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ORIGINAL ARTICLE

Comparison between physiologically based pharmacokinetic and population pharmacokinetic modelling to select paediatric doses of gepotidacin in plague

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Aims: To develop physiologically based pharmacokinetic (PBPK) and population pharmacokinetic (PopPK) models to predict effective doses of gepotidacin in paediatrics for the treatment of pneumonic plague (*Yersinia pestis*).

Methods: A gepotidacin PBPK model was constructed using a population-based absorption, distribution, metabolism and excretion simulator, Simcyp®, with physicochemical and in vitro data, optimized with clinical data from a dose-escalation intravenous (IV) study and a human mass balance study. A PopPK model was developed with pooled PK data from phase 1 studies with IV gepotidacin in healthy adults.

Results: For both the PopPK and PBPK models, body weight was found to be a key covariate affecting gepotidacin clearance. With PBPK, ~90% of the predicted PK for paediatrics fell between the 5th and 95th percentiles of adult values except for subjects weighing ≤5 kg. PopPK-simulated paediatric means for C_{max} and $AUC_{(0-\tau)}$ were similar to adult exposures across various weight brackets. The proposed dosing regimens were weight-based for subjects ≤40 kg and fixed-dose for subjects >40 kg. Comparison of observed and predicted exposures in adults indicated that both PBPK and PopPK models achieved similar AUC and C_{max} for a given dose, but the C_{max} predictions with PopPK were slightly higher than with PBPK. The two models differed on dose predictions in children <3 months old. The PopPK model may be suboptimal for low age groups due to the absence of maturation characterization of drug-metabolizing enzymes involved with clearance in adults.

Conclusions: Both PBPK and PopPK approaches can reasonably predict gepotidacin exposures in children.

KEYWORDS
simulation, modelling, PBPK, pharmacodynamics, population analysis

1 | INTRODUCTION

Antibiotic resistance has been widely recognized as a serious threat to public health worldwide.[1] Research efforts in recent years have become increasingly geared towards discovering and developing new classes of antibiotics with modes of action distinct from those of established agents and activity against resistant strains.

Gepotidacin (GSK2140944) is a novel, first-in-class triazaacenaphthylene antibiotic that inhibits bacterial DNA replication by a distinct mechanism of action which confers activity against most strains of *E. coli*, *S. saprophyticus* and *N. gonorrhoeae*,[2,3] including those resistant to current antibiotics.[4–6] Gepotidacin is in a class of antibiotics known as the bacterial type II topoisomerase inhibitors (BTIs) that prevent bacterial DNA replication by inhibiting bacterial DNA gyrase and topoisomerase IV (homologous type II topoisomerases), which are clinically validated antibacterial targets inhibited by the quinolone family of antibiotics. BTIs and quinolones bind to a similar region of the same target proteins, but they recognize distinctly different amino acids, therefore they inhibit different stages of the catalytic cycle of the target proteins.

Gepotidacin is being developed as part of a public-private partnership between GlaxoSmithKline, the Defense Threat Reduction Agency (DTRA) and the Biomedical Advanced Research and Development Authority (BARDA). Gepotidacin has in vitro activity against susceptible and drug-resistant pathogens associated with a range of conventional and biothreat infections. The efficacy of gepotidacin has been determined in several animal infection models: *Neisseria gonorrhoeae* in a vaginal colonization model; *Escherichia coli* in a pyelonephritis model; *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus* in a lung infection model; *S. aureus* in a subcutaneous abscess model; and *S. pneumoniae* and *S. aureus* in a thigh infection model. In addition, gepotidacin demonstrated activity in both in vitro and in animal models against *Yersinia pestis* causing plague, *Francisella tularensis* causing tularemia and *Bacillus anthracis* causing anthrax. *Y. pestis* is considered a potential agent for bioterrorism, given infection through aerosol and the delay for clinical symptoms postinfection, allowing people to travel and spread the disease before diagnosis.[7] Although there are several antibiotics approved for the treatment of plague, including fluoroquinolones and tetracyclines, gepotidacin would be a potential life-saving treatment option for drug-resistant plague.

While gepotidacin has been administered to adults in clinical trials to describe its safety, pharmacokinetics (PK) and efficacy to nonbiothreat infections,[5,8–11] it has not yet been administered to the paediatric population. The elimination of gepotidacin is primarily renal (approximately 40-50%) and via the oxidative metabolism (approximately 30-35%) by the cytochrome P450 3A4 (CYP3A4) enzyme. Both CYP3A4 and renal function undergo maturational changes during the postnatal age,[12] factors which need to be considered for paediatric subjects. It would not be feasible to conduct paediatric studies for the treatment of certain diseases such as plague, therefore modelling and simulation approaches must be utilized for the selection of optimal dose regimens. Population pharmacokinetic (PopPK) modelling is the classical approach that uses PK data from adults to predict dosing regimens in the paediatric population. Within PopPK modelling, allometric scaling is used to predict paediatric PK while also considering efficacy and safety data obtained from adult subjects (or from preclinical studies for biothreat indications). In the last decade, there has been increased popularity in using a physiologically based pharmacokinetic (PBPK) modelling approach to characterize paediatric PK and predict doses in advance of conducting paediatric trials to minimize the burden in this population.[13–19] PBPK modelling factors in the physiology, pharmacology and mechanistic information for simulating drug exposures in populations of interest. With its unique structure, a PBPK model can account for intrinsic factors such as age-dependent changes in various drug disposition pathways, making it a comprehensive and mechanistic tool to predict gepotidacin exposure in paediatric subjects.

As mentioned above, exposures associated with efficacy and safety data are traditionally obtained from adult subjects. However, in the case of biothreat indications, the efficacy is derived from preclinical models. The United States Food and Drug Administration (FDA) Animal Rule provides the basis to establish efficacy in support of human treatment, using a well-characterized animal efficacy model, in cases where it is not practical or ethical to conduct testing in human patients.[20] The African Green Monkey (AGM) pneumonic plague model has been shown to have similarities to human pneumonic plague and has been recognized as a suitable model to study therapeutic agents. These animal studies are designed to provide pivotal efficacy data under the FDA Animal Rule and to predict effective clinical dosing regimens for pneumonic plague.

In an effort to predict the gepotidacin paediatric dose for plague, both PopPK and PBPK models were initially developed and

What is already known about this subject

- Physiologically based pharmacokinetic (PBPK) and population pharmacokinetic (PopPK) modelling are commonly used to predict paediatric pharmacokinetics.
- PopPK modelling has been used to support paediatric clinical trial design and dosage selection using adult PK information (with or without ontogeny).
- PBPK allows for the incorporation of physiological differences between adults and paediatrics.

