Received: 11 December 2020 | Revised: 29 March 2021 | Accepted: 20 April 2021

DOI: 10.1111/bcp.14894

ORIGINAL ARTICLE

Population pharmacokinetics of raxibacumab in healthy adult subjects

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Funding information
GlaxoSmithKline (GSK)

Aims: Raxibacumab is a fully humanized monoclonal antibody that blocks the interaction of *Bacillus anthracis* toxins, thereby protecting target cells from its effects. Raxibacumab is approved in the USA for the treatment of adults and children with inhalational anthrax in combination with antibiotics, and for prophylaxis of inhalational anthrax. The aim of this investigation was to characterise the population pharmacokinetics and assess the effect of baseline demographic covariates on the disposition of raxibacumab.

Methods: The data used for this analysis were obtained from 3 clinical trials and include 2229 blood samples from 322 healthy subjects who were randomised to receive a 40 mg/kg intravenous dose of raxibacumab over a period of 2.25 hours. Population pharmacokinetic modelling was performed using a nonlinear mixed effects approach. Secondary parameters of interest were the area under the curve, maximum concentration and the time of serum raxibacumab concentrations greater than or equimolar to the highest serum protective antigen concentrations observed for at least 28 days in any monkey challenged with *B. anthracis* that died.

Results: Raxibacumab exposure in healthy subjects was described by a 2-compartment model. Interindividual variability was estimated for all model parameters, whilst residual variability was described by a proportional and additive error model. Weight was the only influential covariate with significant effect on disposition parameters.

Conclusions: A dose of 40 mg/kg provided comparable exposure across the overall healthy subject population. Interindividual variability in raxibacumab *vs.* time profiles could partially be accounted for by differences in body weight.

KEYWORDS
anthrax, antibodies, phase I, population pharmacokinetics, raxibacumab

1 | INTRODUCTION

Bacillus anthracis is the aetiological cause of an infection commonly known as anthrax.[1] In 1979, an unintentional release of *B. anthracis* spores from a military microbiology facility in the former Soviet Union resulted in at least 69 deaths.[2] Later, in 2001, *B. anthracis* spores were intentionally distributed through the US Postal Service[3] underscoring the dangers of this organism as a biothreat and its ability to create

atypical pathways of transmission. Usually, its symptoms can take days to weeks to appear and include blisters, swelling, shortness of breath, nausea, fever and diarrhoea, depending on the type of infection.[4] If left untreated, the infection can result in death.

Guidelines for the treatment of inhalational anthrax include an initial intervention with ciprofloxacin or doxycycline and 1 or 2 other antibacterial drugs followed by treatment with a single antibiotic for 60 days when the condition improves and the sensitivity of the *B. anthracis* strain is known.[5] However, it should be noted that whilst antibiotics can be effective against the bacilli, they do not eliminate the lethal exotoxins, which are in part responsible for the 45–80% mortality rate.[6–8] The anthrax toxin (AT) is a 3-protein exotoxin consisting of 2 enzyme components: oedema factor (EF), lethal factor (LF); and 1 cell-binding protein: protective antigen (PA). Once PA binds to a cell, EF and LF are translocated inside.[7] EF and LF in combination with PA produce oedema toxin and lethal toxin, respectively,[9] which are in turn associated with tissue swelling (EF) and death (LF).

Raxibacumab is a fully humanized monoclonal antibody (mAb) that blocks the PA-receptor interaction of *B. anthracis*,[10] thereby protecting target cells from PA binding to anthrax toxin receptors. Ultimately, this mechanism preserves host cells from AT-mediated effects.[11,12] Raxibacumab is approved in the USA for the treatment of adult and paediatric patients with inhalational anthrax due to *B. anthracis* in combination with appropriate antibacterial drugs, and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.[13]

The specific interference of raxibacumab with the PA-receptor complex, and its protective effect against AT on cultured human macrophages were established in *in vitro* pharmacology studies.[12] In vivo studies were also conducted to determine the efficacy of raxibacumab in relevant animal systems of anthrax challenge. In monkeys and rabbits, a single intravenous (IV) raxibacumab dose (20 or 40 mg/kg) given as prophylaxis or immediately postexposure yielded significant prolongation in time to death and overall survival benefit when administered with antibiotics at the onset of the infection.[9] Furthermore, monkeys that survived a lethal anthrax spore dose following prophylactic administration of raxibacumab were protected against repeat spore challenge 11 months following the initial spore challenge, indicating that raxibacumab did not interfere with the immune system's ability to mount a protective anti-PA response. Another *in vivo* study in New Zealand white rabbits demonstrated the added benefit of raxibacumab treatment in combination with levofloxacin over antibiotic alone.[14]

