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Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Target Attainment Analyses for Dalbavancin in Pediatric Patients

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Background: Dalbavancin, approved for the treatment of pediatric and adult patients with acute bacterial skin and skin structure infections, has a terminal half-life of >14 days allowing administration as a single-dose regimen.

Methods: We developed a population pharmacokinetic (PK) model using 1124 dalbavancin concentrations from 211 pediatric patients, with allometric scaling of clearance and volume parameter exponents fixed at 0.75 and 1, respectively. Serum albumin was included as a covariate on all PK parameters; creatinine clearance or estimated glomerular filtration rate was a covariate on clearance. The final model, qualified by visual predictive checks and bootstrapping, was used to simulate 1000 PK profiles for a range of pediatric age groups. PK/pharmacodynamic target attainment (PTA) was calculated for targets associated with stasis, 1-log kill, and 2-log kill of *Staphylococcus aureus* (neutropenic murine thigh infection model).

Results: Dalbavancin PK was well characterized by a three-compartment model. No additional significant covariates were identified. Simulations showed that single-dose (30-minute intravenous infusion) regimens of 22.5 mg/kg (patients <6 years) and 18 mg/kg (patients 6 years to <18 years) resulted in PTA ≥94% for minimal inhibitory concentrations ≤2 mg/L and ≤0.5 mg/L for the stasis and 2-log kill targets, respectively. PTA for pediatric patients was similar to adults with exposures within the range for adults administered 1500 mg dalbavancin.

Conclusion: Dalbavancin PK in pediatric patients was well characterized by a three-compartment model. Simulations with the final model demonstrated adequate PTA across the entire age range for the approved pediatric dalbavancin doses.

Key Words: acute bacterial skin and skin structure infection, dalbavancin, pediatric, pharmacokinetics, pharmacodynamics

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Acute bacterial skin and skin structure infections (ABSSSI) are a significant source of morbidity in children, with cutaneous abscesses and cellulitis being the predominant skin infections treated by pediatricians.[1] If diagnosed early and treated appropriately, these infections are almost always curable, but some have the potential to cause hospitalization and serious life-threatening complications.[2] Since the year 2000, rates of hospitalizations among pediatric patients with skin and skin structure infections (SSSI) have increased rapidly, with a 2013 survey showing a doubling between 1997 and 2009 to exceed 70,000 per year.[3,4] This increase, which is also seen in adult patients with SSSI, coincided with the emergence of resistant pathogens, including community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA), with many areas in the United States now reporting >40% MRSA rates among SSSI isolates.[5–10]

For more than 50 years, vancomycin has been the mainstay of antibacterial therapy for severe infections caused by resistant Gram-positive organisms, including MRSA. However, vancomycin is associated with a risk of nephrotoxicity, the need for drug monitoring, and the emergence of resistant *S aureus* and enterococci strains.[11] Current guidelines from the Infectious Disease Society of America (IDSA) for the diagnosis and management of ABSSSI[12] were published before the US Food and Drug Administration and the European Medicines Agency approved dalbavancin, a second-generation, intravenous (IV) lipoglycopeptide, in 2014 and 2015, respectively, for the treatment of adults with ABSSSI known or suspected to be caused by susceptible strains of the following Gram-positive microorganisms: *S aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes*, *S agalactiae*, *S dysgalactiae*, *S anginosus* (including *S anginosus, S intermedius, S constellatus*), and vancomycin-susceptible strains of *Enterococcus faecalis*. Dalbavancin is also approved in the United States for the treatment of ABSSSI in pediatric patients from birth to <18 years[13,14] and is the first and only single-dose IV treatment for ABSSSI currently approved in the United States and the European Union. The pharmacokinetic (PK) profile of dalbavancin, including its long half-life, makes it a convenient treatment option, even in the outpatient setting, and a single-dose regimen may improve compliance and reduce healthcare resource use.[11]

The safety and efficacy of IV dalbavancin in adults have been demonstrated in multiple phase 2 (VER001-4,[15] VER001-5[16]) and phase 3 trials (VER001-9,[17] DUR001-301; DUR001-302,[18] and DUR001-303),[19] with its safety and effectiveness for the treatment of ABSSSI in pediatric patients supported by additional PK and safety data in patients from birth to <18 years of age.