What this study adds

- Both the PopPK and PBPK models can be good predictors of gepotidacin dosing in a paediatric population.

TABLE 1 List of studies used for PBPK and PopPK modelling

Study	Subject population	Study information	Gepotidacin dose (IV)	Mean age, years (standard deviation)	PBPK model	PopPK model
115 198	Healthy volunteers including Japanese population (SD, N = 29) (RD, N = 48)	A two-part study to evaluate the safety, tolerability and pharmacokinetics of single and repeat IV doses of GSK2140944 in healthy adult subjects	SD: 1-h (200/600/1200/1800 mg) and 2-h (1800 mg) infusions RD: BID 2-h (400/750/1000 mg) and TID 2-h (1000 mg) infusions SD: 400, 750, 1000 and 1800 mg RD: 1500 mg	SD: 28.7 (9.95) RD: 26.6 (5.54)	Model development	(Initial model development)
115 774	Healthy volunteers (N = 6)	An open-label, nonrandomized, two-period, crossover, mass balance study to investigate the recovery, excretion and PK of ^{14}C-GSK2140944 administered as a single intravenous and single oral dose to healthy adult male subjects (ADME study)	1000	38.2 (7.44)	Model verification	(Initial model verification)
115 775	Healthy volunteers (N = 52)	A phase I, randomized, double-blinded, placebo- and moxifloxacin-controlled, four-period crossover study to evaluate the effect of GSK2140944 on cardiac conduction as assessed by 12-lead electrocardiogram in healthy volunteers	1000, 1800 mg SD	30.8 (9.03)	Model verification	(Initial model development)
116 666	Healthy volunteers (N = 22)	An open-label study to evaluate plasma and pulmonary PK following intravenous administration of GSK2140944 in healthy adult subjects	1000 mg SD	36.5 (9.79)		(Initial model development)
116 849	Renal impaired patients (N = 24)	A phase I, open-label, single-dose, multipart study to assess the PK of gepotidacin (GSK2140944) in male and female adult subjects with varying degrees of renal impairment and in matched control subjects with normal renal function	750 mg SD	65.0 (11.13)	Model verification	
116 704	ABSSSI patients (N = 109)	A phase II, randomized, two-part, multicentre, dose-ranging study in adult subjects evaluating the safety, tolerability and efficacy of GSK2140944 in the treatment of subjects with suspected or confirmed gram-positive acute bacterial skin and skin structure infections	750 mg q12h, 1000 mg q12h, 1000 q8h up to 10 days	44.7 (11.36)		(Final model development)

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; ADME, absorption, distribution, metabolism and excretion; IV, intravenous; N, number of subjects; q8h, every 8 h; q12h, every 12 h; RD, repeat dose; SD, single dose.

qualified using clinical PK data from adults in light of the AGM exposures associated with efficacy and safety. The current report presents the PopPK and PBPK model development, as well as simulations conducted to predict the paediatric dose regimens for gepotidacin in plague. A comparison between both approaches focused on predicting paediatric doses of gepotidacin is also presented. The selection of the paediatric dosage was guided by the dose at which majority of the predicted gepotidacin exposure fell within the 5th and 95th percentiles of the estimated range in adults.

2 | METHODS

2.1 | PBPK model development, qualification and paediatric dose selection

The paediatric PBPK model and workflow (Supporting Information Figure S1) were developed following FDA guidance. A full PBPK model for gepotidacin was previously constructed in the adult population for renal impairment dosing justification.[11] This base gepotidacin PBPK model for adult subjects was constructed using a population-based absorption, distribution, metabolism and excretion (ADME) simulator, Simcyp® version 16, and developed using "middle-out" approaches through integration of gepotidacin-specific physicochemical properties, in vitro ADME drug-dependent parameters and human PK obtained after intravenous (IV) dosing of 1000 mg over 2 hours in a virtual Caucasian population of healthy adult subjects. The model incorporated the relative contribution from CYP3A4 and renal clearance to drug clearance with the assumption that 100% of the drug metabolism was by CYP3A4.[8] The fraction of the hepatic clearance carried out by CYP3A4 was assigned as 0.25 and calculated renal clearance was 16 L/h (~40-45% of total systemic clearance).[11] A description of these studies and the simulation input parameters is provided in Table 1 and Supporting Information Table S1, respectively. Virtual healthy Caucasian and Japanese adult populations and adult subjects with renal impairment were used to verify and qualify the gepotidacin model against the clinical PK results from two clinical studies.

The PBPK model was verified by comparing simulated PK at various dosing regimens with the available clinical data in healthy Caucasian adults (Supporting Information Figure S1). The verified model was then qualified in Japanese populations and in renal impairment populations for which gepotidacin PK data were available to gain confidence in the predictive ability and robustness of the PBPK model.

2.1.1 | Model development and verification with clinical data in adults

For the model development, the PK simulations for single doses (SDs) ranging from 400 mg to 1800 mg of gepotidacin administered as an IV infusion over 2 hours to healthy adult Caucasian subjects was compared to the exposure from the single ascending dose study (Table 1). This developed model was further verified and qualified with the PK of gepotidacin in healthy adult Japanese in both moderate and severe renal impaired populations. The simulation was carried out for a SD of 750 mg gepotidacin IV infusion over 2 hours.

Furthermore, the gepotidacin PBPK model was verified for PK with repeat IV dosing regimens in healthy adult Caucasian subjects, in which 1500 mg of gepotidacin was administered as a single dose IV infusion over 3 hours on day 1 and a three-times-daily (TID) dose IV infusion over 3 hours on days 3 to 12 (repeat dosing interval of 8 hours). The sampling interval used in all simulations was every 0.25 hours.

The sensitivity analysis for hepatic intrinsic clearance as well as the renal clearance contribution were performed by simulation against gepotidacin exposure with the 1000 mg single dose IV infusion over 2 hours (Supporting Information Figures S2 and S3) using the Simcyp automated sensitivity analysis (ASA) tool. This allowed for evaluation of the two major elimination pathways for gepotidacin as incorporated in the PBPK model. The impact of the major elimination routes (intrinsic clearance CYP3A4 and the total renal clearance) on AUC and C_{max} was evaluated.