Based on rabbit and monkey data, it was concluded that the raxibacumab 40 mg/kg provided the desired level of protection against lethality.[12] The pharmacokinetics (PK), safety and tolerability/immunogenicity profile of raxibacumab were, therefore, subsequently evaluated in 4 clinical studies: a Phase 1 study in healthy subjects; a drug interaction study of raxibacumab with ciprofloxacin conducted in healthy subjects; an immunogenicity and safety study in healthy subjects who received a second raxibacumab dose 4 months after their initial dose; and a Phase 3 study in healthy subjects.[10,12] In each of these studies, blood samples were collected for the assessment of serum raxibacumab concentrations and subsequent characterisation of the PK profile. Raxibacumab was well tolerated by healthy subjects as a single agent.

What is already known about this subject

- Raxibacumab is indicated for the treatment of adult and paediatric patients with inhalational anthrax in combination with appropriate antibacterial drugs. It is also indicated for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.

What this study adds

- Here we have characterised the effect of baseline demographic characteristics on the disposition of raxibacumab and their contribution to interindividual differences in systemic exposure.
- The population pharmacokinetic model provides the basis for further evaluation of the dose rationale in a paediatric population in a future postmarketing study.

Whilst an initial analysis has been performed to describe drug exposure in each study, to date a more detailed analysis of the disposition characteristics along with estimates of interindividual variability (IIV) is not available. The aim of this investigation was to characterise the population PK and assess the effect of baseline demographic covariates on the disposition of raxibacumab.

2 | METHODS

2.1 | Analysis population

The data used for this analysis were obtained from 3 clinical trials and include 2229 blood samples from 322 subjects (Table S1), who were randomised to receive a 40 mg/kg IV dose of raxibacumab over a period of 2.25 hours. Most subjects received a single nominal dose of 40 mg/kg raxibacumab, but 43 subjects were administered two doses of 40 mg/kg raxibacumab given either 14 days apart (Study HGS1021-C1063) or at least 4 months apart (Study HGS1021-C1069). The infusion was stopped before delivering the total nominal dose in 6 subjects who showed adverse events associated with the site of infusion. In addition, in 5 individuals the total actual dose was found to be slightly different from the nominal 40-mg/kg dose of raxibacumab (Table 1). All subjects who received raxibacumab that had accurate dosing records, evaluable

TABLE 1 Demographics and baseline characteristics

Baseline demographics	*n*	Mean	SD	CV%	Median	Minimum	Maximum
Age (y)[a]	322	39	15	39.2	37	18	87
Body weight (kg)[a]	322	76.9	17.4	22.6	75.6	44.6	155.9
ALT (IU)[a]	322	21	12	55.6	18	7	108
AST (IU)[a]	322	21	8	38	19	10	87
Bilirubin (mg/dL)[a]	322	0.5	0.3	62	0.4	0.1	2.3
Albumin (g/dL)[a]	322	4.3	0.3	7.2	4.3	3.5	5.1
Total protein (g/dL)[a]	322	7.1	0.5	7	7	5.5	8.4
Albumin:globulin ratio	322	1.59	0.25	15.5	1.6	0.9	2.65
Serum creatinine (mg/dL)[a]	322	0.9	0.2	20.7	0.9	0.5	1.8
Dosing information	***n***	**Mean**	**SD**	**CV%**	**Median**	**Minimum**	**Maximum**
Single dose or 1st dose							
Infusion duration (h)	322	2.38	0.21	8.9	2.33	0.6	3.52
Actual dose (mg/kg)	322	39.68	2.86	7.2	40	8.05	42.93
Actual dose (mg)	322	3050	728	23.9	3018	592	6236
2nd dose, at 14 d post-1st dose							
Time of dosing (d)[b]	23	13.98	0.02	0.2	13.99	13.92	14.01
Infusion duration (h)	23	2.4	0.15	6.2	2.37	2.27	2.95
Actual dose (mg/kg)	23	40	0	0	40	40	40
Actual dose (mg)	23	3 286 783	776 602	23.6	3 176 000	2 096 000	4 916 000
2nd dose, at >4 mo post-1st dose							
Time of dosing (d)[b]	20	225.79	19	8.4	227.03	191.12	279.08
Infusion duration (h)	20	2.31	0.06	2.5	2.3	2.25	2.42
Actual dose (mg/kg)	20	39.93	0.17	0.4	39.94	39.6	40.21
Actual dose (mg)	20	3 207 600	594 247	18.5	3 300 000	2 250 000	4 032 000

[a]Value at baseline for the first raxibacumab dose administered.
[b]Time of administration of the second dose, relative to the first dose. ALT: alanine aminotransferase, AST: aspartate aminotransferase, CV%: coefficient of variation, SD: standard deviation.

concentrations and demographic data were included in the PK analysis population. All volunteers provided written informed consent. These studies were conducted according to the International Conference on Harmonisation Good Clinical Practice standards.

