Population Pharmacokinetic (PK) and Pharmacokinetic/Pharmacodynamic (PK/PD) Target Attainment Analyses for Dalbavancin in Pediatric Patients

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CONCLUSIONS

Dalbavancin PK in pediatric patients was well characterized by a 3-compartment model with allometric scaling of clearance and volume and with albumin and renal function included as covariates

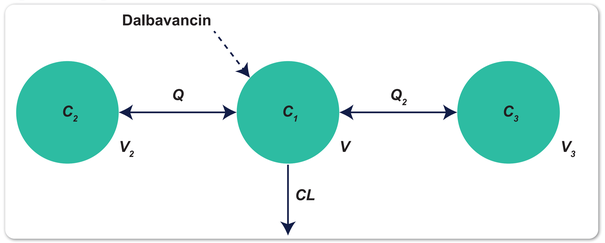
PK simulations with the final pediatric popPK model are supportive of reaching similar exposures to those observed in adults under a single dose posology of 22.5 mg/kg (capped at 1500 mg) for patients aged <6 years and 18 mg/kg (capped at 1500 mg) for patients aged 6–<18 years

Simulations with the final model show adequate PTA across the entire age range for the regimens used in the phase 3 pediatric study

RESULTS

- Dalbavancin PK in this pediatric population (those aged 4 days–17 years) was well characterized by a 3-compartment model (**Figure 1**)

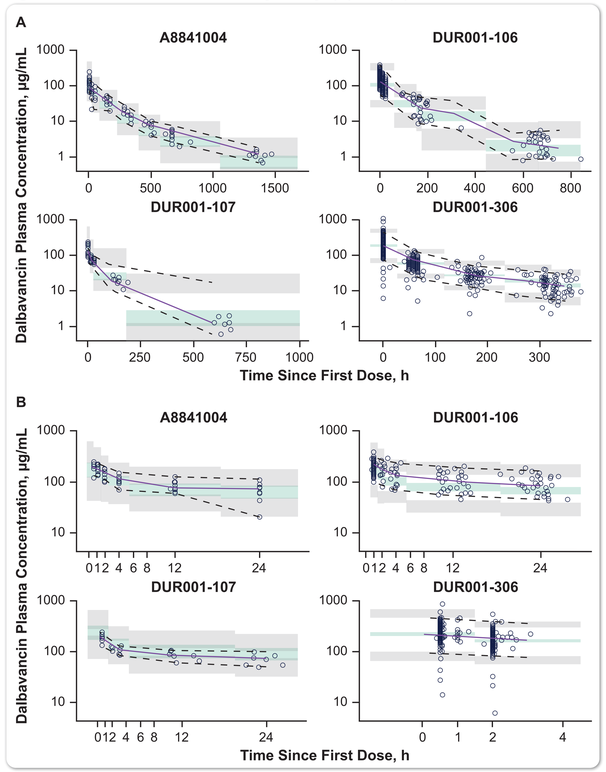
Figure 1. Diagram of the Structural Model



C, Concentrations inside the compartments; CL, clearance; Q, distributional clearances; V, Volumes of distribution.