Using the verified gepotidacin PBPK model, simulations were performed with the Simcyp "Virtual Healthy Volunteer Population" for 10 trials of 100 individuals per trial, with a proportion of females of 0.5 and ages ranging from 20 to 50 years old. From the simulated profiles, the 5th, 50th (median) and 95th percentiles of the predicted steady-state C_{max} and $AUC_{(0-\tau)}$ were used as the reference lines for evaluation and selection of the paediatric dosing regimens.

2.1.2 | Dose selection for the paediatric population

Using the validated PBPK model, gepotidacin exposure was simulated in the Simcyp paediatric module with N = 1000 virtual healthy paediatric subjects in an age group range from approximately 1 day to 20 years old (10 trials, 100 subjects/trial). Various doses of gepotidacin were administered as IV infusion TID over 2 hours based on body weight since clearance of gepotidacin was shown to be affected by body weight in the adult healthy population (Supporting Information Figure S4).

Gepotidacin has been shown to be a CYP3A4 substrate in vitro. The default ontogeny profiles of CYP3A4 in Simcyp were used with a time of maturation for hepatic CYP3A4. The default age-dependent value for the glomerular filtration rate in Simcyp was also used in the paediatric model. As the active uptake renal transporter for tubular secretion of gepotidacin is unknown, this paediatric model only reflected the impact of passive filtration on gepotidacin exposure. To simulate gepotidacin exposure in various age groups, several dose regimen settings were attempted using fixed dose versus dose based on body weight. Selection of the paediatric dosage was guided by the dose at which majority of the predicted gepotidacin exposure fell within the 5th and 95th percentiles of the estimated range in adults.

2.2 | PopPK model development, qualification and paediatric dose selection

All modelling and simulations were performed using NONMEM® program version 7.2 (ICON, Ellicott City, Maryland, USA).

A PopPK model for gepotidacin was previously developed using data from IV infusion in healthy adults and patients with acute bacterial skin and skin structure infections (ABSSSI).[21]

An initial PopPK model was developed using healthy subject data (N = 134) from three different studies, ie, a phase I study BTZ115198 (N = 59), TQTc study BTZ115775 (N = 53) and study BTZ11666 (N = 22) (Table 1). An external validation of the model was done with healthy subject data from ADME study BTZ115774 (N = 6). A base PopPK model was then developed using all healthy subject data (N = 140) and the model was qualified by predicting patient data from the phase II ABSSSI study BTZ116704 (N = 109). A final base model included pooled data from four phase I studies in healthy adult subjects (N = 140) consisting of single IV 1-hour (200/600/1200/1800 mg) and 2-hour (1800 mg) infusions, repeat twice-daily (BID) 2-hour (400/750/1000 mg) and TID 2-hour (1000 mg) infusions, and PK data from a phase II ABSSSI study (N = 109) consisting of BID 2-hour (750 and 1000 mg) and TID 2 hour (1000 mg) infusions (Table 1). The structural model was a three-compartment model with first-order absorption and elimination. The final covariate model included clearance scaled based on body weight using a power model with an exponent of ¾ and centred on a typical adult body weight of 70 kg. Body weight was also a significant predictor of intercompartmental clearance, and central and peripheral volumes of distribution. There was no difference in the PK of gepotidacin between healthy subjects and the ABSSSI patient population. The final covariate population PK model parameter estimates are provided in Supporting Information Table S2.

The predictive performance of the final covariate model was validated through visual predictive check (VPC) simulations by dose and regimen (750 mg IV 2-hour infusion BID, 1000 mg IV 2-hour infusion BID, 1000 mg IV 2-hour infusion TID). The validated PopPK model was used to simulate 250 replicates of the original dataset (single and repeat ascending dose) providing 1500 subjects per dose group (6 total dose groups) was simulated to calculate 5th and 95th percentile ranges of the predicted concentrations.

2.2.1 | Weight versus exposure simulations in adults

A simulation dataset was created with adult subjects (N = 200, weight range 49.5-117.9 kg, age range 18-71 years) who were given a fixed dose of 1000 mg TID via a 2-hour IV infusion for 10 days. Exposures ($AUC_{[0-\tau]}$ and C_{max}) were simulated (500 simulations/subject) at steady state and are summarized at the 5th, 50th and 95th percentiles to derive exposure limits in adults.

2.2.2 | Dose evaluation for the paediatric population

The validated PopPK model for gepotidacin in adults was adapted for the paediatric population and used to simulate exposures ($AUC_{[0-\tau]}$ and C_{max}) in paediatrics. For this purpose, two data sources were used to build a simulation dataset. The first source was from the CDC growth charts and tables for children, which provided data for paediatrics ranging from 2 to 20 years of age and corresponding median body weights ranging from 2 to 79 kg. The second source was a dataset developed using ModelRisk® with simulated age and weight from a joint distribution that provided data for paediatrics from 0.01 to 12 years of age, created based on a WHO Growth Chart (http://www.who.int/childgrowth/standards/weight_for_age/en/). Various doses of gepotidacin were simulated as IV infusion TID over 2 hours based on body weight since clearance of gepotidacin was shown to be affected by body weight in the adult healthy population. The subjects in the dataset were categorized into four weight groups similar to that derived by the PBPK model (≤5, >5 to ≤10, >10 to ≤40 and >40 kg receiving doses of 13, 16 and 19 mg/kg and 1000 mg, respectively). The final simulation dataset contained 400 subjects (N = 100 per cohort, weight range 2.5-79 kg, age range 0.01-19.6 years).

The FDA Animal Rule supports human dosing of 1000 mg every 8 hours (TID) as a 2-hour IV infusion for a duration of 10 days. Therefore, simulations were performed to evaluate the appropriateness of various gepotidacin IV dosing regimens administered as a 2-hour IV infusion every 8 hours in the paediatric population. Sparse and dense PK sampling was used to predict steady-state PK parameters. Similar weight group classification and gepotidacin doses were used for PopPK simulations as were used in PBPK-based simulations. Briefly, with reference to the adult fixed dose of 1000 mg normalized to a typical body weight of 70 kg (14.28 mg/kg), three dose levels of 13, 16 and 19 mg/kg were selected to estimate the exposures in paediatrics with dosing based on body weight.