2.2 | Bioanalytical methods

Serum samples were analysed for raxibacumab using an electrochemiluminescence (ECL)-based assay. Biotinylated PA is bound to a streptavidin-coated Meso Scale Discovery (MSD) 96-well assay plate for raxibacumab capture. The raxibacumab in diluted serum samples binds to the biotinylated PA and is detected by the addition of rabbit anti-raxibacumab followed by goat anti-rabbit antibody labelled with MSD SULFOTAG, an ECL label. MSD read buffer is added to the plate and the plate is inserted into an MSD plate reader, where voltage applied to the plate electrodes causes the MSD SULFOTAG to emit light proportional to the amount of raxibacumab present in the serum. The concentration of raxibacumab in serum samples was interpolated from an 8-point reference standard curve. The lower limit of quantitation was 800 ng/mL of raxibacumab in 100% serum.

2.3 | Model building

Population PK modelling was performed using a nonlinear mixed effects approach, as implemented in NONMEM version 7.3 (5). General model building criteria have been applied to ensure that the appropriate structural model (i.e. the PK compartmental model) was identified. Next, a stochastic model describing between-subject variability was identified to expand the base model.

Both a 1- and 2-compartment structural model were considered during model building. IIV in the PK parameters was assumed to be log-normally distributed. Given subject *i*, the individual parameter value is given by:

$$\theta_i = \theta_{tv} \times e^{\eta_i}$$

where θ_{tv} is the typical value in the population and η_i is a random variable with a mean of zero and variance ω^2. Residual variability was described with a combined additive and proportional error model. Given the j^{th} measurement of individual *i*, the modelled concentration (Y_{ij}) was given by:

$$Y_{ij} = F_{ij} \times (1 + \varepsilon_{ij}) + \varepsilon_{ij}$$

where F_{ij} is the predicted concentration and ε_{ij} a random variable with mean of zero and variance σ^2.

2.4 | Covariate selection and model evaluation

Selected covariates were added to the base model according to a stepwise forward addition-backward elimination procedure. Initially, each factor has been included individually in the base model to identify significant covariates where significance was defined by a reduction in the objective function value (OFV) of ≥3.84, χ^2 < .05 for 1 degree of freedom using the FOCE-I estimation method. Linear, exponential and power functions were investigated initially, but only the power function was selected and included in the final covariate model:

$$\theta_i = \theta_{tv} \times \left(\frac{COV_i}{COV_{med}}\right)^{\theta_{cov}}$$

where θ_{cov} is the covariate effect, COV_i the individual covariate value and COV_{med} the population median.

During the subsequent modelling steps, only the factors (IIV, covariates) which resulted in OFV reduction of ≥7.88 (P < .005) were kept in the model. As shown in Table 1, the wide range of variation in baseline characteristics (e.g. ages and body weights) allowed for a comprehensive evaluation of influential demographic covariates on key PK parameters.

Final measures of model performance included cross-validation, visual predictive checks, bootstrapping, normalised prediction distribution error (NPDE) and mirror plots. Final parameter estimates were summarised along with their confidence intervals (CIs) when appropriate. Bootstrapping was performed to identify bias, stability and accuracy of the parameter estimates and generate standard errors and CIs on the parameter estimates. For bootstrapping, PsN was used to generate 1000 new data sets by sampling individuals with replacement from the original data set and then fitting the model to each new data set.

Further evaluation of the variance–covariance structure and overall random effects in the model was performed using mirror plots and NPDE diagnostics. To generate mirror plots, the population PK parameters estimates were used to simulate concentrations in patients with similar demographic characteristics, dosing regimens and sampling scheme as the original clinical studies. Mirror plots of individual predicted *vs*. observed concentration were created to assess the degree of similarity between the original fit and the pattern obtained from the simulated data sets. Then, the NPDE were derived to evaluate whether the discrepancies between observed and predicted values were normally distributed. This step was based on graphical summaries, including quantile–quantile plots of NPDE *vs*. the expected standard normal distribution, a histogram of NPDE with the density of the standard normal distribution overlaid, a scatter plot of the NPDE *vs*. observed values, and a scatter plot of NPDE *vs*. predicted values.