The PK of dalbavancin in adults is well characterized and has been shown to be linear, with low variability and a long terminal elimination half-life ($t_{1/2}$ >14 days) allowing for single- or double-dose (on days 1 and 8) regimens.[20] Intravenously administered dalbavancin is highly bound (~93%) to serum albumin, with the remaining 7% existing in unbound form,[21] a proportion that is largely unchanged by drug concentration, renal impairment, or hepatic function.[22] The PK profile of dalbavancin in adults is best characterized by a three-compartment model of distribution (one central and two peripheral compartments).[21] Clearance (CL) was influenced by body weight, creatinine clearance (CrCL), and serum

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albumin. Distribution volumes were influenced by body weight and serum albumin, with the peripheral volume of distribution also influenced by age.[21] In adults, the standard regimen is 1500 mg, either as a single dose or as 1000 mg followed 1 week later by a 500-mg dose, administered by IV infusion over 30 minutes.[13,14] Dosage adjustments are required in patients whose CrCL is <30 mL/min and who are not receiving regularly scheduled hemodialysis (1125 mg in the United States; 1000 mg in the European Union [or 750 mg followed 1 week later by a 350-mg dose in the United States and the European Union]).[13,14]

Bradley et al[23] determined that a slightly lower mean plasma dalbavancin exposure (based on the area under the concentration-time curve to infinity [AUC_{inf}] and maximum plasma concentration [C_{max}], and consistent with the enhanced renal and/or hepatic elimination documented in healthy adolescents) was achieved in children (12–17 years old) following administration of a single 1000-mg or 15-mg/kg dose of dalbavancin (individuals >60 kg and <60 kg, respectively), than that reported to be both safe and efficacious in adult patients given 1000 mg, and had a comparable $t_{1/2}$.[23] Using these data and the results from a study of a single IV dose in children 3 months to 11 years of age, Gonzalez et al[24] developed a population PK model for dalbavancin across pediatric age groups in which the PK of dalbavancin in pediatric patients 3 months to ≤17 years is also best characterized by a three-compartment model of distribution with body weight and serum albumin as covariates.

Our current analysis updates the model of Gonzalez et al[24] with the addition of PK data from two recently available pediatric studies: DUR001-107 (PK of a single dose of dalbavancin in hospitalized preterm neonates or infants 0 to <3 months old with suspected or confirmed bacterial infection) and DUR001-306 (PK of a single- or double-dose regimen of dalbavancin versus an active comparator in pediatric patients with ABSSSI). The updated model, in addition to the covariate assessments and PK/pharmacodynamic (PK/PD) target attainment (PTA) simulations, will support dalbavancin dose regimens for ABSSSIs in the pediatric population.

MATERIALS AND METHODS

The overall objective of this analysis was to determine optimized dalbavancin dosing regimens across the entire pediatric age range (birth to <18 years old) based on data from four clinical studies in pediatric patients with ABSSSI or neonatal sepsis (three phase 1 and one phase 3; see table, Supplemental Digital Content 1, http://links.lww.com/INF/E862). This was achieved by (i) characterization of the popPK profile of dalbavancin in pediatric patients as a function of dose, time, and covariates; (ii) evaluation of the impact of covariates on the PK of dalbavancin in pediatric patients; and (iii) simulation of exposures and PTA for various doses in the pediatric population and comparison with adults to identify an optimal dose for each of the pediatric age groups.

A total of 1124 PK observations from 211 children across the four pediatric studies were included in the model development after excluding 33 observations that were below the limit of quantification and a further 18 records for other exclusion reasons, such as predose PK observations, missing PK data, and outlier records based on early conditional weighted residual model assessments. The combined population consisted of 134 male and 77 female patients ranging in age from 4 days to 18 years, and with weight from 3 to 105 kg.

Population Pharmacokinetic Model

A three-compartment popPK model previously shown to be appropriate for describing the concentration-time profiles in adults was used as the initial structural model for the pediatric analysis.[21]

Because of the wide age and body weight range of this analysis data set, the effect of body weight on all CL and volume parameters was included as an *a priori* covariate founded on the principles of allometry with exponents of 0.75 for clearances and 1 for volumes. Based on exploratory data analyses and prior knowledge of dalbavancin PK in adult and pediatric populations, serum albumin was included as a covariate on all PK parameters with the correlated effect modeled via the relative bioavailability parameter (F1); normalized creatinine clearance (CrCLN) or estimated glomerular filtration rate (eGFR) for participants <2 years was included as a covariate on CL. CrCLN was calculated with the bedside Schwartz equation.[25] Furthermore, for patients <2 years old, the impact of renal maturation on CL was accounted for through application of a sigmoidal function based on postmenstrual age (PMA) in place of a CrCL effect on CL (see table, Supplemental Digital Content 2, http://links.lww.com/INF/E862).[26]

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). Model development was carried out using first-order conditional estimation with eta–sigma interaction, and an automated covariate search was performed using PsN, version 4.2.0.[27,28]

The final model was determined based on maximized likelihood of the lowest stable objective function value, physiologic plausibility of parameter values, successful numerical convergence, parameter precision, and acceptable visual predictive check (VPC).