In addition to the allometric exponents accounting for size-related changes on clearance, a maturation function was introduced into the validated population PK model to account for age- and size-related changes on total clearance and thus on the drug exposures according to the following equation[22]:

$$FMAT_i = \frac{PMA_i^{Hill}}{TM_{50}^{Hill} + PMA_i^{Hill}}$$

where $FMAT_i$ is the fractional change in maturation of clearance for an individual i with a postmenstrual age (PMA_i), while TM_{50} described the maturation half-time and the Hill coefficient related to the slope of this maturation process. The fixed values for the Hill coefficient (3.43) and TM_{50} (52.2 weeks) parameters were based on the paracetamol PopPK parameters.[22] The postmenstrual age was derived from the postnatal age (PNA) by converting PNA from months to weeks plus 40 weeks of gestation assuming full-term births. Paracetamol is predominantly cleared by a phase II conjugation mechanism and

is eventually renally eliminated. Thus, it seems to be reasonable that the glomerular filtration rate (GFR) should mature in association with phase II processes.[22] Since gepotidacin's total clearance comprises ~40-45% renal clearance, the paracetamol clearance maturation function was adopted to account for age-related changes on total clearance and drug exposures of gepotidacin. Maturation function on clearance was only applied to subjects under 2 years of age.

Each simulation was performed 200 times/subject in NONMEM using parameter estimates from the validated population PK model in adults, including the interindividual variability and residual error. The steady-state exposure parameters $AUC_{(0-\tau)}$ (linear up/log down trapezoidal rule) and C_{max} were determined by noncompartmental methods. The 5th, geometric mean and 95th percentiles of the exposure parameters were derived for all subjects in each simulation replication and grouped by cohort, and then the median of the geometric means and 95% prediction interval (2.5th and 97.5th percentiles) for these percentiles across all 200 simulations within each cohort were summarized. The summaries of the simulated gepotidacin PK parameters in paediatric subjects were then compared to those in adults derived from adult simulations. In addition, the percentage of simulated paediatric exposures lower than the 5th percentile as well as higher than the 95th percentile of the adult exposures were derived for each cohort.

2.3 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to Pharmacology 2019/20.[56]

3 | RESULTS

3.1 | PBPK modelling

3.1.1 | Model qualification with clinical data

To verify the model, gepotidacin exposure simulated in healthy adult Caucasian subjects were compared with observed data from a clinical study for doses of 400 to 1800 mg (Supporting Information Figure S5). Model simulated and clinically observed gepotidacin pharmacokinetics, both $AUC_{(0-t)}$ and C_{max}, were in good agreement with <10% difference for all dosing regimens.

This model was also verified by comparing simulated and observed PK in Japanese subjects on administration of 750 mg IV 2 hour infusion dose (Supporting Information Figure S6). Simulations were in good agreement with clinical data (~20% and ~12% difference in C_{max} and $AUC_{(0-t)}$ between predicted and observed, respectively).

The model was further qualified for dose justification in renal impaired subjects (both moderate and severe renal impaired groups) (Supporting Information Figure S7). The outcome of these predictions further confirmed the robustness of the PBPK model. Gepotidacin exposure predicted in populations with normal (estimated glomerular filtration rate [eGFR] ≥90 mL/min/1.73 m^2), moderate (eGFR 30 to 59 mL/min/1.73 m^2) and severe renal impairment (eGFR <30 mL/min/1.73 m^2) were overall consistent with the observed data in a renal impairment study where 750 mg was infused over 2 hours. Model simulated and clinically observed gepotidacin exposures were in good agreement with the difference, ranging from 2% to 21% for C_{max} and 7% to 26% for AUC. Gepotidacin has a renal clearance approximately 3.5-fold times the GFR rate for free drug, which indicates the involvement of an active tubular secretion in renal excretion of gepotidacin. However, unpublished in vitro data indicated that gepotidacin is not a substrate of any well-established renal uptake transporters. A general trend for overpredicting of gepotidacin terminal clearance in both renal impairment populations was observed. This was likely caused by an unidentified renal uptake mechanism for active gepotidacin tubular secretion, therefore a mechanistic kidney model for gepotidacin elimination was not incorporated in the current version of the model.

The predicted gepotidacin exposures (C_{max} and $AUC_{(0-\tau)}$, where τ equals an 8-hour dosing interval for the TID regimen) are presented in Supporting Information Figure S8. Overall, the simulated values correlated well with the observed data following repeat dose TID IV infusion over 2 hours. The simulated body weight and age of the 1000 healthy subjects in the PBPK model were comparable to those observed in the phase 1 study. From the simulated profiles, the 5th, 50th (median) and 95th percentiles of the predicted steady-state C_{max} and $AUC_{(0-\tau)}$ were used as the reference lines for evaluation and selection of the paediatric dosing regimens.

3.1.2 | Dose selection for the paediatric population

To estimate gepotidacin exposure in various age brackets ranging from 1 day to 20 years old, several dose regimen settings were attempted using fixed dose *vs* dose based on body weight. Selection of paediatric doses was based on the dose at which the majority of the predicted gepotidacin exposure fell within the 5th and 95th percentiles of the exposure range in adults, which was shown to be efficacious in the AGM studies. The predicted gepotidacin exposure for various weight brackets provided in Figure 1 illustrates gepotidacin exposure (C_{max} and $AUC_{(0-\tau)}$) at various dosing regimens. The predicted average C_{max} and $AUC_{(0-\tau)}$ values for targeted efficacious exposure in paediatrics were within the 95% percentile of the adult exposure, which is 2-3-fold higher than those observed in the pivotal AGM plague efficacy study dosed at 48 mg/kg/day. In addition, Figure 1 shows that the lowest predicted C_{max} and $AUC_{(0-\tau)}$ values in paediatric subjects were

