

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