Monte Carlo Simulations of Exposures and Probability of PTA

The final popPK model was used to simulate individual PK profiles for the entire pediatric age range (preterm neonates at birth and term neonates up to adolescents of 18 years). A simulation data set was created for the following age groups: 12 to <18 years, 6 to <12 years, 2 to <6 years, 3 months to <2 years, 1 to <3 months, birth to <1 month (term neonates), and preterm neonates at birth (gestational age [GA] 26 weeks to <37 weeks). For each age group, sex, and dose regimen, 500 individuals were simulated for a total of 7000 simulated patients for the single-dose regimens used in DUR001-306. A similar data set of 7000 simulated patients was created for the two-dose regimen simulations.

For term neonates and older children, age in months was simulated random-uniformly from the age ranges previously noted. Serum albumin concentration was imputed as random uniform deviates on the interval 1.9–5.3 g/dL (observed range in analysis data set). Serum creatinine was likewise imputed as random uniform deviates on the interval 0.13 to 1.29 mg/dL. eGFR was calculated using a sigmoidal function based on PMA[26] where PMA = 40 + age (weeks), and CrCLN was calculated using the bedside Schwartz equation.[25] Height and body weight were simulated in a coordinated fashion. For preterm neonates, body weight, eGFR,[26] and serum albumin concentration[29] were simulated for age 0 days (i.e., at birth). Age-group–specific correlations were calculated for 3359 individuals from the 2017–2018 National Health and Nutrition Examination Survey results. Cholesky decomposition was used to generate bivariate random normal deviates having the observed group-wise correlations. Deviates were Box–Cox transformed using the age- and sex-specific parameters from the relevant Word Health Organization and Centers of Disease Control and Prevention tables. Patients <2 years old were simulated using the infant-specific weight-for-age and length-for-age parameters. Additionally, recumbent length was used interchangeably with stature for calculating derived variables.

For preterm neonates, age in months, relative to a term GA of 40 weeks, was simulated random-uniformly over the GA range. Preterm neonate birth weight-for-age was obtained similarly using the lambda-mu-sigma chart from Olsen et al.[30] Serum albumin concentrations have been reported to be significantly lower

in preterm neonates, exhibiting GA-dependent development.[29] To accommodate lower serum albumin concentrations in this specific simulation population, the albumin covariate was simulated with log-normal distributed inter-individual variability (IIV) and normally distributed residual variability based on GA according to the derived sigmoidal relationship. The previously mentioned height and body weight correlation does not extend to preterm neonates, thus height and height-related covariates, including body surface area and body mass index, were not derived for this population.

The PK/PD index associated with the efficacy of dalbavancin and used in previous probability of PTA assessments for adult and pediatric patients[21] was the 24-hour free-drug AUC/minimum inhibitory concentration (*f*AUC/MIC) based on a neutropenic murine thigh infection model. A published reevaluation of the initial preclinical targets resulted in bacterial stasis, 1-log kill, and 2-log kill targets for *S aureus* of 27.1 hours, 53.3 hours, and 111.1 hours, respectively.[31] PTA simulations with the adult popPK model indicated that for both the 1000- (double-dose) and 1500-mg (single-dose) doses of dalbavancin, >99% of simulated patients were predicted to achieve the stasis target at MIC ≤2 mg/L.[21] The 24-hour free dalbavancin exposure metric was defined as $f\text{AUC}_{0\text{-}120}/5$ with the assumption of 93% protein binding and the remaining 7% existing in unbound form.