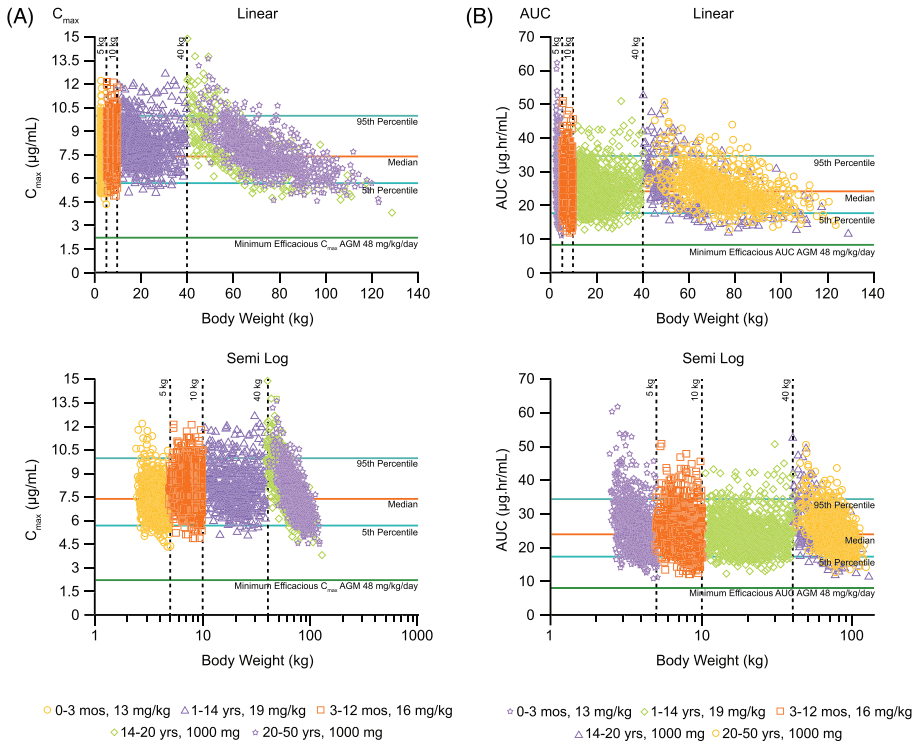

FIGURE 1 Simulated gepotidacin pharmacokinetics based on the PBPK model in healthy adult Caucasian subjects (20-50 years old) and paediatric subjects (approximately 1 day to 20 years old). AUC, area under the curve; C_{max}, maximum plasma concentration

TABLE 2 Simulated percentage of paediatric subjects outside the 5th and 95th percentile range of gepotidacin adult exposures for the proposed paediatric doses: PBPK and PopPK

			C_{max} (µg/mL)		$AUC_{(0-\tau)}$ (µg*h/mL)	
Age brackets	Weight range (kg)	Dose	<5th percentile of adults (%)	>95th percentile of adults (%)	<5th percentile of adults (%)	>95th percentile of adults (%)
PBPK[a]						
<3 mo	≤5	13 mg/kg	5.3	2.0	7.8	11
3 mo to <1 yr	>5 - ≤ 10	16 mg/kg	1.3	4.5	6.4	5.6
1-14 yr	>10 - ≤ 40	19 mg/kg	0.6	11	6.4	6.3
>14-20 yr	>40	1000 mg	4.6	8.4	5.6	6.1
PopPK[b]						
<3 mo	≤ 5	10 mg/kg	7.0	1.0	5.0	8.0
<3 mo	≤ 5	13 mg/kg	0.0	16.0	0.0	40
3 mo to <1 yr	>5 - ≤ 10	16 mg/kg	2.0	11	5.0	15
1-14 yr	>10 - ≤ 40	19 mg/kg	0.0	9.0	3.0	5.0
>14-20 yr	>40	1000 mg	0.0	21	1.0	22

Abbreviations: PBPK, physiologically based pharmacokinetics; PopPK, population pharmacokinetics.
[a]N = 1000 (simulation of 10 trials with 100 subjects per trial).
[b]N = 80 000 (four cohorts of 100 subjects per cohort and 200 simulations per subject).

higher than the minimum C_{max} and $AUC_{(0-\tau)}$ values shown to be effective in the AGM pivotal efficacy study dosed at 48 mg/kg/day. The average predicted C_{min} for the selected paediatric dosing regimens exceeds the gepotidacin minimum inhibitory concentration (MIC) of 0.25 µg/mL for *Y. pestis* (plague) in the AGM studies.

In general, approximately 90% of the predicted PK values for paediatrics fell between the 5th and 95th percentiles of the adult PK values except for the paediatric subjects with the lowest body weight (≤5 kg). For the lowest body weight group (≤5 kg), about 82% of the paediatric PK parameter values fell between the 5th and 95th percentiles of the adult values. The percentages of paediatric subjects whose C_{max} or $AUC_{(0-\tau)}$ fell below the 5th percentile or exceeded the 95th percentile values of adults are summarized in Table 2. It should be noted that the highest C_{max} predicted in this weight group was 12.2 μg/mL, which is still below the threshold of 14 μg/mL to minimize adverse events associated with inhibition of acetylcholinesterase. Adverse effects consistent with increased cholinergic tone, including central nervous system and gastrointestinal effects (increased salivation, slurred speech, blurred vision, dizziness, lightheadedness and gastrointestinal upset) appeared to be related to C_{max} but were significantly attenuated when C_{max} was below 14 μg/mL in clinical observations.

3.2 | PopPK modelling

3.2.1 | VPC of the population PK model in adults

Observed concentrations were overlaid on the predicted concentration-time profiles and the majority of the observed concentrations were within the 90% prediction intervals, implying concordance between the simulated and observed data in adults (Supporting Information Figure S9).

3.2.2 | Weight versus exposure simulations in adults

The medians of the geometric mean values of simulated steady-state C_{max} and $AUC_{(0-\tau)}$ in adults was 8.93 μg/mL and 25.3 μg*h/mL, respectively, and were similar to the observed steady-state geometric mean C_{max} (9.55 μg/mL) and $AUC_{(0-\tau)}$ (29.2 μg*h/mL) in adult subjects who received 1000 mg TID dose via 2-hour IV infusion for 10 days (Table 3). These simulated parameters were also in agreement with the predicted steady-state geometric mean exposure parameters (C_{max} 7.50 μg/mL, $AUC_{(0-\tau)}$ 24.4 μg*h/mL) from PBPK-based simulations (Table 3). Visual predictive check plots of exposure parameters show that the majority of the observed exposure parameter values were within the 90% prediction interval, indicating a good predictive performance of the model (Supporting Information Figures S10 and S11).

3.2.3 | Dose selection for the paediatric population

The PopPK approach applied the same procedure as that used for the PBPK model in which the paediatric doses were based on the dose at which majority of the predicted gepotidacin exposure fell within the 5th and 95th percentiles of the exposure range in adults that was shown to be efficacious in the AGM studies. Simulations were performed by applying an age maturation function on the CL of gepotidacin in paediatrics under 2 years of age based on the selected doses (Table 2). Steady-state geometric mean $AUC_{(0-\tau)}$ and C_{max} in subjects in all cohorts were within the range of 5th and 95th percentile of adults (Supporting Information Figures S12 and S13). The proportion of paediatric subjects within each cohort achieving C_{max} below the 5th percentile (5.98 μg/mL) of adults was ≤7% and above the 95th percentile (13.4 μg/mL) of adults was ≤21%. Similarly, the proportion of paediatric subjects achieving $AUC_{(0-\tau)}$ below the 5th percentile (17.5 μg*h/mL) of adults was ≤5% and above the 95th percentile (36.5 μg*h/mL) of adults was ≤22% in all cohorts.

