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ARTICLE

The use of extrapolation based on modeling and simulation to support high-dose regimens of ceftaroline fosamil in pediatric patients with complicated skin and soft-tissue infections

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Abstract

A model-informed drug development approach was used to select ceftaroline fosamil high-dose regimens for pediatric patients with complicated skin and soft-tissue infections caused by *Staphylococcus aureus* with a ceftaroline minimum inhibitory concentration (MIC) of 2 or 4 mg/L. Steady-state ceftaroline concentrations were simulated using a population pharmacokinetics (PK) model for ceftaroline fosamil and ceftaroline including data from 304 pediatric subjects and 944 adults. Probability of target attainment (PTA) for various simulated pediatric high-dose regimens and renal function categories were calculated based on patients achieving 35% *f*T>MIC (*S. aureus* PK/pharmacodynamic target for 2-$\log_{10}$ bacterial killing). For extrapolation of efficacy, simulated exposures and PTA were compared to adults with normal renal function receiving high-dose ceftaroline fosamil (600 mg 2-h infusions every 8 h). For safety, predicted ceftaroline exposures were compared with observed pediatric and adult data. Predicted ceftaroline exposures for the approved pediatric high-dose regimens (12, 10, or 8 mg/kg by 2-h infusions every 8 h for patients aged >2 to <18 years with normal/mild, moderate, or severe renal impairment, respectively; 10 mg/kg by 2-h infusions every 8 h for patients aged ≥2 months to <2 years with normal renal function/mild impairment) were well matched to adults with normal renal function. Median predicted maximum concentration at steady state ($C_{max,ss}$) and area under the plasma concentration-time curve over 24 h at steady state pediatric to adult ratios were 0.907–1.33 and 0.940–1.41, respectively. PTAs (>99% and ≥81% for MICs of 2 and 4 mg/L, respectively) matched or exceeded the adult predictions. Simulated $C_{max,ss}$ values were below the maximum observed data in other indications, including a high-dose pediatric pneumonia trial, which reported no adverse events related to high exposure.

An abstract summarizing these analyses has been published in lieu of presentation at the 30th European Congress of Clinical Microbiology and Infectious Diseases, Paris, France, April 18–21, 2020.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Although ceftaroline fosamil standard dose regimens are appropriate for most patients, based on clinical data and modeling/simulations, the European product labeling includes high-dose recommendations for the treatment of complicated skin and soft-tissue infections (cSSTI) caused by rare *Staphylococcus aureus* with ceftaroline minimum inhibitory concentrations of 2 or 4 mg/L.

WHAT QUESTION DID THIS STUDY ADDRESS?

In place of a previously planned prospective clinical trial, population pharmacokinetics modeling leveraged available data across adult and pediatric indications. Exposure and probability of target attainment simulations with matching to adult subjects were conducted (with regulatory agreement) to select ceftaroline fosamil high-dose regimens for pediatric patients with cSSTI (aged >2 months to <18 years).

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

These analyses enabled extrapolation of the expected safety and efficacy of the selected ceftaroline fosamil high-dose regimens for pediatric patients with cSSTI caused by *S. aureus* isolates with ceftaroline minimum inhibitory concentrations of 2 or 4 mg/L within a shorter timeframe than that required for a clinical trial.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

This work illustrates the practical utility of model-based extrapolation approaches for pediatric drug development.

INTRODUCTION

Complicated skin and soft-tissue infections (cSSTI) cause significant morbidity and mortality, particularly in children and the elderly.[1] Predominant bacterial pathogens implicated in cSSTI include *Staphylococcus aureus*, *Streptococcus pyogenes* (and other β-hemolytic streptococci), enterococci, and Gram-negative bacteria.[1,2]

Ceftaroline is a broad-spectrum cephalosporin with *in vitro* activity against Gram-positive bacteria associated with cSSTI, including *S. aureus* (methicillin-susceptible and methicillin-resistant [MRSA] strains) and streptococci as well as common nonextended spectrum β-lactamase–producing Gram-negative species.[3] Ceftaroline fosamil is rapidly converted to active ceftaroline by plasma phosphatases, with concentrations of the prodrug generally not measureable beyond the completion of an intravenous (i.v.) infusion; ceftaroline has linear pharmacokinetics (PK) with plasma clearance in healthy subjects of 10 L/h, renal clearance of 4–7 L/h, volume of distribution of 30–40 L, and half-life of approximately 2.6 h.[4–6] Elimination is predominantly renal, necessitating dose adjustments for patients with moderate or severe renal impairment.[7–9] Renal function, age, and presence of acute infection (cSSTI or community-acquired pneumonia [CAP]) have been shown to affect clearance, and the presence of infection also affects distribution.[8,9] Common adverse effects of ceftaroline fosamil are typical of the cephalosporin class and include gastrointestinal, immunological, and administration site disorders. As a β-lactam, ceftaroline has a wide therapeutic index, with the kidney being the primary organ of toxicity in preclinical studies.[10]

Ceftaroline fosamil is approved in Europe for the treatment of cSSTI and CAP from birth onward,[10] with similar indications in the United States[11] and other countries. For adults with estimated creatinine clearance (CrCL) >50 ml/min calculated using the Cockcroft–Gault formula,[12] the standard dose is 600 mg by a 5–60-min i.v. infusion every 12 h, with dose adjustments recommended for CrCL ≤50 ml/min.[10,11] This regimen provides adequate exposure and PK/pharmacodynamic (PD) target attainment for patients with cSSTI caused by *S. aureus* with ceftaroline minimum inhibitory concentration (MIC) ≤1 mg/L,[9] which comprise the vast majority of *S. aureus* clinical isolates in contemporary global surveillance studies.[13–19] Ceftaroline fosamil standard-dose regimens for pediatric patients aged ≥2 months to <18 years (Table 1) were approved in Europe and the United States based on clinical data and population PK modeling demonstrating exposures and probability of target attainment (PTA) similar to those achieved in adults.[7] The respective product labels were recently extended to include standard-dose recommendations for neonates and infants aged <2 months.[10,11]

Although most *S. aureus* clinical isolates have ceftaroline MIC ≤1 mg/L, surveillance data have identified MRSA isolates with MICs of 2 or 4 mg/L in various regions.[13,15,18,19] In 2015–2016, the overall percentages of MRSA isolates with MIC >1 mg/L from skin and soft-tissue infections

