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ORIGINAL PAPER

Study design and population pharmacokinetic analysis of a phase II dose-ranging study of interleukin-1 receptor antagonist

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Abstract Interleukin-1 receptor antagonist, a naturally-occurring antagonist to the pro-inflammatory cytokine Interleukin-1, is already in clinical use. In experimental models of stroke, Interleukin-1 receptor antagonist in cerebrospinal fluid has been associated with cerebral neuroprotection and in a phase I clinical trial in patients with subarachnoid haemorrhage it crosses the blood-cerebrospinal fluid barrier. The aims of the current work were to design a dose-ranging clinical study in patients and to analyse the plasma and cerebrospinal fluid data obtained using a population pharmacokinetic modelling approach. The study was designed using prior information: a published population pharmacokinetic model and associated parameter estimates. Simulations were carried out to identify combinations of intravenous bolus and 4 h infusion doses that could achieve a concentration of 100 ng/ml in cerebrospinal fluid within approximately 30 min. The most informative time points for plasma and cerebrospinal fluid were obtained prospectively; optimisation identified five sampling time points that were included in the 15 time points in the present study design. All plasma and cerebrospinal fluid concentration data from previous and current studies were combined for updated analysis. The result of the simulations showed that a dosage regimen of 500 mg intravenous bolus and 10 mg/kg/h could achieve the target concentration, however four other regimens that represent a stepwise increase in maximum concentration were also selected. Analysis of the updated data showed improvement in parameter accuracy and predictive performance of the model; the percentage relative standard errors for fixed and random-effects parameters were <15 and 35 % respectively. A dose-ranging study was successfully designed using modelling and simulation.

Keywords Population pharmacokinetics · Anakinra · Interleukin-1 receptor antagonist · Optimal design · Simulation

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Introduction

Cerebrovascular disease is the leading cause of disability and the second leading cause of death and dementia worldwide [1]. Abrogation of inflammation-mediated pathological processes after cerebral ischaemia have repeatedly demonstrated efficacy in models of cerebral ischaemia. Interleukin-1 (IL-1) is implicated in brain injury such as that occurring after ischaemic stroke and subarachnoid haemorrhage (SAH) [2, 3]. Interleukin-1 receptor antagonist (IL-1Ra), a naturally-occurring antagonist to the pro-inflammatory cytokine IL-1, is already in clinical use to treat a select variety of auto-immune diseases [4].

Recombinant formulation of IL-1Ra, anakinra is in market as Kineret. In experimental preclinical study of stroke in rats, a 100 ± 82 ng/ml (mean $\pm$ SD) concentration of IL-1Ra in cerebrospinal fluid (CSF) has been associated with cerebral neuroprotection [4]. Following intravenous bolus dose of 10 mg and 0.8 mg/h 24 h infusion, concentration of approximately 100 ng/ml was maintained in the CSF between 30 min and end of infusion.

In a phase I clinical trial in patients with SAH, we have previously demonstrated that IL-1Ra crosses the blood-CSF barrier (BCB) and that our target concentration of 100 ng/ml was attained, albeit slowly [4]. Using data from this study, a population pharmacokinetic (PK) model was developed to describe the PK of IL-1Ra in plasma and CSF following intravenous (IV) administration in patients with intracranial haemorrhage [5]. This previous population PK model was developed using data obtained from six SAH patients administered IL-1Ra using a regimen used previously in sepsis patients on intensive care—a 100 mg IV bolus followed by a 2 mg/kg/h infusion and average of 19 plasma and CSF samples each.

The establishment of a clinical PK model in this particular cohort of patients is of significant importance for both clinical trial simulation and dose optimisation. Numerous experimentally efficacious neuroprotective drugs have failed to translate into clinical practise despite highly encouraging preclinical effects in animal models of the disease [6]. In light of this, the stroke therapy academic industry roundtable (STAIR) committee recommended criteria for successfully translating experimental therapeutic agents in stroke [6]. Appreciation of the differences in pharmacology between humans and other animal species is cited as one of the most important factors. In the case of IL-1, the cytokine is transported from blood to brain and CSF by a highly specific saturable system in the healthy rat [3]. By contrast, clinical studies have demonstrated that most of the transport across the blood-CSF barrier is largely passive in humans [4, 5]. We have shown previously that although IL-1Ra administered IV penetrates into CSF in patients with SAH, the rate of transfer is in the order of six times slower than in the rat brain [4]. In ischaemic stroke, this delay in achieving potentially therapeutic concentrations in CSF is further exacerbated by the time from diagnosis to starting treatment that averages a few hours in most hospital settings [7]. With a quantifiable loss of neuronal tissue every minute after acute stroke [8], establishing a dosing regimen that achieves experimentally therapeutic concentrations of IL-1Ra within time frames observed in experimental studies is crucial before proceeding to efficacy studies.