Since the proportion of paediatric subjects with $AUC_{(0-\tau)}$ above the 95th percentile in adults was very high (40%) in subjects that weighed ≤5 kg, the dose was reduced from 13 to 10 mg/kg. With a reduced dose of 10 mg/kg, the proportion of subjects with exposures below the 5th or above the 95th percentiles of adults was <10% for both C_{max} and $AUC_{(0-\tau)}$ for paediatric subjects weighing ≤5 kg.

TABLE 3 Comparison of observed and simulated gepotidacin exposure (AUC and C_{max}) parameters in adults using PBPK and PopPK approaches

	AUC (μg*h/mL)[b] geomean (95% CI)			C_{max} (μg/mL) geomean (95% CI)		
Study description[a]	Observed	PBPK	PopPK	Observed	PBPK	PopPK
400 mg (SD)	8.77 (7.15, 10.8)	9.74 (9.33, 10.2)	9.65 (9.42, 9.89)	3.05 (2.25, 4.15)	2.83 (2.73, 2.92)	3.02 (2.93, 3.12)
750 mg (SD)	23.6 (20.4, 27.3)	18.3 (17.5, 19.1)	18.1 (17.7, 18.5)	7.76 (6.82, 8.83)	5.3 (5.12, 5.48)	5.66 (5.50, 5.85)
1000 mg (SD)	23.8 (17.9, 31.6)	24.3 (23.3, 25.4)	24.1 (23.5, 24.7)	7.24 (5.52, 9.49)	7.07 (6.83, 7.31)	7.55 (7.33, 7.80)
1500 mg (SD)[c]	34.0 (30.4, 38.0)	36.5 (34.9, 38.1)	37.3 (36.4, 38.2)	7.87 (6.88, 8.99)	8.09 (7.82, 8.38)	10.0 (9.80, 10.3)
1800 mg (SD)	47.6 (41.8, 54.1)	43.8 (42.0, 45.7)	43.4 (42.4, 44.5)	13.3 (11.5, 15.5)	12.7 (12.3, 13.2)	13.6 (13.2, 14.0)
1000 mg (TID)[d]	29.2 (26.6, 32.1)	24.4 (24.1, 24.7)	25.3 (24.6, 25.9)	9.55 (8.70, 10.5)	7.50 (7.42, 7.58)	8.93 (8.68, 9.16)

Abbreviations: PBPK, physiologically based pharmacokinetics; PopPK, population pharmacokinetics; SD, single dose; TID, three times daily.

[a]All data are from healthy volunteers after administering various doses of gepotidacin as a 2-h IV infusion.

[b]$AUC_{(0-t)}$ for single dose and $AUC_{(0-\tau)}$ for repeat dose using TID regimen.

[c]Administered as 3-h IV infusions.

[d]TID regimen.

3.3 | PBPK *vs* PopPK

Comparison of observed and predicted gepotidacin exposures in adults indicated that both the PBPK and the PopPK modelling achieved generally comparable results for AUC and C_{max} for a given dose (Table 3 and Figure 2), but the C_{max} predictions using the PopPK were slightly higher than those obtained by PBPK simulations. Similarly, paediatric drug exposures were verified via both modelling approaches, taking into consideration the different dosage recommendations for subjects below 5 kg (Figure 3). Exposure projections based on the PopPK model were slightly higher compared to PBPK.

4 | DISCUSSION

Conducting paediatric clinical trials to guide dose optimization remains a huge challenge given the vulnerability of this population.[13,23] A substantial number of drugs are currently prescribed to children off-label or in an unlicensed manner for which dosing regimens are empirically derived using extrapolation based on body weight.[24,25] In studies that are conducted in the paediatric population, a considerable number fail to meet their objectives for approval.[26,27] Dose selection is the biggest challenge in these studies[28] and is the primary reason for failure to obtain paediatric approval for anti-infective agents.[27]

The Best Pharmaceuticals for Children Act (BPCA) of the Food and Drug Administration[29] in the United States along with the Paediatric Regulation from the European Medicines Agency[30] were created in order to prevent nonevidence-based drug use and to address the gap in drug safety to expand drug labelling to the paediatric population. Both the BPCA and EMA provide incentives of additional 6 months of patent protection to stimulate the conduct of paediatric studies. The FDA requires submission of plans for paediatric studies before the completion of phase II trials, while the EMA requires an approved plan before a marketing authorization application can be submitted. In addition to the rewards provided by the regulatory agencies, there is an increased societal consciousness regarding the importance of conducting paediatric clinical trials and label expansion to this population.[13,23]

Given the limited opportunities to collect data in children, modelling and simulation methodologies are being utilized by

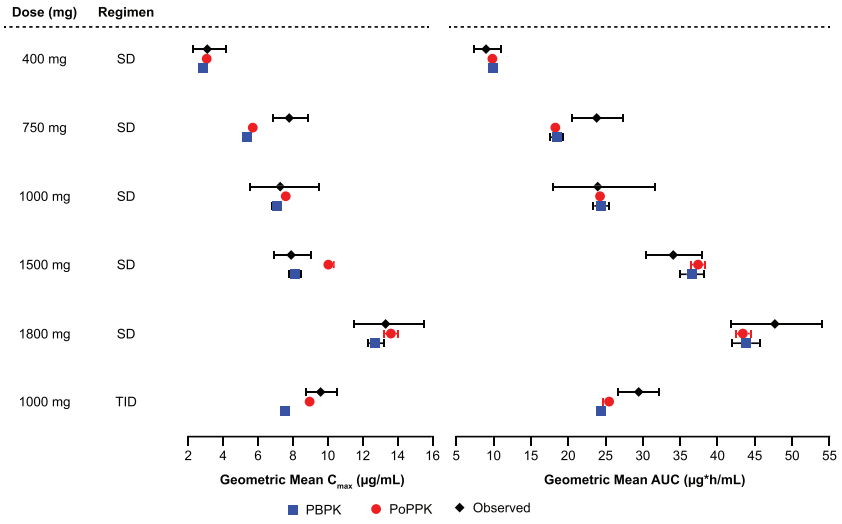

FIGURE 2 Comparison of observed to simulated exposures (C_{max} and $AUC_{(0-\tau)}$) at different doses in adults with PBPK and PopPK approaches. $AUC_{(0-\tau)}$, area under the curve over the dosing interval at steady state; C_{max}, maximum plasma concentration; PBPK, physiologically based pharmacokinetics; PopPK, population pharmacokinetics; SD, single dose; TID, three times daily