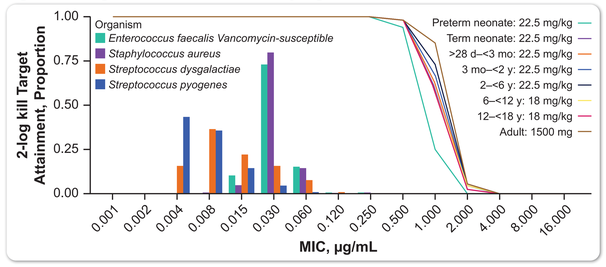
- Statistically significant covariates were albumin, weight, and renal function; the stepwise covariate search did not identify additional significant covariates. Visual predictive checks (VPCs) showed that the final model has good predictive performance across the full age range (**Figure 2A** and **2B**)
- Simulations showed that single-dose regimens of 22.5 mg/kg for patients aged <6 years and 18 mg/kg for patients aged 6–<18 years resulted in PTA ≥94% for MICs ≤2 mg/L for the stasis target and ≤0.5 mg/L for the 2-log kill target (**Figure 3**)
- The comparison between the Clinical & Laboratory Standards Institute susceptibility breakpoint for dalbavancin (0.25 µg/mL), the MIC_{90} for dalbavancin against *S aureus* (0.06 µg/mL), and the MIC where predicted TA starts to decrease under the current treatment regimen indicates that this regimen would continue to provide attainment of the preclinical PK/PD target for several additional MIC dilutions beyond those currently observed in the United States and Europe
- The PTA for pediatric patients was similar to that of adults, and mean exposures ($AUC_{0\text{-}120h}$) for pediatric patients were generally within 20% of the median exposures previously observed in adults administered a single dose of 1500 mg (**Table 2, Figure 4**)
  - Preterm neonates were predicted to have approximately 38% lower median $AUC_{0\text{-}120h}$ than adults (**Table 2**)
  - Median maximum observed concentration (C_{max}) for values of pediatric patients was 30%–47% lower than in adult patients given a single 1500-mg dose (**Table 2**)

Figure 2. VPC of the Final Model by Study. (A) All; (B) First 24 Hours



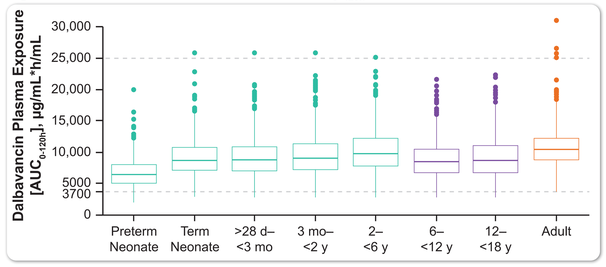
Circles, observations; solid purple line, median of the observed dalbavancin concentrations; dashed lines, 2.5th and 97.5th percentiles of the observed dalbavancin concentrations; shaded areas, 95% CI around the simulated median (green), and 2.5th and 97.5th percentiles of the simulated concentrations (gray). VPC, visual predictive check.

Figure 3. Target Attainment Results by Age and MIC



Histogram: MIC distributions from 2017 surveillance data for the 4 most relevant pathogens. Solid lines, projected 2-log kill target attainment by age–group-specific treatment regimen (1500 mg [adults], 18 mg/kg [adolescents, aged 12–<18 y; children, aged 6–<12 y], or 22.5 mg/kg [other age groups]). MIC, minimal inhibitory concentration (µg/mL).

Figure 4. Simulated Pediatric vs Adult $AUC_{0\text{–}120h}$



Central line, sample median; boxes, interquartile range; whiskers extend to 1.5 times the interquartile range; dots, data points outside the whiskers; dashed lines, exposure ($AUC_{0\text{-}120h}$) range observed in phase 3 studies in adults treated with a single 1500-mg dose.