TABLE 1 Ceftaroline fosamil standard-dose and high-dose regimens for adults and pediatric subjects (aged ≥2 months to <18 years)[10a]

Renal function (nCrCL in ml/min/1.73 m^2)	Dosing[b]	Adults[c]		Pediatric subjects[c] (aged ≥2 to <18 years)		Pediatric subjects[c] (aged ≥2 months to <2 years)	
		Dose	Frequency	Dose (maximum)	Frequency	Dose	Frequency
Normal/mild impairment (≥50)	Standard	600 mg	Every 12 h	12 mg/kg (400 mg)	Every 8 h	8 mg/kg	Every 8 h
	High	600 mg	Every 8 h	12 mg/kg (600 mg)	Every 8 h	10 mg/kg	Every 8 h
Moderate impairment (≥30 to <50)	Standard	400 mg	Every 12 h	8 mg/kg (300 mg)	Every 8 h	Not applicable	
	High	400 mg	Every 8 h	10 mg/kg (400 mg)	Every 8 h	Not applicable	
Severe impairment (≥15 to <30)	Standard	300 mg	Every 12 h	6 mg/kg (200 mg)	Every 8 h	Not applicable	
	High	300 mg	Every 8 h	8 mg/kg (300 mg)	Every 8 h	Not applicable	

Abbreviations: nCrCL, body surface area–normalized creatinine clearance.

[a]High-dose regimens approved in Europe.

[b]Standard doses infused over 5–60 min; high doses infused over 2 h.

[c]nCrCL calculated using the Cockcroft–Gault formula[12] for adults and Schwartz (bedside) formula[24] for pediatric patients.

clinical specimens were 1.0% (Oceania), 3.1% (Europe), 3.8% (Africa), 7.6% (South America), and 7.8% (Asia).[18] In United States surveillance studies from 2010 to 2016, 2.8% of MRSA clinical isolates had ceftaroline MIC >1 mg/L.[19] In the phase III The CeftarOline versus Vancomycin and aztrEonam tReating cSSTI (COVERS) trial (NCT01499277) in adults with cSSTI and evidence of systemic inflammation or underlying comorbidities, a high-dose ceftaroline fosamil regimen administered by longer infusions (600 mg 2-h i.v. infusions every 8 h) was generally well tolerated and demonstrated noninferiority versus vancomycin plus aztreonam.[20] A pooled analysis of safety outcomes across six phase III trials in adults has shown a similar pattern, and the incidence of adverse events between standard-dose and high-dose ceftaroline fosamil, infusion site phlebitis, and reversible rash were more frequent events in patients receiving high-dose treatment.[21]

Based on population PK modeling using an updated PK/PD target for *S. aureus* and PK and safety data from the COVERS trial, a high-dose ceftaroline fosamil regimen (600 mg 2-h i.v. infusions every 8 h, adjusted for estimated CrCL ≤50 ml/min) was approved in Europe in 2017 for cSSTI in adults caused by *S. aureus* isolates with ceftaroline MICs of 2 or 4 mg/L.[10] The higher daily (every 8 h) ceftaroline fosamil dose is also reflected in European Committee on Antimicrobial Susceptibility Testing guidance, which introduced intermediate and resistant MIC breakpoints for ceftaroline against *S. aureus* of 2 mg/L and >2 mg/L, respectively, for high doses, with breakpoints for standard doses (susceptible ≤1 mg/L and resistant >1 mg/L) remaining unchanged.[22] Reflecting the availability of the high-dose regimens in countries outside the United States, the Clinical and Laboratory Standards Institute also introduced modified MIC breakpoints for ceftaroline against *S. aureus* of susceptible ≤1 mg/L, susceptible dose-dependent 2−4 mg/L, and resistant ≥8 mg/L.[23]

In 2019, high-dose recommendations for pediatric patients (aged ≥2 months to <18 years) with cSSTI caused by rare *S. aureus* isolates with ceftaroline MICs of 2 or 4 mg/L (Table 1) were also approved in Europe: 12 mg/kg (maximum 600 mg) 2-h i.v. infusions every 8 h for aged 2 to <18 years and 10 mg/kg 2-h i.v. infusions every 8 h for infants aged ≥2 months to <2 years, with corresponding recommended dose adjustments for estimated CrCL ≤50 ml/min (calculated using the Schwartz bedside formula) for children aged ≥2 years.[10,24] Approval of the pediatric high-dose regimens was supported by a model-informed drug development (MIDD) approach involving population PK modeling and simulations to match predicted pediatric exposures to the adult population and comparing with observed data in other pediatric indications and adults rather than undertaking an interventional high-dose clinical trial in pediatric patients with cSSTI.[25]

METHODS

Study subjects

Population PK models were built using PK data from participants enrolled in the ceftaroline fosamil clinical development program. All trials and procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation or with the Helsinki Declaration of 1975 (as revised in 1983). Various PK sampling schedules were employed across the different adult and pediatric trials; in general, the adult phase I PK trials included intensive sampling (12 samples/patient following the start of infusion), and the phase II–IV clinical trials included sparse sampling (4 samples/patient). In COVERS, different subsets of patients underwent intensive ($n = 17$) and sparse ($n = 379$) sampling.[20] Sparse sampling (2 or 4 samples per subject) was

done in all except one of the pediatric studies, for which 8 samples per subject were collected in subjects aged 12 to <18 years. Samples below the lower limit of quantification (0.01 mg/L for ceftaroline and 0.05 mg/L for ceftaroline fosamil) were excluded from the population PK analyses.

Modeling software

Population PK analysis was conducted via nonlinear mixed-effects modeling methodology, as implemented in the NONMEM software system, version 7.4.1, using the first-order conditional estimation algorithm with interaction (ICON Development Solutions, Hanover, MD). Perl-speaks NONMEM version 4.7.9 was used for prediction-corrected visual predictive check (pcVPC) and sampling importance resampling for generating estimation of model parameter uncertainty. R version 3.4.1 and/or R libraries (such as ggplot2 version 2.2.1, dplyr version 0.7.4) were used for data manipulations, creation of simulation data sets, exploratory analysis, model diagnostics, postprocessing of NONMEM output, and generating summary statistics.