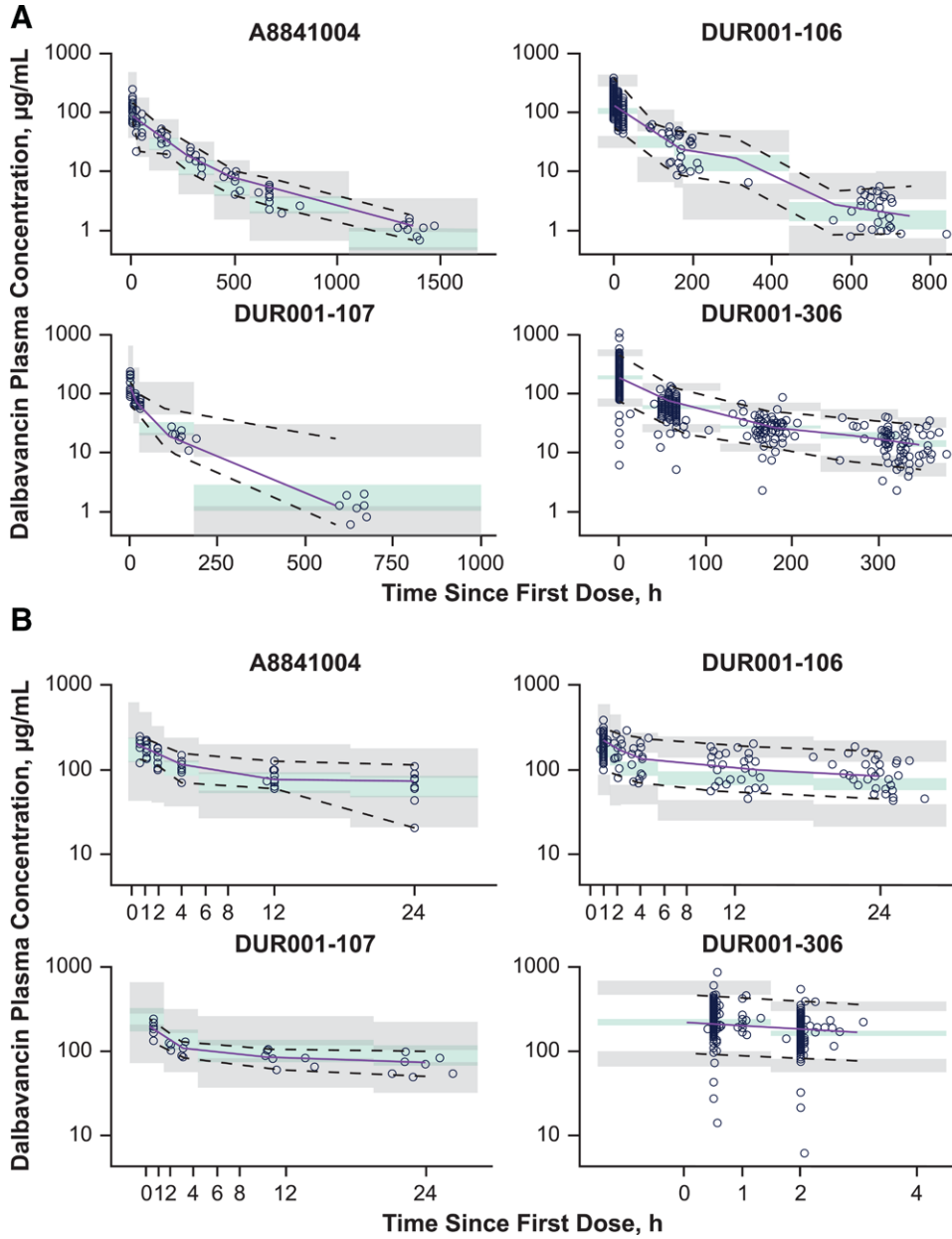

FIGURE 1. VPC of the final model by study for all times since first dose (A) and the first 24 hours (B). VPC, visual predictive check. Circles, observations; solid purple line, median of the observed dalbavancin concentrations; dashed lines, 2.5th and 97.5th percentiles of the observed dalbavancin concentrations; shaded areas, 95% CI around the simulated median (green), and 2.5th and 97.5th percentiles of the simulated concentrations (gray). full color online

RESULTS

Dalbavancin PK in this pediatric population (4 days to 18 years old) was well characterized by a three-compartment model (see figure, Supplemental Digital Content 3 http://links.lww.com/INF/E862). The standardized reference body 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. w_X: variance of the IIV of parameter X, IIV as a % of clearance volume was derived from variance according to $(e^{\omega}X - 1) \times 100$. Covariances are reported as correlations between the indicated parameters. Median and 95% CIs were calculated from a 1000-sample bootstrap, with 952 successful minimizations. Stepwise covariate modeling did not identify any additional significant covariates beyond those incorporated *a priori*. A VPC demonstrated that the final model had good predictive performance across the range of observed data (Figure 1).