Lastly, the overall predictive performance was tested by cross validation. The full data set was randomly split into an index data set (comprising ~70% of the data) and a reference data set (comprising the remaining portion of the data). This was repeated 30 times, using sampling with replacement. The index data sets were fit to the final population PK model, and the resulting final parameters were summarised. In addition, the final parameters resulting from each index fit were used to predict the reference data set based on an empirical Bayes approach. Graphical examination of the predicted *vs*. observed concentrations derived from the reference data set was used to complete the assessment of model performance.

2.5 | Secondary PK parameters

Secondary parameters of interest were the area under the curve (AUC), maximum concentration (C_{max}) and the time of serum raxibacumab concentrations greater than or equimolar to the highest serum PA concentrations observed in preclinical prophylactic studies for at least 28 days in any monkey (cynomolgus macaques) challenged with *B. anthracis* that died (i.e., 760 nM).[12]

Secondary parameters were calculated with individually simulated profiles. C_{max} was calculated by sampling the first concentration at the last point of infusion. AUC values were derived using the trapezoidal rule to ensure direct comparison with data previously collected in preclinical species. The time above the monkey threshold was approximated in R using the individually simulated profiles.

All data preparation, statistical and graphical summaries were created using R version 3.1.3.[15]

3 | RESULTS

Raxibacumab exposure in healthy subjects was characterised by a 2-compartment PK model. IIV was estimated for CL, V1, V2 and Q, and residual variability was described by a combined (proportional and additive) error model (Table 2). Weight was the only influential covariate with significant effect on CL, V1, V2 and Q.

All parameters were well estimated without significant correlations between parameters. Fixed effect parameters showed good precision (relative standard error [RSE] < 27%), as did the corresponding IIV estimates (RSE < 42%; Table 2).

The diagnostic plots for the final model in Figure 1 show that the model adequately explained the variability in the data, yielding unbiased population and individual predictions. Additionally, the distribution of individual η values was close to normal and data were found to be uncorrelated. No correlations or trends were noted between the conditional weighted residuals or body weight.

The visual predictive checks (Figure 2) showed accurate description of the variability, with most observed concentrations falling within the 95% CIs of the simulated values. Model stability and precision of the parameter estimates were confirmed by the nonparametric bootstrap (Table 2). In addition, the mirror

TABLE 2 Final parameter estimates

Parameter (unit) [a]	Notation	Population estimate	RSE (%)	Bootstrap mean (95% CI)
Systemic clearance, CL (mL/d) = θ1*(WT/76.9)^θ6	θ1	187	1.22	187.0 (182.7–191.8)
	θ6	0.83	6.84	0.83 (0.72–0.94)
Central volume of distribution, V1 (mL) = θ2*(WT/76. 9)^θ5	θ2	3230	0.96	3231 (3173–3292)
	θ5	0.70	6.37	0.7 (0.61–0.78)
Intercompartmental clearance, Q (mL/d) = θ3*(WT/76. 9)^θ8	θ3	500	7.86	498.5 (431.4–584.4)
	θ8	1.16	26.55	1.17 (0.53–1.75)
Peripheral volume of distribution, V2 (mL) = θ4*(WT/76. 9)^θ7	θ4	2290	2.35	2294 (2194–2400)
	θ7	0.85	11.65	0.84 (0.65–1.05)
Interindividual variability [b]		**Population estimate (CV%)**	**RSE (%)**	**Bootstrap mean (95% CI)**
ηCL variance	Ω1	0.04 (20.0%)	10.65	0.04 (0.03–0.05)
ηV1 variance	Ω2	0.03 (16.6%)	9.13	0.03 (0.02–0.03)
ηV2 variance	Ω3	0.05 (21.4%)	37.99	0.04 (0.02–0.09)
ηQ variance	Ω4	0.11 (33.2%)	41.73	0.1 (0.03–0.21)
Residual error		**Population estimate (CV%)**	**RSE (%)**	**Bootstrap mean (95% CI)**
Proportional error (μg/mL)	σ1	0.01 (9.6%)	52.83	0.01 (0.01–0.01)
Additive error (μg/mL)	σ2	88.50	1.46	87.8 (40.5–141.8)

CI: confidence interval, CV%: coefficient of variation, RSE: relative standard error, WT: body weight, θ: PK parameter estimate, η: interindividual variability, Ω: interindividual variability in population PK parameter, σ: population variance.
[a]Population parameter point estimates for the 2-compartment model are presented along with the 95% CI and %CV from a nonparametric bootstrap.
[b]Value between parentheses represents the interindividual variability of the PK parameter calculated as the square root of Ω x 100%.