Base population PK model

A combined population PK model for ceftaroline fosamil and ceftaroline developed using data from 5 pediatric and 15 adult studies, including 305 pediatric patients and 415 healthy adults and patients with CAP or cSSTI,[7] was the base model for the current analysis. The pediatric trials included two single-dose phase I/IV studies in patients with suspected or confirmed infection and three multiple-dose phase II/III/IV studies in CAP or cSSTI and covered ages from birth to <18 years.[7] Adult subjects had varying degrees of renal function. All pediatric patients (with one exception) had either normal renal function or mild renal impairment.[7]

The base population PK model described the PK of ceftaroline fosamil and ceftaroline using a simultaneous modeling approach with a two-compartment disposition model each for ceftaroline fosamil and ceftaroline. The model parameterized the disposition kinetics in terms of clearance (CLcf), intercompartmental clearance, volume of distribution for central (Vccf) and peripheral (Vp1cf) compartment of ceftaroline fosamil; absorption rate constant of ceftaroline fosamil; and clearance (CLc), intercompartmental clearance, volume of distribution for central (Vcc), and peripheral compartment of ceftaroline. Allometric scaling of body weight on ceftaroline fosamil and ceftaroline clearances and volumes of distribution was applied, with exponents fixed to 0.75 and 1, respectively.[7]

In adults and pediatric subjects aged >2 years, the base model included effects of body surface area–normalized CrCL (nCrCL) on CLc and was adjusted for end-stage renal disease. For pediatric patients aged ≤2 years, a sigmoidal renal maturation function based on postmenstrual age[26] (fractional change in ceftaroline clearance due to maturation) replaced the term representing the effect of nCrCL on CLc.[7]

Updated population PK model

To enable comparison of exposures and PTA for potential pediatric high-dose regimens to adults receiving high-dose ceftaroline fosamil, the base population PK model was updated to incorporate additional data (previously not available for base model development) from 529 adults from three phase I studies (including 72 healthy or renally impaired subjects) and two phase III studies (including 371 patients with cSSTI in the high-dose COVERS trial and 86 patients with CAP; Table S1).[20,27–29] Model parameters were re-estimated using the combined data set. All prior clinical and demographic covariates were retained in the model, but separate patient effects on CLc and Vcc for the CAP and cSSTI populations were tested (healthy and renally impaired subjects were used as the reference group). Assessment of model adequacy and decisions about possible lack of fit or violation of assumptions were driven by the data and guided by goodness-of-fit criteria, including plots of (1) observed (dependent variable) versus population predicted values, (2) dependent variable versus individual predicted values, (3) conditional weighted residuals versus time, and (4) individual weighted residuals versus time.

Predictive performance of the updated PK model was evaluated by pcVPC, with stratification by study design variables and covariates, including age group, population (adults vs. pediatric patients), and type of infection (healthy and renally impaired [no infection] vs. cSSTI vs. CAP and suspected/confirmed infection). A total of 200 data sets with an identical design to the original data set were simulated using the final parameter estimates, including interindividual variability and residual variability but excluding model uncertainty. Median, 5th, and 95th percentiles of the simulated concentrations were plotted versus the time since last dose and compared with observed concentrations.

Exposure and PTA simulations

The updated population PK model was used to simulate ceftaroline exposures at steady state and perform PTA calculations. Simulations were performed for adults with normal renal function receiving the high-dose ceftaroline fosamil regimen evaluated in the COVERS study (600 mg 2-h infusions every 8 h)[20] and for a range of high-dose regimens in pediatric patients with normal renal function and mild, moderate, or severe renal impairment (nCrCL>80, ≥50 to <80, ≥30 to <50, and 30 ml/min/1.73 m^2, respectively). For adults, 300 patients

were simulated for each of the 100 simulated data sets (i.e., 30,000 simulated patients). For pediatric patients, 100 simulations were performed for each dose (mg/kg) and renal function category, with 100 patients in each 1-month age group (50% male, 50% female) for ages 2 to <24 months (i.e., 10,000 simulated patients/category), and 600 patients each in the age 2 to <6 years, 6 to <12 years, and 12 to <18 years groups (i.e., 60,000 simulated patients/category). Covariates for simulations are described in the Supplementary Methods. PK exposure parameters for ceftaroline at steady state, including area under the concentration-time curve over 24 h at steady state ($AUC_{0–24,ss}$) and median maximum plasma concentration ($C_{max,ss}$) were generated for pediatric patients and adults with normal renal function based on simulated plasma concentration-time profiles. Proportions of simulated patients achieving the percent time of free plasma concentration (%*f*T)>MIC values of 27%, 31%, and 35% (PK/PD targets for bacterial stasis, 1-$\log_{10}$ kill, and 2-$\log_{10}$ kill, respectively, for ceftaroline vs. *S. aureus*)[9,30] during a dosing interval were calculated using a free fraction value of 80%. PTA by MIC was calculated as the percentage of simulated patients who met the specified %*f*T>MIC targets (27%, 31%, and 35%) at MICs of 1, 2, and 4 mg/L. Pediatric dose recommendations were based on attainment of >90% PTA for the 2-$\log_{10}$ kill target and achievement of median $AUC_{24,ss}$ and $C_{max,ss}$ not appreciably greater than in adults with normal renal function receiving high-dose ceftaroline fosamil (600 mg 2-h infusions every 8 h).

Extrapolation of efficacy and safety

For extrapolation of efficacy, ratios of median predicted $C_{max,ss}$ and $AUC_{0–24,ss}$ for pediatric patients to adults with normal renal function receiving high-dose ceftaroline fosamil were calculated to compare steady-state systemic exposures. For safety, the similar estimated patient or indication effects for cSSTI and CAP (vs. healthy and renally impaired volunteers) on CLc and Vcc supported comparison across pediatric studies in patients with different infections. Median $C_{max,ss}$ 95% prediction intervals for the simulated pediatric high-dose regimens were compared with observed data from pediatric studies in subjects with CAP, cSSTI, or other suspected/confirmed acute infections and to adult data from the high-dose COVERS trial.