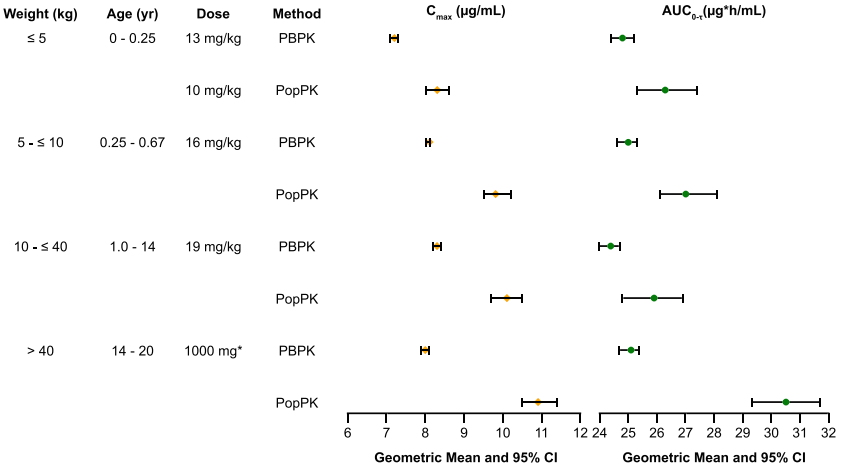

FIGURE 3 Comparison of simulated exposure parameters (C_{max} and $AUC_{(0-\tau)}$) at different doses in paediatrics with PBPK and PopPK approaches. To maintain the target gepotidacin exposure in paediatric subjects, the doses were different between PBPK and PopPK models due to the built-in ontogeny of drug-metabolizing enzyme-CYP3A4 profiles within Simcyp simulator. *1000 mg dose was a fixed dose. $AUC_{(0-\tau)}$, area under the curve over the dosing interval at steady-state; C_{max}, maximum plasma concentration; PBPK, physiologically based pharmacokinetics; PopPK, population pharmacokinetics. $AUC_{(0-\tau)}$ and C_{max} were represented as geometric means and 95% confidence interval

academia, industry and regulatory agencies as powerful tools to optimize resources to design meaningful paediatric clinical studies for drug development.[26,31] Although there is no current agreement on the ideal approach for dose selection,[28] in multiple studies modelling and simulation have been shown to result in better recommendations of paediatric doses.[32,33] For most anti-infective agents, efficacy can be extrapolated from adults to paediatrics given similar disease pathophysiology and therapeutic exposure.[27,28] In such cases, adult exposure matching is used, for which the paediatric dose is adjusted based on pharmacokinetic changes in the paediatric population accounting for differences in the maturation of drug-eliminating organs.

PopPK and PBPK are two modelling approaches used to describe and predict pharmacokinetics that are commonly used by the industry and recommended by regulators to bypass some difficulties in developing paediatric drugs.[31] PopPK models characterize the concentration versus time relationship based on the compartmental modelling approach, where structural, statistical and covariate elements can be incorporated.[34] Therefore, rather than considering an individual, PopPK leverages the pharmacokinetics of the population, which represents a great advantage in paediatrics, for example, when the information might be limited due to sparse sampling.[32] PopPK provides an opportunity to evaluate covariates on drug exposure and effect, allowing the evaluation of a potential need for dose adjustment. In addition, mechanistic elements and extrapolation factors can be incorporated to predict the paediatric profiles in children according to different age ranges.[34] Paediatric PopPK modelling has been a conventional approach to support clinical trial design and dosage selection in children using adult PK information with or without consideration of ontogeny.[28,35–38] However, PopPK is limited regarding the extent of the information about the physiology and the drug that can be easily incorporated in the model, which restricts the ability to predict and extrapolate PK to different physiological conditions.[39] PBPK addresses these limitations given that the models consist of both drug-specific and system-related input parameters. PBPK models are constructed based on the same mathematical principles as the empirical PopPK models, but with a "bottom-up" approach parameterized based on the physiology and composed of a larger number of compartments, each representing one anatomical organ or tissue. The compartments are connected by flow rates based on the circulating blood system, allowing the determination of the absorption, distribution, metabolism and excretion (ADME), and ultimately the human concentration versus time profile.[28,39] Therefore, physiological conditions can be incorporated in the model to predict the drug exposure under special conditions (eg, in paediatrics, renal and hepatic impairment) providing continued value to the clinical development of new drugs. In the context of paediatric drug development, PBPK allows the incorporation of detailed physiological differences between adults and paediatrics, including different aspects of growth development, such as body size and composition, tissue blood flows and biochemical features of the developing body.[28,32] Regulatory agencies have been increasingly endorsing the use of PBPK as a powerful tool to inform drug development.[40–48]

The primary focus of the present analysis was to identify paediatric dose regimens for gepotidacin in plague, a drug with two major elimination pathways, renal and hepatic. In that regard, both PopPK and PBPK models were explored regarding their ability to predict gepotidacin exposures in paediatrics and ultimately the doses. To our knowledge, the use of PBPK has not been implemented for paediatric dose selection based on the FDA Animal Rule. The combined evaluation of PopPK and PBPK for paediatric dose recommendation was also used in a previous study by Jorga and colleagues.[34] In their study both methodologies supported the regulatory approval of a dosing algorithm for valganciclovir in children <4 years old. Another study by Zhou and colleagues evaluated the predictive performance of PopPK and PBPK for several compounds predominantly eliminated through the kidneys.[49] Furthermore, given increasing interest from both industry and regulatory agencies on quantitative tools for paediatric dosing recommendation, the use of both PopPK and PBPK models has been further evaluated within the last few years.[50–54] In conclusion, both model-based approaches successfully predicted the clearance of the drugs, indicating that these two methodologies can complement each other for dose predictions in children older than 1 month. Consistent with the two cited studies,[34,49] this work explored the usefulness of the PopPK and PBPK modelling approaches in the prediction of gepotidacin doses for the different paediatric ranges for age and body weight.