Modelling and simulation have been widely used in clinical pharmacology experiments especially in drug development and the benefits have been discussed [9]. One very important use of this approach is design of future experiments using prior information, at every stage of the drug development programme information about the model and parameter estimates are updated and are also used to make decisions and design the next phase. This can be achieved through the use of simulation and optimal design theories [10, 11]. Design optimisation involves the use of prior information about the model and parameter estimates to optimise a function of the Fisher information matrix within experimental constraints [9]. This provides opportunity to design data collection for a study using a sampling design that provides maximum information about the pharmacokinetics of the drug. Methodologies and tools for optimal design of experiments in clinical pharmacology have been widely discussed in the literature [12].

The results obtained from previous clinical trials including the published population PK model, provide prior information that can be used for prospective design of future studies. Although the data analysis of the previous studies showed that IL-1Ra does cross the blood–brain barrier (BBB) and BCB, the time taken to achieve experimentally therapeutic concentrations was 3 h [4, 5]. The aim of this study was to use prior information to inform an open-labelled multicentre dose-ranging study for IL-1Ra in SAH patients through simulations, design optimisation and predictive interval planning. The main aim of the study was to determine a dosage regimen that will achieve a target concentration (100 ng/ml), selected based on preclinical studies [4] within approximately 30 min.

Materials and methods

Study design—simulations

The proposed dose ranging study was designed using a previously published population PK model [5]. The parameter estimates obtained from this publication was refined in the NONMEM (version VI) programme using the first order (FO) approximation [13]. Simulations were carried out using different permutations of IV bolus (100–1000 mg) and 4 h infusion (1–10 mg/kg/h) doses of anakinra. Plasma and CSF concentrations at different time points were simulated for 1000 individuals for each combination of IV bolus and infusion doses. The aim of the simulation was to determine time to reach the target concentration of 100 ng/ml in CSF by different combinations.

Design optimisation

To improve the efficiency of the proposed study, sampling times were optimised in PopDes [14], which allows identification of the most informative time points for sampling

of both plasma and CSF in a multiresponse study design. The previous model and parameter estimates were used as prior information for the optimisation (Table 1). The initial options used in PopDes include a multiresponse design, five time points for joint sampling of plasma and CSF, 25 subjects with the same number of sampling times (one elementary design) and one dosing regimen (100 mg bolus and 2 mg/kg/h infusion), Fedorov exchange optimiser and a sampling time interval between 10 and 1440 min (with 10 min increment). To increase the speed of computation, analytical solutions to the differential equations were obtained for both plasma and CSF drug concentrations using Laplace transformation techniques.

Clinical study

The study was conducted primarily at Salford Royal Foundation Trust, Salford, UK which was also the sponsor. Anakinra used for the study was provided by Amgen (Thousand Oaks, CA, USA). The study protocol was approved by the Medicine and Healthcare Product Regulatory Agency and the hospital and National Research Ethics Committee. Patients were recruited at Salford Royal Foundation Trust and Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK between December 2007 and December 2008. Galea et al. [15] provided detailed information on the demographics, general and neurosurgical characteristics of the cohorts including inclusion and exclusion criteria, which were representative of the target population suffering from subarachnoid haemorrhage. Patients received anakinra as an IV bolus followed by a 4 h IV infusion of the drug using a clinical grade volumetric pump as per the allocated regimen in an open-labelled design. Deviations from the planned administration such as delay between bolus or infusion or interruptions (e.g. due to venous access problems) were documented to the nearest minute. Plasma and CSF samples were obtained simultaneously at defined time intervals.

Population pharmacokinetic data analysis

Plasma and CSF drug concentrations from this study were used to update the previous population PK model (Gueorguieva et al. [5]) and the performance of the two models (previous and updated model) were assessed. The modelling was done using the combined data, including data from the two different studies, from a total of 31 subjects. The first set of data included the six subjects that received a 100 mg IV bolus followed by a 24 h IV infusion of IL-1Ra at 2 mg/kg/h and was used to develop the previous population PK model (Gueorguieva et al. [5]). The second set of data was obtained from 25 subjects in the dose-ranging study and received one of 5 different combinations of IV bolus and 4 h infusion doses of IL-1Ra given simultaneously and shown in Table 2 (five subjects in each dosage regimen). The modelling was done in NONMEM (version VII) using the two-compartment first order elimination model for plasma and one compartment for CSF proposed by Gueorguieva et al. [5]. The model assumes drug