TABLE 2 Number of evaluable samples, pediatric patients, and subject demographics by age group

	Age group				
	≤28 days	≤28 days to <2 years	2 to <6 years	6 to <12 years	12 to <18 years
Number of subjects	23	64	102	73	42
Number of plasma samples[a]					
Ceftaroline fosamil	20	39	54	38	40
Ceftaroline	80	147	212	164	118
Sex, n (%)					
Male	15 (4.9)	40 (13.2)	57 (18.8)	40 (13.2)	20 (6.6)
Female	8 (2.6)	24 (7.9)	45 (14.8)	33 (10.9)	22 (7.2)
Type of infection, n (%)					
cSSTI	0	23 (7.6)	21 (6.9)	33 (10.9)	22 (7.2)
CAP	0	29 (9.5)	73 (24.0)	30 (9.9)	13 (4.3)
Suspected/confirmed infection	23 (7.6)	12 (4.0)	8 (2.6)	10 (3.3)	7 (2.3)
Body weight, kg					
Median (range)	3.3 (1.5–4.6)	9.5 (4.6–13.3)	16.7 (9.6–33.0)	28.1 (13.0–76.0)	57.6 (19.9–100.0)
Chronological age, years					
Median (range)	0.03 (0.003–0.077)	1.0 (0.18–1.9)	3.8 (2.1–6.0)	8.1 (6.0–11.9)	14.9 (12.0–18.0)
Gestational age, weeks[b]					
Median, weeks (range)	38.0 (32.0–40.0)	40.0 (25.0–40.0)	–	–	–
Baseline nCrCL, ml/min/1.73 m^2[c]					
Median (range)	53.6 (20.2–115.0)	110 (44.7–306.0)	114 (50.0–210.0)	114 (53.2–194.0)	102 (59.6–180.0)

Abbreviations: CAP, community-acquired pneumonia; cSSTI, complicated skin and soft-tissue infections; nCrCL, body surface area–normalized creatinine clearance.

[a]Excludes samples below the lower limit of quantification (0.01 mg/L for ceftaroline and 0.05 mg/L for ceftaroline fosamil).

[b]Assumed to be 40 weeks for subjects aged ≥2 years, when missing or not collected.

[c]Computed using the Schwartz bedside formula.

RESULTS

Study population

The final simultaneous population PK model for ceftaroline fosamil and ceftaroline included data from 1248 subjects (304 pediatric subjects [after exclusion of one subject with missing CrCL data] and 944 adults) contributing 2762 (ceftaroline fosamil) and 8860 (ceftaroline) measurable plasma concentrations. Compared with the previous population PK data set,[7] the additional 529 adults in the updated model contributed 1041 plasma ceftaroline fosamil and 4045 plasma ceftaroline concentrations (Table S1). The number of subjects and evaluable PK samples and demographics for the pediatric and adult subjects are shown in Tables 2 and 3, respectively.

Final population PK models

The population PK of ceftaroline fosamil and ceftaroline in pediatric (birth to <18 years) and adult subjects were adequately characterized using a simultaneous modeling approach with two-compartment disposition models for both ceftaroline fosamil and ceftaroline. Covariates identified in the prior model[7] were retained in the base model. The only covariate tested in the updated model was a separate patient/indication effect for cSSTI on CLc and Vcc (Table S2). The final population PK models were used to describe the combined pediatric and adult data, including the five additional adult studies. To stabilize the ceftaroline model, parameters for the maturation effects on clearance (CLc) and central volume of distribution (Vcc) were fixed to the values in the final model of the previous population PK analysis based on fewer adult subjects[7] as there were no additional pediatric data incorporated into the current analysis. While different than the reference group (healthy and renally impaired), separate patient or indication effects (cSSTI vs. CAP and suspected/confirmed infection) on CLc and Vcc were unnecessary. The estimated cSSTI effect on CLc was smaller than the effects for CAP and suspected/confirmed infection population (1.11 vs. 1.25), whereas the overall combined patient/indication effect on CLc was 1.16. The estimated patient/indication effect on Vcc was also similar across patient populations (cSSTI 1.76 vs. CAP and suspected/confirmed 1.68; overall 1.73). In general, the parameter estimates for ceftaroline were

TABLE 3 Number of evaluable samples and subject demographics by renal function for adults

	Renal function group[a]				
	Normal renal function	**Mild renal impairment**	**Moderate renal impairment**	**Severe renal impairment**	**End-stage renal disease**
Number of subjects	632	216	68	14	14
Number of plasma samples[b]					
Ceftaroline fosamil	2030	318	102	42	79
Ceftaroline	5951	1272	373	132	411
Sex, n (%)					
Male	318 (33.7)	126 (13.3)	34 (3.6)	9 (1.0)	10 (1.0)
Female	314 (33.3)	90 (9.5)	34 (3.6)	5 (0.5)	4 (0.4)
Type of infection, n (%)					
Healthy	195 (20.7)	39 (4.1)	11 (1.2)	8 (0.8)	14 (1.5)
cSSTI	352 (37.3)	84 (8.9)	22 (2.3)	5 (0.5)	0
CAP	85 (9.0)	93 (9.6)	35 (3.7)	1 (0.1)	0
Body weight, kg					
Median (range)	74.0 (40.6–134.0)	72.0 (41.0–120.0)	70.0 (40.0–121.0)	78.5 (58.0–125.0)	88.8 (61.4–115.0)
Chronological age, years					
Median (range)	41.0 (18.0–80.0)	66.0 (20.0–87.0)	75.0 (20.0–93.0)	66.5 (46.0–89.0)	49.5 (21.0–59.0)
Baseline nCrCL, ml/min/1.73 m^2					
Median (range)	110.0 (80.1–467.0)	64.3 (50.0–79.9)	42.4 (30.0–49.9)	24.9 (11.5–28.7)	10.0 (6.7–12.6)

Abbreviations: CAP, community-acquired pneumonia; cSSTI, complicated skin and soft-tissue infections; nCrCL, body surface area–normalized creatinine clearance.