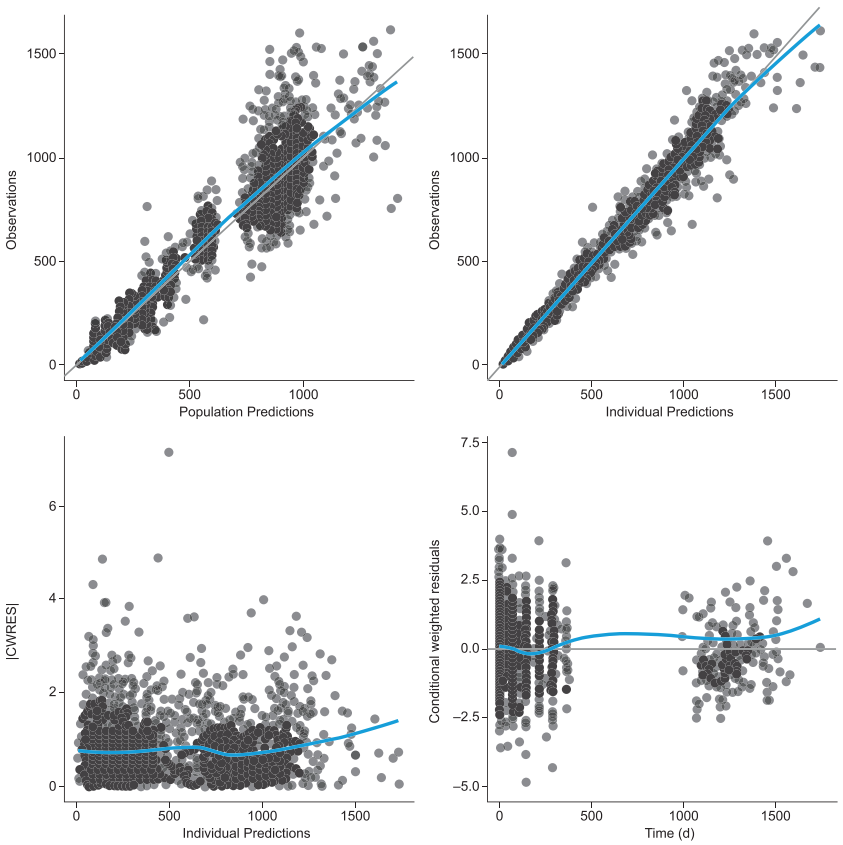

FIGURE 1 Goodness-of-fit plots. Panels show the goodness-of-fit plots for the final model. Black circles represent individual observations/predictions. Blue line is a general smoothing function. Population and Individual refer to population and individually predicted concentrations, respectively. Time is in days; concentrations are in μg/mL

plots in Figure S1 show that the final variance–covariance structure accurately replicates the profiles of raxibacumab in healthy subjects.

The NPDE plots displayed the prediction errors according to a standard normal distribution and did not reveal any particular bias in model predictions following IV doses (Figure S2). These findings were