Table 1 Parameters estimates for the previous and updated models and bootstrap analysis using all data

Parameter	Description	Previous		Updated		Bootstrap	
		Est	RSE (%)	Est	RSE (%)	Est	RSE (%)
$CL\,(L/h)$	Clearance	7.8	9.54	7.86	5.05	7.86	5.12
$V1\,(L)$	Central volume	4.43	12.39	5.74	4.93	5.70	5.19
$CLD\,(L/h)$	Inter-compartmental clearance	1.14	20.90	0.65	11.2	0.67	14.08
$V2\,(L)$	Peripheral volume	8.89	24.41	3.56	10.03	3.63	11.58
$CL_{IN}\,(L/h)$	Plasma to CSF transfer clearance	0.0087	21.45	0.0071	11.34	0.0071	11.55
$CL_{OUT}\,(L/h)$	Transfer clearance out of CSF	0.487	7.80	0.44	11.21	0.44	11.23
ω^2_{CL}	CL BSV	0.0295	55.59	0.052	28.46	0.050	27.41
ω^2_{V1}	V1 BSV	0.0745	57.32	0.0381	34.12	0.0380	35.67
ω^2_{CLD}	CLD BSV	0.266	77.82	0 (FIXED)	–	0 (FIXED)	–
ω^2_{V2}	V2 BSV	0.153	46.60	0.0399	31.83	0.041	34.94
$\omega^2_{CL_{IN}}$	CL_{IN} BSV	0.129	115.50	0.261	28.39	0.250	29.13
$\omega^2_{CL_{OUT}}$	CL_{OUT} BSV	0.365	106.58	0.250	31.92	0.242	33.19
σ^2_{Plas}	Plasma residual error	0.0667	49.78	0.10	12.5	0.10	12.23
σ^2_{CSF}	CSF residual error	0.320	39.38	0.193	13.63	0.193	13.37

Base—mean (SD): plasma 0.57 ng/ml (0.67), CSF 0.47 ng/ml (0.51), BSV is between subject variability

Table 2 Proposed dosage regimen and results of simulations and observed data on time to reach 100 ng/ml in CSF, maximum concentration (C_{max}) and time of maximum concentration (T_{max}) in the CSF

Regimen	Doses		Simulation (CSF)			Observed (CSF)	
	Bolus (mg)	Infusion (mg/kg/h)	Time (min) to 100 ng/ml[a]	C_{max} (ng/ml)	T_{max} (min)	Subjects to 100 ng/ml[b]	Individual time (min) to 100 ng/ml
1	100	4	110 (40–237)	206 (109–530)	275 (246–359)	5/5	80,140,116,140,185
2	200	2	135 (28–247)	145 (102–347)	270 (244–369)	2/5	253,217
3	300	2	94 (16–241)	158 (103–382)	265 (243–347)	3/5	69,113,199
4	400	6	43 (12–161)	326 (138–856)	271 (244–377)	4/5	35,55,102,209
5	500	10	30 (8–110)	527 (191–1461)	273 (244–361)	5/5	44,45,73,82,87

[a] Median (95 % prediction interval)

[b] Number of subjects that reached 100 ng/ml concentration in the CSF/number of subjects in the group

elimination from the CSF compartment and the drug does not return to plasma. Details of this model and assumptions are described in Gueorguieva et al. [5]. Population parameters were estimated using a nonlinear mixed-effects modelling approach using the FOCE/INTERACTION option. Typical individual parameters (fixed-effects), between-subject and residual variability (random-effects) were estimated simultaneously. Lognormal distributions were assumed for both the interindividual and residual variabilities. Baseline concentrations of naturally occurring IL-1Ra were accounted for in the model. The equation for the updated model is described in Eq. (1)

$$y_{ijk} = \left(f_k(\theta_i, t_{ij}) + Base_k\right)e^{\varepsilon_{ijk}} \quad (1)$$

where y_{ijk} is the observed plasma ($k = 1$) and CSF ($k = 2$) concentration for the $i^{th}(i = 1, \ldots, N)$ individual at the $j^{th}(j = 1, \ldots, n_i)$ time, t_{ij} and ε_{ijk} is the residual error ($\varepsilon_{ijk} \sim N(0, \sigma_k^2)$). $f_k(\theta_i, t_{ij})$ is the k^{th} model prediction and θ_i is the vector of individual parameters estimates, where $\theta_i = \theta \cdot e^{b_i}$. θ is the vector of typical individual parameter estimates and b_i is the vector of individual deviations from the typical individual parameter estimates, where $b_i \sim N(0, \Omega)$ and Ω is a diagonal element matrix with variances of the individual parameter (inter-individual variability) as the diagonal elements. $Base_k$ is the baseline IL-1Ra concentration in plasma or CSF. The structural model was parameterised in terms of clearances and volumes which were the volume of distribution of the plasma compartment ($V1$), volume of distribution of the peripheral compartment ($V2$), total plasma clearance (CL), intercompartmental clearance (CLD), clearance for the transfer of drug from plasma to CSF compartment (CL_{IN}) and clearance for the transfer of drug out of CSF (CL_{OUT}). For identifiability purposes, the volume of distribution in the CSF compartment (V_{CSF}), was fixed to the volume of distribution of the central compartment ($V1$) (Gueorguieva et al. [5]). The lists of parameters estimated are given by.