Table 2. Simulated Pediatric vs Adult PK Metrics

Age Group	GA 26–<37 wk	Birth–1 mo	1–<3 mo	3 mo–<2 y	2–<6 y	6–<12 y	12–<18 y	≥18 y
N	1000	1000	1000	1000	1000	1000	1000	1000
Dose	22.5 mg/kg	22.5 mg/kg	22.5 mg/kg	22.5 mg/kg	22.5 mg/kg	18 mg/kg	18 mg/kg	1500 mg
C_{max} (µg/mL)								
Mean (SD)	232 (90)	309 (130)	309 (130)	310 (140)	307 (130)	262 (120)	254 (120)	425 (100)
Median (range)	220 (55.4–702.0)	283 (73.1–1100.0)	289 (67.9–1210.0)	288 (81.3–1010.0)	282 (54.7–958.0)	239 (52.2–851.0)	233 (60.5–869.0)	412 (134.0–1420.0)
$AUC_{0\text{–}Inf}$ (µg*h/mL)								
Mean (SD)	14,100 (4500)	15,800 (5200)	16,000 (5500)	17,300 (5800)	20,300 (6600)	18,900 (6300)	21,100 (7200)	28,800 (8000)
Median (range)	13,600 (5100–39,800)	14,800 (5540–41,500)	15,300 (5410–44,500)	16,200 (5940–47,600)	19,500 (6410–49,000)	17,900 (6690–48,300)	19,900 (7380–49,000)	27,700 (11,600–75,300)
$AUC_{0\text{–}120h}$ (µg*h/mL)								
Mean (SD)	6750 (2100)	9130 (2900)	9200 (3100)	9570 (3200)	10,200 (3300)	8930 (3000)	9120 (3100)	10,800 (3200)
Median (range)	6480 (1860–20,000)	8710 (2910–25,800)	8790 (2780–25,800)	9070 (3440–25,800)	9730 (3210–25,200)	8530 (2940–21,700)	8670 (2810–22,400)	10,400 (3720–31,000)
$fAUC_{avg}$ (µg*h/mL)								
Mean (SD)	94.5 (29)	128 (41)	129 (43)	134 (45)	143 (46)	125 (42)	128 (43)	152 (45)
Median (range)	90.8 (26.0–279)	122 (40.7–362.0)	123 (38.9–361.0)	127 (48.2–362.0)	136 (44.9–352.0)	119 (41.2–304.0)	121 (39.3–313.0)	146 (52.1–434.0)

$AUC_{0\text{–}120h}$, area under the curve from time 0 to 120 h; $AUC_{0\text{–}Inf}$, area under the curve from time 0 extrapolated to infinity; C_{max}, maximum observed concentration; $fAUC_{avg}$, 24-h free dalbavancin exposure metric; GA, gestational age; PK, pharmacokinetic; SD, standard deviation.

INTRODUCTION

- Dalbavancin is a lipoglycopeptide approved for treating adults with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible strains of the following Gram-positive microorganisms: *Staphylococcus aureus (S aureus)* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus* group (including *S anginosus, S intermedius, S constellatus*), and *Enterococcus faecalis* (vancomycin-susceptible strains)[1,2]
- The pharmacokinetics (PK) of dalbavancin have been well-characterized in adults and shown to be linear, with low variability and a long terminal elimination half-life (>14 days) allowing for simplified dose regimens.[3,4]
- Plasma protein binding is approximately 93% and unchanged with drug concentration, renal impairment, or hepatic function.[5]
- In adults, the standard regimen is 1500 mg, either as a single dose or 1000 mg followed 1 week later by 500 mg, administered by intravenous (IV) infusion over 30 minutes. Dosage adjustment is required in patients whose creatinine clearance is <30 mL/min and who are not receiving regularly scheduled hemodialysis (1125 mg in the United States; 1000 mg in Europe)[5]
- Pediatric studies for dalbavancin include three phase 1 studies and a phase 3 study in patients from birth–17 years with ABSSSI or neonatal sepsis (patients aged <3 months)

Objectives

- To characterize the population pharmacokinetic (popPK) profile of dalbavancin as a function of dose, time, and covariates in the pediatric population
- To evaluate the impact of covariates on the PK of dalbavancin
- To simulate exposures and probability of target attainment (PTA) for various doses in the pediatric population, thus identifying an optimal dose to achieve the predefined PK/PD targets (free-drug area under the concentration-time curve/minimum inhibition curve [fAUC/MIC]) for each of the pediatric age groups

METHODS

Data

- Development of the pediatric popPK model used all PK sampling conducted in the 4 pediatric studies (**Table 1**)
- The combined population consisted of 134 males and 77 females ranging in age from 4 days–17.9 years, and weights ranging from 3–105 kg for all patients aged ≥2 years