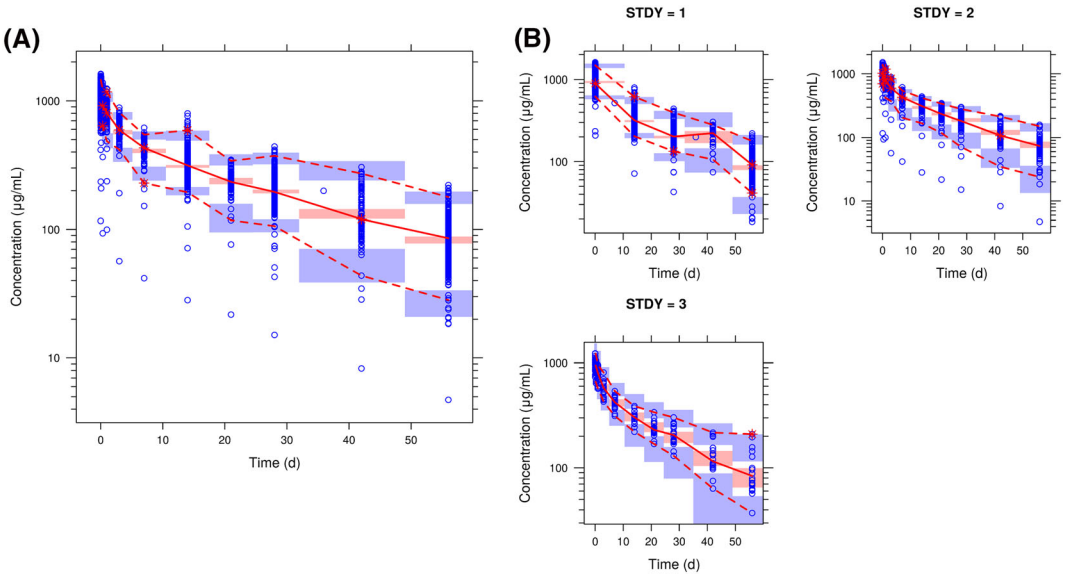

FIGURE 2 Panels show the visual predictive checks of final model including all data (A) and stratified by study (B). Blue shaded areas are the 95% prediction intervals of the 2.5th and 97.5th percentiles. Red dashed lines are the observed 2.5th and 97.5th percentiles of the data. The red shaded area is the 95% prediction interval of the median. The solid red line indicates the median of the observed data. Stdy = 1 refers to Study HGS1021-C1063, Stdy = 2 to HGS1021-C1064 and Stdy = 3 to HGS1021-C1069

TABLE 3 Summary of secondary PK parameters

Variable	Median value	2.5th and 97.5th percentiles
$AUC_{0-\infty}$ (µg d/mL)	16 446	11 280–24 286
C_{max} (µg/mL)	939	704–1288
Time above monkey threshold (d)	46.9	32.2–68.1
Half-life (d)	22.0	15.4–30.9

$AUC_{0-\infty}$: area under the curve from time zero to infinity, C_{max}: maximum concentration.

corroborated by cross-validation procedures, which confirmed overall goodness-of-fit and satisfactory model performance (Figure S3).

Based on the goodness-of-fit, as well on the results from the bootstrap, visual predictive check and NPDE, the final model was deemed to have acceptable predictive performance to describe raxibacumab exposure in adult subjects. Subsequently, secondary parameters including AUC from time zero to infinity ($AUC_{0-\infty}$), C_{max} and time above the observed maximum level of protective antigen in serum in monkeys were calculated and are summarized in Table 3. The median $AUC_{0-\infty}$ was 16 446 µg d/mL, with 10th and 90th percentiles of 12 845 and 20 778 µg d/mL, respectively. C_{max} was found to have a median of 939 µg/mL, with 10th and 90th percentiles of 762 and 1177 µg/mL, respectively. The median half-life was 22.0 days, and 90% of the half-lives were within the range of 17.5–27.6 days.

4 | DISCUSSION

Since 2014, updated therapy guidelines for *B. anthracis* recommend the use of antitoxin treatment.[16] Raxibacumab was the first monoclonal antitoxin shown to provide additional protection against inhalational anthrax via a mechanism different from that of either antibiotics or active immunization. At the recommended doses, and in combination with currently available and recommended therapies, raxibacumab has been shown to reduce the morbidity and mortality of inhalational anthrax in animal models. Given the mechanism by which raxibacumab neutralizes PA during an infection, characterisation of systemic exposure represents a proxy for efficacy. The use of nonlinear mixed effects modelling for the assessment of the disposition properties in humans allows further understanding of IIV and contribution of baseline demographic covariate factors to differences in systemic exposure.

Furthermore, availability of a population PK model may provide valuable information in the event of clinical use of raxibacumab (e.g. in the event of bioterrorism). *Post-hoc* estimates of individual exposure can be obtained after collection of sparse blood samples during a postmarketing study. Predicted raxibacumab concentration *vs.* time profiles may be used to further characterise treatment response in a setting which would be difficult to control, given the circumstances of suspected exposure or inhalation of anthrax.[17]

From a PK perspective, the time course of raxibacumab concentrations in plasma was best described by a 2-compartment model with first order elimination. As for many other mAbs, body weight was found to be the only significant covariate on clearance, intercompartment clearance, central and peripheral volume of distribution. Even though PK data in disease state patients are not available, it can be anticipated that the disposition properties of raxibacumab will be comparable to healthy subjects.

It should also be noted that estimated allometric exponents deviated from the typical values observed for clearance and volume of

distribution (i.e. 0.75 and 1). However, the exponent estimated on clearance (0.83) is close to what has been reported in literature for other mAbs.[18]

Previous reports have suggested that in such cases, body surface area, lean body weight or ideal body weight could also be considered instead of total body weight.[19] Unfortunately, height, which is a requirement for the calculation of body surface area, lean body weight and ideal body weight, was not collected for the majority of the subjects (73%).