$$\theta = [CL, V1, V2, CLD, CL_{IN}, CL_{OUT}] \quad (2)$$

$$\Omega = diag\left[\omega_{CL}^2, \omega_{V1}^2, \omega_{V2}^2, \omega_{CLD}^2, \omega_{CL_{IN}}^2, \omega_{CL_{OUT}}^2\right] \quad (3)$$

$$\sigma^2 = \left[\sigma_{Plas}^2, \sigma_{CSF}^2\right] \quad (4)$$

Visual inspection of the diagnostic plots of residual and population and individual predictions were used to support model selection. Peal-speaks NONMEM (PsN) was used for nonparametric bootstrap analysis of the updated model [16, 17], one-thousand bootstrap replicates were sampled from the original data using individual's datasets as sampling unit, parameter estimates from the replicates were used to obtain mean and percentage relative standard error (RSE%). The predictive performance of the updated population PK model was assessed by the visual predictive check (VPC) using the model and parameter estimates. Ten-thousand plasma and CSF IL-1Ra concentrations were simulated at each time points and the 2.5th, 50th (median) and 97.5th percentiles were generated to obtain 95 % prediction intervals.

Results

Study design

The refined parameter estimates from the previous study are shown in Table 1, and Fig. 1 shows the results of the simulation for selected combinations of IV bolus (0–500 mg) and infusion (2–10 mg/kg/h) based on the mean time to reach 100 ng/ml in CSF (mean of 1000 simulated individual's time to reach 100 ng/ml). The selected dosage regimens for the proposed dose-ranging study are shown in Table 2. This table also include simulated (median and 95 % prediction intervals) time to reach 100 ng/ml, CSF maximum concentration (C_{max}) and time of maximum concentration (T_{max}) for each of the five dosage regimens.

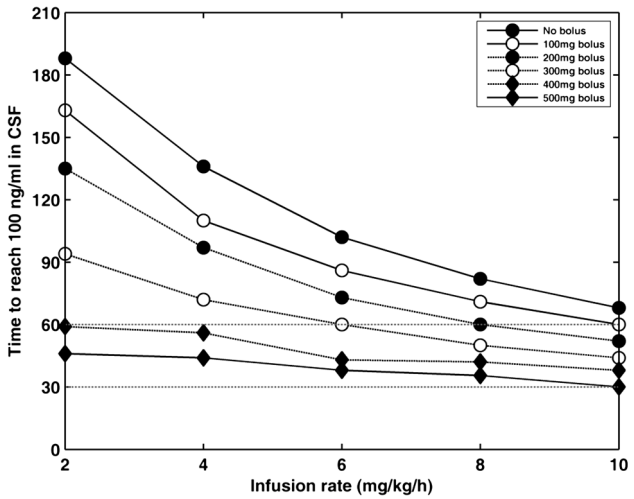

Fig. 1 Results of the simulation based on the mean time to reach 100 ng/ml in CSF for different combination of intravenous bolus and 4 h infusion doses

The selected regimen that will achieve the target concentration of 100 ng/ml in CSF within approximately 30 min was Regimen 5 (500 mg bolus and 10 mg/kg/h infusion doses). This regimen was selected because it would achieve the target with the lowest mean C_{max} in the CSF. Four other regimens were selected for safety reasons and these regimens represent a stepwise increase in C_{max} before Regimen 5. Anakinra has been shown to have a good safety and tolerability profile and no serious adverse reactions was expected, however the regimens were selected only as a precaution.

Design optimisation

Table 3 shows a summary of optimal and evaluated designs. The optimal design (Design 1) obtained assuming five sampling times in 25 subjects with a dosing regimen of 100 mg bolus and 2 mg/kg/h infusion was 10, 300, 360, 540 and 1440 min. This design was evaluated for the five dosage regimens in Table 2 assuming these sampling times are implemented with five subjects per regimen and in Design 3, the optimal five sampling times points were included in a 15 time points design that was proposed for the trial. The predicted percentage relative standard errors (RSE%) obtained in PopDes for these designs are shown in Table 4.