PopPK Model

- A 3-compartment popPK model was previously shown to be appropriate for describing the concentration-time profiles in adults, and was used as the initial structural model for the pediatric analysis
- Because of the wide age (and weight) range of this analysis dataset, the effect of body weight on all clearance and volume parameters was included as an *a priori* covariate based on the principles of allometry with exponents of 0.75 for clearances and 1 for volumes
- Based on exploratory data analysis and prior knowledge of dalbavancin PK in adult and pediatric populations, serum albumin was included as **one** covariate on all PK parameters, and creatinine clearance or estimated glomerular filtration rate (eGFR; for participants aged <2 years) was included as a covariate on clearance
- The eGFR in patients aged <2 years was determined using the Rhodin method, and was based on postmenstrual age, accounting for renal function maturation[6]
- Standard techniques for popPK modeling were used with a validated installation of the nonlinear mixed-effects modeling software (NONMEM®, version 7.4.0, ICON Development Solutions, Hanover, MD, United States)
  - Model development was performed using first-order conditional estimation with eta-sigma interaction (FOCE-I)
  - Automated covariate search was performed using PsN, version 4.2.0
- The final model was determined on the basis of maximized likelihood (lowest stable objective function value), physiologic plausibility of parameter values, successful numeric convergence, parameter precision, and acceptable visual predictive checks (VPC)

Table 1. Overview of Studies Included in the Population PK and Target Attainment Analyses

Phase	Study ID	Study Design	N	N_{obs}/Subject	Dose*/Treatment/Schedule
1	A8841004 (NCT00678106)	A phase 1, open-label, single-dose study to investigate the PK, safety, and tolerability of dalbavancin in hospitalized adolescents aged 12–17 y receiving standard IV antiinfective treatment for bacterial infections	10	13	Patients weighing >60 kg: 1000 mg <60 kg: 15 mg/kg
1	DUR001-106 (NCT01946568)	A phase 1 study to characterize the PK of dalbavancin in pediatric patients aged 3 mo–≤11 y after IV administration of a single dose of dalbavancin	33	6	≥5 y: 15 mg/kg (≤1000 mg) 2–<5 y: 25 mg/kg (≤1000 mg) 3 mo–<2 y: 10 mg/kg (≤1000 mg)
1	DUR001-107 (DAL-PK-02) (NCT02688790)	A phase 1 safety, tolerability, single-dose PK study in neonates and infants aged 0–≤ 3 mo with known or suspected bacterial infection	8	6	22.5 mg/kg
3	DUR001-306 (DAL-MD-02) (NCT02814916)	A phase 3, multicenter, open-label, randomized, comparator-controlled trial of the safety and efficacy of dalbavancin vs active comparator in pediatric patients with ABSSSI	SD: 86 2 doses: 75	5	Birth–<3 mo (SD only): 22.5 mg/kg 3 mo–<6 y SD: 22.5 mg/kg 3 mo–<6 y 2 dose: Day 1, 15 mg/kg; Day 8, 7.5 mg/kg 6–<18 y SD: 18 mg/kg 6–<18 y 2 dose: Day 1, 12 mg/kg; Day 8, 6 mg/kg

ABSSSI, acute bacterial skin and skin structure infections; IV, intravenous; N, planned number of subjects; N_{obs}, planned number of observations; PK, pharmacokinetic; SD, single dose.
*All doses were 30 minute intravenous infusions.

Monte Carlo Simulations of Exposures and Probability of Target Attainment

- The final popPK model was used to conduct Monte Carlo simulations to predict exposures and probability of target attainment after a single dose of dalbavancin (30-minute IV infusion) by age and renal function groups
  - For each age group, sex, and dose regimen, 500 patients were simulated
- Simulations were performed for patients with normal renal function
  - The PK/PD index associated with efficacy of dalbavancin and used in previous PTA assessments for adult and pediatric patients was 24-hour fAUC/MIC based on a neutropenic murine thigh infection model
  - The PK/PD targets based on this non-clinical model were 27.1, 53.3, and 111.1 hours for bacterial stasis, 1-log kill, and 2-log kill of *S aureus*, respectively[7]
  - The 24-hour free dalbavancin exposure metric ($fAUC_{avg}$) used for calculating fAUC/MIC was defined as $fAUC_{0\text{-}120h}/5$
- Plasma protein binding of dalbavancin was assumed to be 93%[1,2]

DISCLOSURES

The study was sponsored by Allergan (prior to its acquisition by AbbVie). Todd A. Riccobene and Timothy J. Carrothers are employees of AbbVie and may hold stock in the company. H. Maxime Lagraauw and Lars Lindbom are employees of qPharmetra.

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