Simulations showed that single-dose regimens of 22.5 mg/kg for patients <6 years and 18 mg/kg for patients 6 years to <18 years (both capped at a maximum of 1500 mg) resulted in PTA ≥94% for MIC ≤2 mg/L for the stasis target and up to 0.5 mg/L for the 2-log kill target (Figure 2).

The comparison between the Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoint for dalbavancin (0.25 µg/mL), the MIC_{90} for dalbavancin against *S aureus* (0.03 µg/mL), and the MIC where predicted PTA starts to decrease indicated that these dose regimens would continue to provide attainment of the preclinical PK/PD targets for several additional MIC dilutions beyond those currently observed in the United States and European Union.

The PTA for pediatric patients was similar to that for adults, and mean exposures (AUC_{0-120h}) for pediatric patients were generally within 20% of the median exposures previously observed in adults administered a single dose of dalbavancin 1500 mg (Table 1 and Figure 3). Across the simulated range of preterm births at GA 26 to <37 weeks, preterm neonates were predicted to have approximately 38% lower median AUC_{0-120h} than adults. In addition, median C_{max} for values of pediatric patients was predicted to be approximately 30% to 45% lower than values in adult patients given a single 1500-mg dose (Table 1). However, as noted previously, in all pediatric age groups, the percentage of patients attaining PK/PD targets were >90% for MICs up to and exceeding the CLSI breakpoint of 0.25 mg/L.

DISCUSSION

The overall objective of the current study was to determine optimal dalbavancin dosing regimens across the pediatric population with ages ranging from birth to <18 years. This study represents a comprehensive popPK examination of all currently available pediatric dalbavancin PK data collected and expands the previous model by broadening the age range and including more than twice the number of individuals.

Dalbavancin PK in pediatric patients was well characterized by a three-compartment model with allometric scaling of CL and volume with serum albumin and renal function included as covariates. PK simulations with the final pediatric popPK model were supportive of reaching similar exposures to those observed in adults, under a single-dose regimen (capped at 1500 mg) of 22.5 mg/kg for patients <6 years old and 18 mg/kg for those 6 to <18 years old administered as a 30-minute IV infusion.

Extrapolation of clinical efficacy and safety from adults to pediatric patients has been applied to other antibiotics approved for ABSSSI in children.[32] The appropriate dose for pediatric patients is one that will achieve comparable plasma exposures to those observed in adults. This is based on assumptions that the disease, mechanism of action, and thus PK/PD are the same in pediatric patients as they are in adults. Therefore, the doses selected for pediatric patients should achieve similar plasma exposures and probability of PTA in children as in adults. If the adult dose is shown to be efficacious, the same exposure in pediatric patients also should be associated with clinical efficacy.

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

Safety outcomes, efficacy endpoints (clinical response, clinical cure), and microbiological outcomes in this study were consistent across the 5 age cohorts and across all populations evaluated in study DUR001-306.[33] That study, comprising 191 patients, including five in the youngest cohort (birth to <3 months), is the first to report safety and efficacy outcomes in very young children with ABSSSI treated with dalbavancin. The safety profile of dalbavancin in pediatric patients was consistent with that in adults with ABSSSI, with no new clinically relevant safety signals identified. Clinical response in the microbiological intent-to-treat (ITT) population was 97.4% and 98.6% for the single- and double-dose regimens, respectively, at 48–72 hours postinfusion, 94.8% and 97.3% at end-of-treatment, and 97.4% and 97.3% at follow-up. At