IIV in clearance was estimated as 0.04 (Table 2); however, the variability of the *post-hoc* individual parameters in the investigated subjects was 0.07. This suggests that slightly more that 40% of the total IIV was due to differences in body weight. While the distribution of body weight of the healthy subjects was narrow with a standard deviation of 17 kg, the variability in clearance is likely to be higher in younger subjects due to a large range in body weight. Due to the nonlinear relationship of bodyweight and clearance, a 10-kg difference in younger subjects could result in a change of clearance of 20% (e.g., from 20 to 30 kg) while a 10-kg increase in older, adult subjects could result in a change of only 10% (e.g., from 80 to 90 kg). Furthermore, in the current analysis, any time-dependent effect on disposition parameters has not been identified. Interoccasion variability was not identified for the 43 subjects who received a second raxibacumab dose given either 14 days (Study HGS1021-C1063) or at least 4 months (Study HGS1021-C1069) after their initial dose.

With regard to the potential impact of drug–drug interactions, the effect of ciprofloxacin on the PK of raxibacumab was formally assessed in Study HGS1021-C1064, which showed no interaction between the 2 moieties. Secondary parameters (Table 3) matched those that were observed previously.[12] A separate analysis has also shown that coadministration of raxibacumab with subcutaneous administration of Anthrax Vaccine Adsorbed, as part of a post-exposure prophylaxis regimen in healthy subjects, did not affect the disposition of raxibacumab.[20] In addition, PK parameter estimates were of the same order of magnitude of obiltoxaximab, which is another mAb against AT.[21] Raxibacumab was found to have a lower clearance and total volume of distribution compared to obiltoxaximab, which were ~50% and 25% higher, respectively. These differences are reflected in the slightly longer half-life of raxibacumab: 22.0 *vs.* 20.2 days in the largest study ($n = 202$) of obiltoxaximab.[22]

In summary, we have developed a population PK model including covariate effects and stochastic components that enable accurate description of the disposition characteristics of raxibacumab in adult subjects. Parameter estimates were sufficiently precise for subsequent use of the model for extrapolation of the PK properties and investigation of the dosing requirements for the paediatric population.[23] Both the IIV and the effect of potential covariates are important factors when defining the dose rationale across the paediatric population, as they influence the circulating concentration and time that raxibacumab concentrations remain above the minimum efficacious levels in preclinical species. As administration of raxibacumab to healthy paediatric subjects for the sole purpose of investigating its safety and PK profile is not ethical, the use of an extrapolation approach that accounts for the impact of developmental growth and maturation processes becomes critical.[24]

In conclusion, doses of 40 mg/kg provided comparable exposure across the overall healthy subject population. IIV in raxibacumab concentration *vs.* time profiles could partially be accounted for by differences in body weight. The availability of a population PK model in the event of anthrax inhalation will allow characterisation of the disposition characteristics in patients using sparse blood sampling and support the evaluation of efficacy in a future postmarketing study.

ACKNOWLEDGEMENTS

The authors are thankful to the reviewers from Emergent BioSolutions who contributed to review of the final manuscript. Editorial support in the form of formatting and redrawing figures was provided by Lisa Auker, PhD, of Fishawack Indicia Ltd. part of Fishawack Health (funded by GSK). This work was funded by GSK.

CONTRIBUTORS

S.P.O. analysed the data and wrote the manuscript. O.D.P. designed the research study, wrote the manuscript and contributed to interpretation of results.

COMPETING INTERESTS

S.P.O. declares no conflict of interest. O.D.P. is an employee of GSK and holds stocks/shares in GSK.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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REFERENCES