The gepotidacin PBPK model was previously built[11] using physicochemical and in vitro data, then further optimized with observed clinical data from dose-escalation IV study as well as human mass balance study. Because the metabolism of gepotidacin is primarily catalysed by CYP3A4,[8] an ASA on the estimated fm_{CYP3A4} was conducted. The ASA indicated that a change in fraction of metabolism by CYP3A4 can affect the overall gepotidacin exposure (higher impact on AUC than C_{max}). Therefore, the CYP3A ontogeny was integrated in the model for paediatric subjects younger than 2 years of age. In the current model, an age-dependent value for GFR in Simcyp was also used in the paediatric model for gepotidacin. Additionally, gepotidacin is excreted in the urine with a calculated renal clearance of approximately 3.5-fold higher than GFR corrected for protein binding. Thus, an active tubular secretion has been suggested to contribute to the renal excretion of gepotidacin. However, given the unknown mechanism of active gepotidacin tubular secretion, the uptake transporter mechanism was not included in the simulations of the paediatric population. Several dose regimen settings for the paediatric population were attempted using fixed dose *vs* dose based on body weight. Body weight was also found to be a key covariate affecting the clearance in the adult healthy population and it was even more significant in the paediatric group.

The PopPK structural model in adults indicated that body weight was a significant predictor of gepotidacin clearance. Therefore, body weight was included as a covariate on clearance. It is known that hepatic activity of major CYP450 enzymes and renal function reach adult levels by approximately 2 years of age.[12,55] Given that enzymatic maturation (ie, metabolic capacity) is completely unrelated to body weight and that age-related changes

in the hepatic and renal elimination pathways could greatly influence the overall disposition of gepotidacin in paediatrics (especially in those ≤2 years of age), age maturation effects on total systemic clearance were incorporated in the PopPK model. Since the elimination of gepotidacin is primarily renal and via the oxidative metabolism by CYP3A4 enzyme, the model utilized for this purpose was derived from the paracetamol example[22] because the maturation effects were considered on total systemic clearance rather than specific components such as hepatic or renal.

PopPK simulated paediatric geometric means of C_{max} and $AUC_{(0-\tau)}$ were similar to the observed adult exposures across all weight brackets. In addition, the proposed dosing regimens were weight-based for subjects ≤40 kg and fixed-dose for subjects >40 kg. Simulations to support fixed dosage adult regimens at various weight cut-offs below and above 40 kg indicated that as the lower cut-off moved away from 40 kg (ie, 30-35 kg), the proportion of subjects achieving exposures >95th percentile of adults could be as high as 49%, posing a safety risk. However, when the cut-off was set at >40 kg to receive the adult fixed dose, this proportion was at a reasonable rate of 20%. Based on these observations, it was inferred that the lowest weight for paediatric subjects that can be administered a fixed adult dose regimen is >40 kg, while subjects ≤40 kg should be dosed based on body weight.

Additionally, the PBPK and PopPK models differed on the dose predictions in children <3 months old although the gepotidacin data analysis demonstrates that both PBPK and PopPK approaches can reasonably predict gepotidacin exposure in children. The built-in ontogeny of drug-metabolizing enzymes in PBPK offers opportunities to incorporate mechanistic understanding of drug elimination pathways on top of physiological modifications towards the paediatric population. The performance of the PopPK model may be suboptimal for low age groups (<3 months old), which may result from missing maturation characterization of drug-metabolizing enzymes such as CYP3A4, which is the major contributor of total hepatic clearance in adults. This finding is aligned with a publication by Sinha and colleagues[41] that reviewed the application of PBPK modelling for various approved drugs. They concluded that although standard modelling approaches (eg, PopPK using allometry) works well in subjects >2 years of age, PBPK simulations may provide a greater utility in younger subjects, since this approach factors in the maturation differences of multiple physiological processes, which is consistent with our observations.

Comparisons of actual exposures to gepotidacin demonstrate that gepotidacin is effective in AGM with exposure profiles significantly below those seen with 1000 mg IV BID or TID clinical regimens and provides confidence that these clinical doses will be effective in the treatment of human pneumonic plague. The proposed paediatric dosing regimen was determined to be acceptable for treatment of plague. Evaluation of PK parameters in AGM and in clinical subjects further supports the human dose as either a BID or TID regimen. Gepotidacin is administered at a concentration of 4 mg/mL over 2 hours after dilution in 0.9% sodium chloride injection (normal saline) to a final volume of 250 mL (1000 mg/250 mL) TID for 10 days (adults and children >40 kg). The recommended dose of gepotidacin will be weight-based in paediatric subjects ≤40 kg. It will be given as an IV infusion to a volume computed based on the child's weight to be infused over 2 hours using an appropriate compatible diluent solution.

Overall, the simulated paediatric exposures from the PopPK model were in good agreement with that of the PBPK model for similar dosing regimens. The PBPK model takes into consideration mechanistic understanding of drug disposition and therefore provides advantages for special groups such as paediatrics or disease populations. Both PopPK and PBPK models provide good predictions for gepotidacin dosing regimens in the paediatric population to be confirmed in future paediatric PK studies for nonbiothreat indications such as urinary tract infection.

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D.N. and J.S.S. contributed to acquisition of data and to data analysis/interpretation. C.T. and C.P. contributed to conception/design. E.D. and D.G. contributed to conception/design and to data analysis/interpretation. G.T., A.B. and R.S. contributed to data analysis/interpretation. M.H. contributed to conception/design, data analysis/interpretation acquisition of data and data analysis/interpretation. All authors played a role in drafting the article or revising it critically for important intellectual content, and all authors approved the final draft for submission.

COMPETING INTERESTS

This study was funded by GSK. All authors were employees of GSK when this work was completed and meet the criteria for authorship set forth by the International Committee for Medical Journal Editors. C.A. is currently at Gan & Lee Pharmaceuticals, Bridgewater, New Jersey, USA. M.H. is currently at Agios Pharmaceuticals, Cambridge, Massachusetts, USA. D.G. is currently at CSL Behring, 1020 1st Ave, King of Prussia, PA 19406. There was no principal investigator for this study since this work presents an analysis of data collected from previous clinical trials. All of the previous clinical trials were conducted according to the ethical principles of "Good Clinical Practice" and the Declaration of Helsinki after obtaining written informed consent from each subject. In addition, all pertinent protocols were approved by an accredited investigational review board or ethics committee.

Data sharing is not applicable for this publication; no new clinical data were generated in this modelling study.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable for this publication; no new clinical data were generated in this modeling study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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