[a]Normal renal function defined as nCrCL>80 ml/min/1.73 m^2; mild renal impairment defined as nCrCL ≥50 to 80 ml/min/1.73 m^2; moderate renal impairment defined as nCrCL ≥30 to <50 ml/min/1.73 m^2; severe renal impairment defined as nCrCL ≥15 to <30 ml/min/1.73 m^2; end-stage renal disease defined as nCrCL <30 ml/min/1.73 m^2.; [b]Excludes samples below the lower limit of quantification (0.01 mg/L for ceftaroline and 0.05 mg/L for ceftaroline fosamil).

comparable between the base and the final models (Table S3). All parameters were well estimated, with relative standard errors <11%, including interindividual variability. With the introduction of new data from the five additional adult studies, most parameters in the final model did not deviate by >10%, except for ceftaroline fosamil PK (CLcf increased 28.3%, Vccf increased 28.2%, and Vp1cf decreased 16.2%). The addition of new adult data from the two phase III studies including COVERS (predominantly from sparse PK sampling) significantly increased interindividual variability on CLcf (from 72.9% to 130%) and Vccf (from 87.7% to 155%) as well as on CLc (from 24.2% to 31.4%) and Vcc (from 32.9% to 42.7%).

The pcVPCs for ceftaroline using the final population PK model stratified by age group in pediatric subjects and dosing method in adults (Figure 1) and stratified by population (pediatric or adult) and type of infection (Figure 2) demonstrated that the final model was suitable for simulations in adults and pediatric age groups aged ≥2 months as the medians of the simulated data overlapped with the observed data in all scenarios. The NONMEM code and goodness-of-fits plots for the final model are available in the Supplementary Results and Figure S1, respectively. When stratified by age group, the conditional individual weighted residuals were reasonably normally distributed (Figure S2).

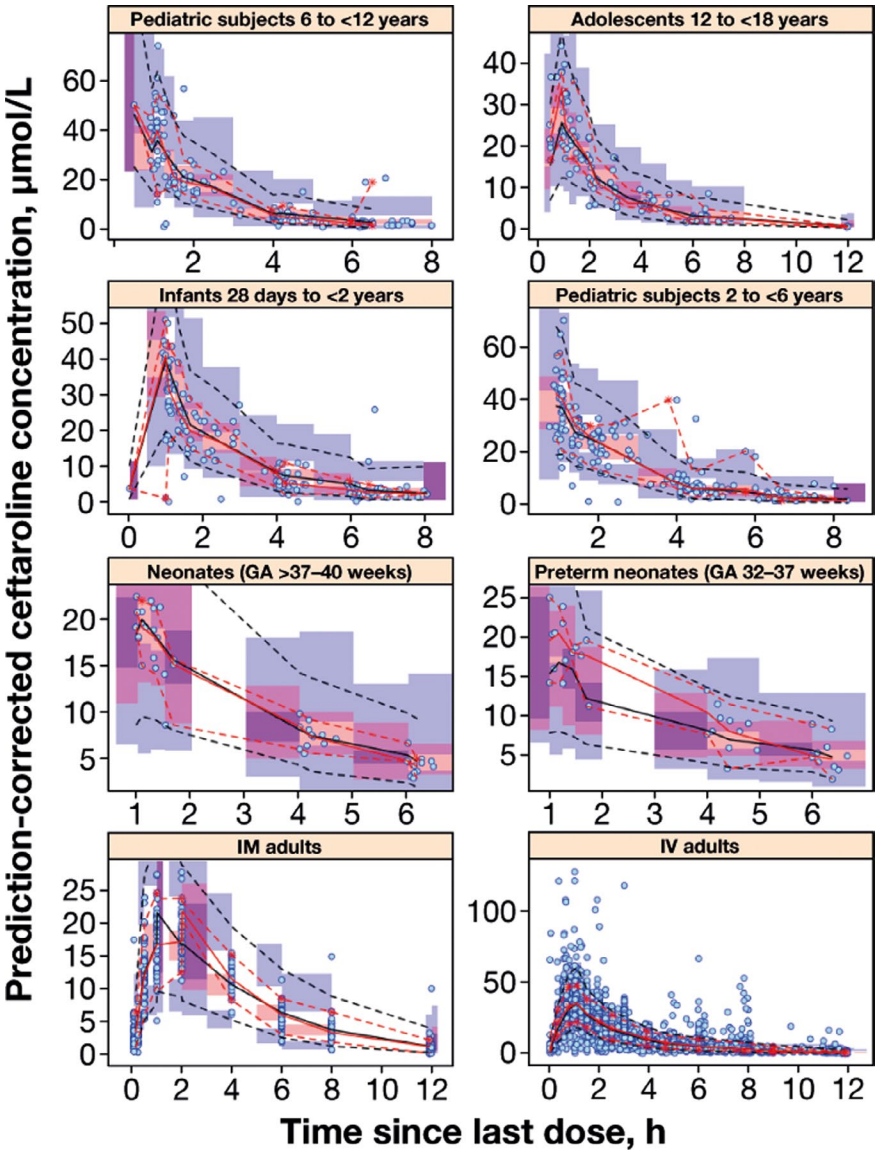

FIGURE 1 Prediction-corrected visual predictive check for the final ceftaroline population pharmacokinetics model stratified by age group. Symbols, observed ceftaroline concentrations; red solid and broken lines, median, 5th, and 95th confidence intervals of the observed data; black solid and broken lines, median, 5th, and 95th confidence intervals from 200 simulations with surrounding 95% shaded area in pink and blue. GA, gestational age; IM, intramuscular; IV, intravenous