1. Holty JE, Bravata DM, Liu H, Olshen RA, McDonald KM, Owens DK. Systematic review: a century of inhalational anthrax cases from 1900 to 2005. *Ann Intern Med*. 2006;144(4):270-280.
2. Meselson M, Guillemin J, Hugh-Jones M, et al. The Sverdlovsk anthrax outbreak of 1979. *Science*. 1994;266(5188):1202-1208.
3. US Department of Justice. Amerithrax investigative summary, 2010. Available at: https://www.justice.gov/archive/amerithrax/docs/amx-investigative-summary.pdf (last accessed on 05/11/20).
4. Centers for Disease Control and Prevention. Anthrax symptoms. Available at: https://www.cdc.gov/anthrax/basics/symptoms.html (last accessed on 05/11/20).
5. The National Institute for Health and Care Excellence (NICE). Anthrax, 2019. Available at: https://bnf.nice.org.uk/treatment-summary/anthrax.html (last accessed on 05/11/20).
6. Holty JE, Kim RY, Bravata DM. Anthrax: a systematic review of atypical presentations. *Ann Emerg Med*. 2006;48(2):200-211.
7. Inglesby TV, O'Toole T, Henderson DA, et al. Anthrax as a biological weapon, 2002: updated recommendations for management. *JAMA*. 2002;287(17):2236-2252.
8. Jernigan JA, Stephens DS, Ashford DA, et al. Bioterrorism-related inhalational anthrax: the first 10 cases reported in the United States. *Emerg Infect Dis*. 2001;7(6):933-944.

9. Pimental RA, Christensen KA, Krantz BA, Collier RJ. Anthrax toxin complexes: heptameric protective antigen can bind lethal factor and edema factor simultaneously. *Biochem Biophys Res Commun*. 2004; 322(1):258-262.
10. Subramanian GM, Cronin PW, Poley G, et al. A phase 1 study of PAmAb, a fully human monoclonal antibody against *Bacillus anthracis* protective antigen, in healthy volunteers. *Clin Infect Dis*. 2005;41(1): 12-20.
11. Hering D, Thompson W, Hewetson J, Little S, Norris S, Pace-Templeton J. Validation of the anthrax lethal toxin neutralization assay. *Biologicals*. 2004;32(1):17-27.
12. Migone TS, Subramanian GM, Zhong J, et al. Raxibacumab for the treatment of inhalational anthrax. *N Engl J Med*. 2009;361(2): 135-144.
13. U.S. drug label. Raxibacumab (2018 rev.), 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125349s022lbl.pdf (last accessed on 05/11/20).
14. Migone TS, Bolmer S, Zhong J, et al. Added benefit of raxibacumab to antibiotic treatment of inhalational anthrax. *Antimicrob Agents Chemother*. 2015;59(2):1145-1451.
15. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2015.
16. Hendricks KA, Wright ME, Shadomy SV, et al. Centers for Disease Control and Prevention Expert Meetings on Prevention and Treatment of Anthrax in Adults, 2014. Available at: https://wwwnc.cdc.gov/eid/article/20/2/13-0687_article (last accessed on 05/11/20).
17. Kummerfeldt CE. Raxibacumab: potential role in the treatment of inhalational anthrax. *Infect Drug Resist*. 2014;7:101-109.
18. Deng R, Iyer S, Theil FP, Mortensen DL, Fielder PJ, Prabhu S. Projecting human pharmacokinetics of therapeutic antibodies from nonclinical data: what have we learned? *MAbs*. 2011;3(1): 61-66.
19. Azzopardi N, Lecomte T, Ternant D, et al. Cetuximab pharmacokinetics influences progression-free survival of metastatic colorectal cancer patients. *Clin Cancer Res*. 2011;17(19):6329-6337.
20. Skoura N, Wang-Jairaj J, Della Pasqua O, et al. Effect of raxibacumab on immunogenicity of Anthrax Vaccine Adsorbed: a phase 4, open-label, parallel-group, randomised non-inferiority study. *Lancet Infect Dis*. 2020;20(8):983-991.
21. Greig SL. Obiltoxaximab: First Global Approval. *Drugs*. 2016;76(7): 823-830.
22. Nagy CF, Leach TS, Hoffman JH, Czech A, Carpenter SE, Guttendorf R. Pharmacokinetics and tolerability of obiltoxaximab: a report of 5 healthy volunteer studies. *Clin Ther*. 2016;38(9): 2083-2097 e7.
23. Bellanti F, Della Pasqua O. Modelling and simulation as research tools in paediatric drug development. *Eur J Clin Pharmacol*. 2011; 67(Suppl 1):75-86.
24. Robbie GJ, Zhao L, Mondick J, Losonsky G, Roskos LK. Population pharmacokinetics of palivizumab, a humanized anti-respiratory syncytial virus monoclonal antibody, in adults and children. *Antimicrob Agents Chemother*. 2012;56(9):4927-4936.

SUPPORTING INFORMATION

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

How to cite this article: Oosterholt SP, Della Pasqua O. Population pharmacokinetics of raxibacumab in healthy adult subjects. *Br J Clin Pharmacol*. 2021;1–8. https://doi.org/10.1111/bcp.14894