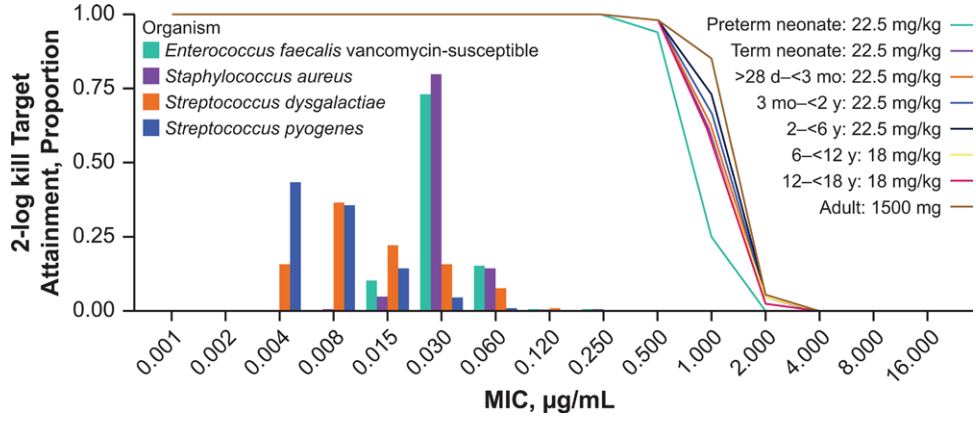

FIGURE 2. PTA results by age and MIC. MIC, minimal inhibitory concentration (µg/mL). Histogram: MIC distributions from 2017 surveillance data for the four most relevant pathogens. Solid lines, projected 2-log kill target attainment by age-group–specific treatment regimen (1500 mg [adults], 18 mg/kg [adolescents,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

TABLE 1. Simulated Pediatric vs Adult PK Parameters

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

*To a maximum dose of 1500 mg.
†Administered as a 30-minute IV infusion.
AUC_{0-120h}, area under the curve from time 0 to 120 h; AUC_{0-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, pharmacokinetics.

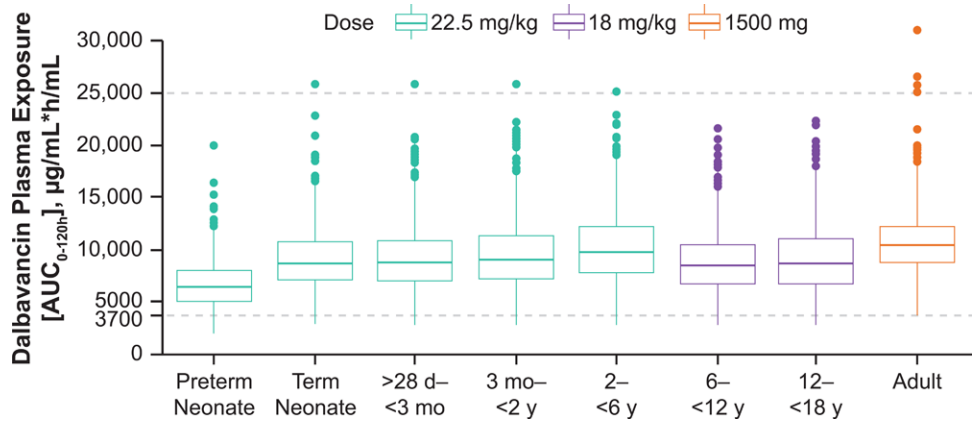

FIGURE 3. Simulated pediatric vs adult AUC_{0-120h}. Central line, sample median; boxes, interquartile range; whiskers extend to 1.5 times the interquartile range; dots, data points outside the whiskers; dashed lines, exposure (AUC_{0-120h}) range observed in phase 3 studies in adults treated with a single 1500-mg dose of dalbavancin. full color online

test-of-cure, >96% of patients treated with dalbavancin achieved a clinical cure. The rate of favorable clinical response in the microbiological ITT population at all time points in study DUR001-306 was similar regardless of baseline pathogen, including MRSA,[33] the most common cause of purulent skin infection in the United States, and associated with complications, recurrence, and treatment failure that often results in hospitalization.[34] In pediatric patients, particularly younger children, early empiric treatment of MRSA purulent skin infection based on clinical symptoms (pending determination of microbiological origin) is paramount to avoiding serious infection and infant mortality.[35]

In summary, this analysis demonstrates that dalbavancin will be a valuable addition to the armamentarium of antibiotics for the treatment of ABSSSI in pediatric patients. Based on studies in adults, the drug offers a number of benefits, such as treatment compliance, ease of use, and reduction in healthcare resource use.[11,36–38] The long half-life (>14 days) of dalbavancin allows for a single-dose regimen and an opportunity to improve adherence with therapy relative to daily administration of either IV or oral drugs. As shown in adults, pediatric patients also may benefit from the PK profile of dalbavancin, which reduces the inconvenience associated with multiple daily IV infusions. Furthermore, treatment with

dalbavancin may avoid the requirement for long-term IV access and the measurement of serial trough levels seen with other antibiotics, which could lead to a potential shorter hospital stay for children with ABSSSI and a reduction in overall associated healthcare costs.