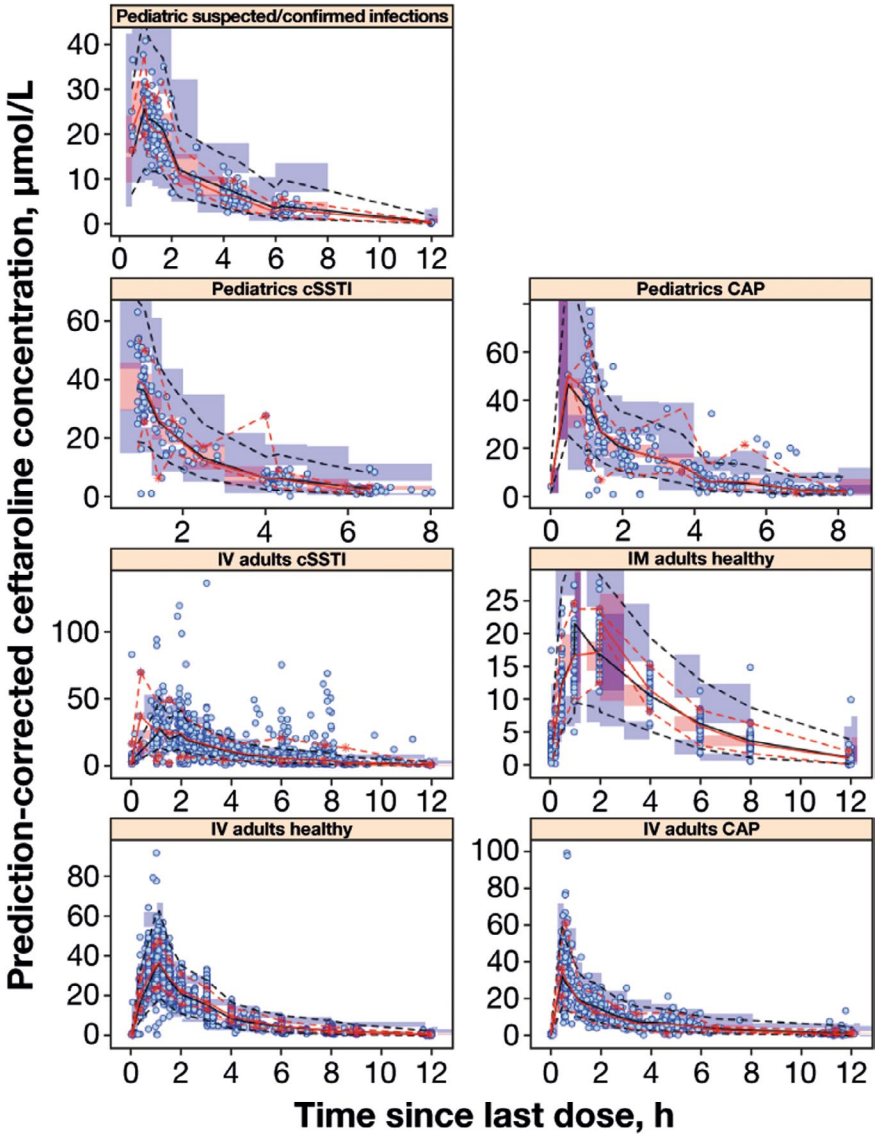

FIGURE 2 Prediction-corrected visual predictive check for the final ceftaroline population pharmacokinetics model stratified by population and type of infection. Symbols, observed ceftaroline concentrations; red solid and broken lines, median, 5th, and 95th confidence intervals of the observed data; black solid and broken lines, median, 5th, and 95th confidence intervals from 200 simulations with surrounding 95% shaded area in pink and blue. CAP, community-acquired pneumonia; cSSTI, complicated skin and soft tissue infections; IM, intramuscular; IV, intravenous

Exposure and PTA simulations

Steady-state ceftaroline exposures and PTA results for the approved high-dose regimens based on simulated pediatric patients with cSSTI with normal renal function or renal impairment and adults with normal renal function receiving high-dose ceftaroline fosamil (600 mg 2-h infusions every 8 h) are shown in Table 4. Across the approved pediatric doses and renal function groups, the median predicted ceftaroline $C_{max,ss}$ ratios to adults were 0.907 to 1.33, and median $AUC_{24,ss}$ ratios were 0.94 to 1.41. PTAs for the *S. aureus* PK/PD target of 35% *f*T>2 mg/L in simulated pediatric patients ranged from 99.5% to 100%, and from 80.8% to 98.7% for 35% *f*T>MIC of 4 mg/L.

Extrapolation of efficacy and safety

Median pediatric to adult $C_{max,ss}$ and $AUC_{24,ss}$ ratios (Table 4) were close to 1 and within the ranges reported in a systematic review of exposure matching and exposure agreement for adult and pediatric patients.[31] Considered together with the PTA results indicating that the simulated pediatric high-dose regimens achieved predicted PK/PD target attainment similar to or exceeding those in adults, the findings support extrapolation of efficacy from adults.

For extrapolation of safety, median predicted ceftaroline $C_{max,ss}$ values for the approved pediatric high doses (Table 4) were compared with observed data from five single-dose and multiple-dose studies of ceftaroline fosamil in pediatric

TABLE 4 Steady-state ceftaroline exposures and PTA based on simulations for adults with normal renal function and pediatric patients (aged ≥2 months to <18 years) by renal function: ceftaroline fosamil high-dose regimens

Age group	Ceftaroline fosamil dose (2-h i.v. infusions every 8 h)	$C_{max,ss}$ (mg/L)[a]	$AUC_{24,ss}$ (mg/L*h)[a]	$C_{max,ss}$ ratio to adults	$AUC_{24,ss}$ ratio to adults	35% *f*T>MIC of 2 mg/L	35% *f*T>MIC of 4 mg/L
Normal renal function							
Adults	600 mg	18.4 (10.4, 32.2)	155 (85.7, 285.0)	–	–	99.7	82.7
12 to <18 years	12 mg/kg (max 600 mg)	21.7 (12.6, 35.9)	173 (99.1, 299.0)	1.18	1.12	99.8	90.2
6 to <12 years		23.5 (14.5, 37.5)	178 (106, 302.0)	1.28	1.15	99.8	91.8
2 to <6 years		21.4 (13.2, 33.9)	153 (90.9, 258.0)	1.16	0.987	99.5	81.8
12 to <24 months	10 mg/kg	19.2 (11.9, 30.4)	146 (86.9, 247.0)	1.04	0.940	99.7	80.8
2 to <12 months		20.3 (12.6, 32.0)	168 (98.9, 284.0)	1.11	1.08	99.9	90.8
Mild renal impairment							
Adults (normal)	600 mg	18.7 (10.5, 33.5)	158 (86.8, 293.0)	-	-	99.7	83.7
12 to <18 years	12 mg/kg (max 600 mg)	23.2 (13.5, 38.6)	193 (111, 334.0)	1.23	1.22	100.0	94.6
6 to <12 years		24.9 (15.3, 39.7)	197 (116, 333.0)	1.33	1.25	100.0	95.3
2 to <6 years		22.7 (14.1, 36.1)	170 (101, 286.0)	1.22	1.08	99.8	89.7
12 to <24 months	10 mg/kg	21.8 (13.3, 35.2)	183 (104, 322.0)	1.16	1.16	99.9	93.0
2 to <12 months		23.2 (14.1, 37.3)	210 (119, 370.0)	1.23	1.32	100.0	97.0
Moderate renal impairment							
Adults (normal)	600 mg	18.7 (10.5, 33.5)	158 (86.8, 293.0)	–	–	99.7	83.7
12 to <18 years	10 mg/kg (max 400 mg)	18.2 (10.4, 31.6)	168 (94.2, 299.0)	0.974	1.06	100.0	88.7
6 to <12 years		23.1 (14.1, 37.0)	201 (119, 338.0)	1.23	1.28	100.0	96.8
2 to <6 years		21.7 (13.4, 34.4)	178 (106, 301.0)	1.16	1.13	100.0	93.2
Severe renal impairment							
Adults (normal)	600 mg	18.7 (10.5, 33.5)	158 (86.8, 293.0)	–	–	99.7	83.7
12 to <18 years	8 mg/kg (max 300 mg)	17.0 (9.58, 30.0)	178 (98.7, 326.0)	0.907	1.13	100.0	91.2
6 to <12 years		22.3 (13.5, 36.1)	222 (130, 379.0)	1.19	1.41	100.0	98.7
2 to <6 years		21.2 (13.1, 33.9)	200 (119, 343.0)	1.13	1.27	100.0	97.2

Note: Normal renal function and mild, moderate, and severe renal impairment defined as nCrCL ≥80, ≥50 to <80, ≥30 to <50, and <30 ml/min/1.73 m^2, respectively. %*f*T>MIC, percent of time that free plasma concentration is above minimum inhibitory concentration; $AUC_{24,ss}$, area under the plasma concentration-time curve over 24 h at steady state; $C_{max,ss}$, maximum concentration at steady state; i.v., intravenous; nCrCL, body surface area–normalized creatinine clearance; PTA, probability of target attainment.

[a]Median (5th, 95th percentiles) based on a summary of 100 trials; corresponds to median (90% prediction interval).

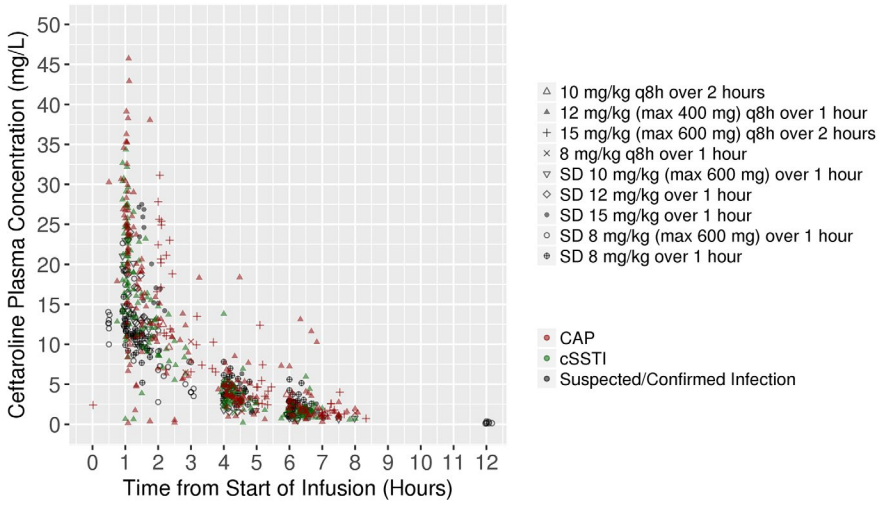

FIGURE 3 Observed ceftaroline concentrations versus time since last dose for pediatric subjects treated with single-dose and multiple-dose ceftaroline fosamil. CAP, community-acquired pneumonia; cSSTI, complicated skin and soft tissue infections; q8h, every 8 h; SD, single dose

subjects (Figure 3). Of note, median simulated $C_{max,ss}$ values across the approved pediatric high-dose regimens and renal function groups were below the highest observed ceftaroline concentrations from sparse sampling observed in a phase IV, high-dose ceftaroline fosamil study in pediatric patients with complicated CAP and in a phase II/III study of standard-dose ceftaroline fosamil (given as 1-h i.v. infusions) in pediatric patients with acute bacterial skin and skin structure infections (ABSSSIs).[32,33] In the study in pediatric patients with complicated CAP, there were no serious adverse events related to high-dose ceftaroline exposure (10 or 15 mg/kg every 8 h 2-h infusions, up to a maximum daily dose 1800 mg).[32] In the study of standard-dose ceftaroline fosamil in pediatric patients with cSSTI, there were two instances (<5%) of drug-related serious adverse events (*Clostridium difficile* colitis and hypersensitivity) and no deaths; neither of these events are considered related to high exposure. In addition, the upper bounds of the 95% median $C_{max,ss}$ prediction intervals for the approved pediatric high doses were all <40 mg/L (Table 4). In adults with cSSTI in the high-dose COVERS trial, the highest observed concentration was 74.3 mg/L, and there were seven other patients with concentrations >40 mg/L (unpublished data).

DISCUSSION

The current population PK analysis was undertaken, with regulatory agency agreement, in lieu of a previously planned prospective clinical trial to evaluate the efficacy and safety of high-dose ceftaroline fosamil in pediatric patients with cSSTI. While the analysis fulfilled its primary objective of providing predictive information to support the selection of ceftaroline fosamil pediatric high-dose regimens, an inherent limitation concerns the inability of this approach to provide forward evaluation of model predictions. The lack of patients with impaired renal function in the pediatric data set, and the absence of efficacy data for high MIC *S. aureus* isolates in adults, are further limitations. It should also be emphasized that the high-dose recommendations are specifically for patients with cSSTI caused by rare *S. aureus* isolates with ceftaroline MIC >1 mg/L. There are no corresponding high-dose recommendations approved for either adults or children with CAP. Notwithstanding the availability of ceftaroline fosamil high-dose regimens, the identification of high MIC *S. aureus* isolates in either adult or pediatric patients should prompt discussion between the microbiology laboratory and clinical teams.