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Data Sharing

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (e.g., protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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Current Abstracts

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Outbreak of Acute Gastroenteritis Among Rafters and Backpackers in the Backcountry of Grand Canyon National Park, April–June 2022

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On May 11, 2022, the National Park Service (NPS) Office of Public Health (OPH) and Coconino County Health and Human Services in Flagstaff, Arizona, contacted the Centers for Disease Control and Prevention (CDC) about a rising number of acute gastroenteritis cases among backcountry visitors to Grand Canyon National Park (Grand Canyon). The agencies reviewed illness report forms, assessed infection prevention and control practices and distributed a detailed survey to river rafters and hikers with backcountry permits (backpackers) who visited the Grand Canyon backcountry. During April 1–June 17, a total of 191 rafters and 31 backpackers reported symptoms consistent with acute gastroenteritis. Specimens from portable toilets used by 9 river rafting trip groups were tested using real-time reverse transcription-polymerase chain reaction, and test results were positive for norovirus.

Commercially operated Colorado River rafting trips are allowed within the Grand Canyon during April–October. OPH surveillance of river rafting trip illnesses requires that guides on commercially operated trips report the occurrence of <3 illnesses at each trip's end, contact the NPS by satellite phone as soon as possible when 3 or more illnesses occur and complete an illness report form for each ill person. Private rafting trip guides must report illnesses within 7 days after completing the trip. Backpackers are encouraged to report illnesses.

During April–May 2022, approximately 4770 rafters visited the Grand Canyon backcountry. On April 8, 2022, OPH was notified by a commercially operated rafting group within Grand Canyon of 7 persons experiencing vomiting or diarrhea. After 9 additional rafting trips (173 rafters), multiple cases of acute gastroenteritis were reported. OPH and Coconino County Health and Human Services contacted CDC on May 11, 2022. By May 21, 13 additional rafting trips with 102 reported cases of acute gastroenteritis were documented, and several backpackers reported symptoms consistent with acute gastroenteritis. A specific source of virus transmission had not been identified. On May 24, 2022, NPS requested CDC assistance, and an investigation was initiated.

A case of acute gastroenteritis was defined as vomiting or diarrhea (at least 3 loose stools during a 24-hour period) <24 hours before trip launch through 3 days after the end of the trip in a person who participated in a river rafting trip or backcountry backpacking in the Grand Canyon during April 1–June 17, 2022. Among 116 illness report forms collected through July 8, 2022, a total of 94 (81%) rafters reported vomiting, 79 (68%) reported diarrhea, and 74 (64%) reported nausea. Acute onset, short symptom duration (median 24 hours) and predominance of vomiting suggested norovirus.

The date of first illness among rafters was April 6, 2022; the trip had an attack rate of 39% (11/28 rafters). Rafting trip attack rates ranged from 10% (3/31) to 83% (29/35). During April 1–June 17, 2022, a total of 222 persons had an illness that met the case definition for acute gastroenteritis. Most respondents reported illness onset during the trip (178; 80%), with 5 persons from separate trips (2 river rafters and 3 backpackers) reporting illness onset <24 hours before their trip started (different illness onset dates). Most cases occurred among park visitors (191; 86%) and the remaining cases (31; 14%) among professional guides. Ill visitors were from 34 US states and four additional countries.

Public health partners shared norovirus infection prevention and control education messages tailored to the backcountry environment immediately after notification. This included recommendations for symptom screening and exclusion of ill persons from joining a rafting trip, disinfection of potable water, separation of ill persons from healthy persons, enhanced environmental cleaning and strict precautions for food storage and preparation on river rafts in addition to environmental inspections of the commercial outfitters' warehouses.

Outfitter staff members were advised to promote handwashing with soap and water, monitor adherence and isolate or cohort persons with acute gastroenteritis during the trip whenever possible. Many outfitter staff members were unaware that alcohol-based hand sanitizer is ineffective in mitigating norovirus transmission.

Comment: An increase in norovirus activity was observed at a national level in spring 2022, with the number of outbreak reports returning to prepandemic levels for the first time since March 2020. Prevention and control of future outbreaks in the setting of rafting and backpacking include rapid case reporting, symptom screening before trip start, water disinfection, prompt separation of ill passengers, strict adherence to hand hygiene with soap and water and minimizing interactions among rafting groups.