Clinical trials in pediatric populations can be challenging to conduct for ethical, logistical, and technical reasons, prompting regulatory agencies to publish guidance on the use of extrapolation approaches in the development of medicinal products for pediatric use.[34–36] MIDD, including the use of modeling and simulation to predict clinical outcomes and evidence of effectiveness, is integral to antibacterial development as true dose-ranging efficacy studies for drugs to treat serious infections cannot ethically be conducted.[37–39] MIDD has been widely used to support dose selection, optimizing and informing clinical trial design, particularly in pediatric drug development because of the challenges in subject recruitment and the limitations of blood sample collection.[37]

In the current analysis, the population PK of ceftaroline fosamil and ceftaroline in pediatric subjects (birth to <18 years) with CAP, cSSTI, or suspected/confirmed infection and healthy adult volunteers, adult subjects with various degrees of renal function, and adults with CAP or cSSTIs were adequately characterized using a simultaneous modeling approach with two-compartment disposition models. As there were no significant patient or indication effect differences on CLc and Vcc for cSSTIs and CAP (vs. healthy and

renally impaired volunteers), the final population PK model without separation of patient or indication effects was used for exposures and PTA simulations. PK parameter estimates for ceftaroline were comparable between the base[7] and final models. With the introduction of new data from five adult studies, including COVERS (phase III high-dose in adults with cSSTI), most PK parameters (other than structural parameters for ceftaroline fosamil: CLcf, Vccf, and Vp1cf) deviated by <10%.

For drug development in pediatrics, it can be challenging to obtain extensive clinical trial data, especially in very young patients, and extrapolation approaches, that is, extending information and conclusions available from studies in one or more subgroups of the source population to make inferences for another target population, are encouraged by the major regulatory agencies.[34,36] An extrapolation approach to guide ceftaroline fosamil dosage recommendations, in place of a prospective clinical trial, was considered appropriate for the indication of cSSTI in pediatric patients caused by *S. aureus* isolates with high ceftaroline MIC.[25] Data from global surveillance studies indicate that the majority of *S. aureus* isolates from pediatric subjects have ceftaroline MIC ≤1 mg/L (unpublished data), and given that no isolates with ceftaroline MIC >1 mg/L were observed in the COVERS trial (apart from in one patient in an MRSA-focused expansion period),[20] such a trial in pediatric patients would be unlikely to recruit a sufficient number of patients.

The matching of systemic drug exposures from adults to pediatric patients is commonly used to guide dose selection in pediatric patients and relies on assumptions that the course of disease, drug responses, and exposure-response relationships are comparable between the adult and intended pediatric populations.[31,40] Across pediatric age and renal function groups, ceftaroline $C_{max,ss}$ ratios (relative to adults with normal renal function) were 0.907 to 1.33, and $AUC_{24,ss}$ ratios were 0.940 to 1.41. These values are within the ranges reported in a systematic review of exposure matching and exposure agreement for adult and pediatric patients.[31] Since no patients with *S. aureus* with ceftaroline MIC >1 mg/L were identified in the main COVERS study, no prospective efficacy data are available for the high-dose adult regimens against isolates with MICs of 2 or 4 mg/L; instead, approval of the adult high-dose regimens was based on exposure and PTA simulations demonstrating >90% PTA for MICs of 2 mg/L and 4 mg/L, respectively, using the PK/PD target of 35% *f*T>MIC.[9] The current analysis demonstrating that the approved high-dose regimens achieved similar predicted exposures for pediatric patients with cSSTI compared with adults with normal renal function receiving ceftaroline fosamil 600 mg every 8 h thus extends the existing rationale for adult high-dose regimens to pediatric subjects ages ≥2 months to <18 years. Notably, PTA in pediatric patients was >99% for MICs of 2 mg/L. For MICs of 4 mg/L, PTA was close to or greater than 90% for all age and renal function groups except for those in the 2 to <6 years and 12 to <24 months (normal renal function) groups, for whom PTA was 81.8% and 80.8%, respectively; these are similar to the equivalent PTA for adults (82.7%).

Extrapolation of safety was done for populations with similar patient characteristics, making use of available data from pediatric subjects with CAP, cSSTI, and with suspected or confirmed infection, including doses higher than the approved pediatric standard doses of 8 or 12 mg/kg 1-h infusions every 8 h. Median predicted ceftaroline $C_{max,ss}$ values for simulated pediatric patients were below the highest observed concentrations in studies of high-dose ceftaroline fosamil in pediatric patients with CAP and of standard-dose ceftaroline fosamil in pediatric patients with ABSSSIs.[32,33] Moreover, the 95th percentiles of median ceftaroline $C_{max,ss}$ prediction intervals in simulated pediatric patients were all <40 mg/L, well below the highest observed concentration in adults in the COVERS trial. Hence the safety profile of the approved pediatric high-dose regimens can be expected to be consistent with that observed in these prospective randomized trials. A recent systematic review and meta-analysis of pediatric antibiotic trials including >27,000 patients concluded that "adverse events were predictable and class-specific, and no unexpected (age-specific) side effects were identified"[41]; this is supportive of the expected safety profile of high-dose ceftaroline fosamil based on the extrapolations noted previously. Moreover, the wide therapeutic index of β-lactams provides additional assurance that increased exposures with high-dose ceftaroline fosamil regimens are unlikely to be associated with toxicity, thus further facilitating extrapolation of safety for the current analysis.[42]

In conclusion, exposure and PTA simulations based on an updated population PK model showed that the proposed pediatric high-dose regimens (included in the European product labeling in 2019) achieved predicted ceftaroline steady-state exposures comparable with those in adults with normal renal function receiving ceftaroline fosamil 600 mg 2-h infusions every 8 h. For the approved pediatric high-dose regimens, PTA for 35% *f*T>MIC of 2 mg/L was >99%. For MIC of 4 mg/L, PTA for this target was >80% (i.e., similar to or exceeding that predicted for adults with normal renal function). These analyses support extrapolating efficacy by exposures and PTA from adult to pediatric patients ≥2 months to <18 years and extrapolating safety data across pediatric indications by matching PK predictions.

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CONFLICT OF INTEREST

P.L.S.C., L.M., A.Q., H.L.-T., V.M.H., J.H., and S.R. are employees of and shareholders in Pfizer.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. A.Q., H.L.-T., V.M.H., J.H., and S.R. designed the research. A.Q., H.L.-T., V.M.H., J.H., and S.R. performed the research. P.L.S.C., L.M., and S.R. analyzed the data.

DATA AVAILABILITY STATEMENT

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the United States and/or European Union or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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