Population pharmacokinetics data analysis

The predictive performance of the previous model (Gueorguieva et al. [5]) was accessed using the data from the new trial. The 95 % prediction intervals and the median lines obtained from this model were superimposed with observed plasma and CSF IL-1Ra concentration data in Figs. 2 and 3 respectively for different dosage regimen. The data from the previous study (Gueorguieva et al. [5]) and the new trial were combined for analysis as described under Methods. The parameter estimates and RSE% obtained from this updated analysis in NONMEM and nonparameteric bootstrap estimates and RSE% are shown in Table 1. Of the 1000 bootstrap runs that were carried out, 914 resulted in successful minimisation and 838 resulted in a successful covariance step. The replicates with successful minimisation were used to obtain the mean parameter estimates and the RSE% was obtained from the standard deviation of individual estimates from replicates. Plots of 2.5th, 50th (median) and 97.5th percentiles (95 % prediction intervals) as VPC for all the data using the updated model and parameter estimates overlaid with the observed plasma and CSF IL-1Ra concentration data are shown in Figs. 4 and 5 respectively for different dosage regimens. Plots of population and individual predictions for plasma and CSF for each individual and the observed plasma and CSF IL-1Ra concentration data are shown in Fig. 6. Plots of observed and population predicted, observed and individual predicted, conditional weighted residual (CWRES) and population model predicted and CWRES and time for both plasma and CSF IL-1Ra concentrations using the updated model and parameter estimates were also obtained (Supplementary Material). Anakinra was well tolerated during the study as there were no suspected unexpected serious adverse reactions attributed to the drug; the incidence of infections was comparable to other studies in neurosurgical units [15].

Discussion

This work has presented the design and analysis of a dose-ranging study in relevant patients using prior information from the literature. A previous model (Gueorguieva et al. [5]) was used for dose and sampling times optimisation of a prospective study. A combination of IV bolus and 4 h infusion doses of 500 mg and 10 mg/kg/h respectively that allows a target concentration of 100 ng/ml to be achieved within approximately 30 min was selected using simulation. This combination allows the target to be achieved with the lowest C_{max}. Although the initial aim was the target to be achieved in CSF within 60 min, approximately 30 min was selected to guard against any possible prediction error by the model. The data obtained from the previous study (Gueorguieva et al. [5]) had an average of 21 and 22 samples per patient for plasma and CSF respectively. Due to practical and ethical constraints with this number of samples, it was decided that the number of samples needed to be reduced to 15 samples each for plasma and CSF. The

Table 3 Summary of optimal and evaluated designs

Designs optimisation and evaluation			
Design #	Dose {# of subjects}	# of time points	Time points (min)
1	100 mg, 2 mg/kg/h {25}	5	10,300,360,530,1440
2	100 mg, 4 mg/kg/h {5}	5	10,300,360,530,1440
	200 mg, 2 mg/kg/h {5}		
	300 mg, 2 mg/kg/h {5}		
	400 mg, 6 mg/kg/h {5}		
	500 mg, 10 mg/kg/h {5}		
3	100 mg, 4 mg/kg/h {5}	15	10,20,30,45,60,90,120,240,300, 360,540, 1440,2880,4320,10080
	200 mg, 2 mg/kg/h {5}		
	300 mg, 2 mg/kg/h {5}		
	400 mg, 6 mg/kg/h {5}		
	500 mg, 10 mg/kg/h {5}		

Table 4 Predicted percentage relative standard error (RSE%) for different designs

Parameter	Description	Predicted RSE%		
		Design 1	Design 2	Design 3
CL	Clearance	5.079	5.092	3.804
$V1$	Central volume	6.682	6.717	6.524
CLD	Inter-compartmental clearance	12.80	12.85	11.79
$V2$	Peripheral volume	10.78	10.81	9.123
CL_{IN}	Plasma to CSF transfer clearance	14.05	14.09	9.848
CL_{OUT}	Transfer clearance out of CSF	14.06	14.10	13.43
ω^2_{CL}	CL BSV	43.26	43.38	32.72
ω^2_{V1}	V1 BSV	43.08	43.56	35.00
ω^2_{CLD}	CLD BSV	45.65	45.76	30.40
ω^2_{V2}	V2 BSV	53.87	53.77	30.63
$\omega^2_{CL_{IN}}$	CLIN BSV	77.31	77.71	45.94
$\omega^2_{CL_{OUT}}$	CLOUT BSV	55.06	54.97	20.91
σ^2_{prop} (Plas)	Plasma residual error	25.11	25.09	9.348
σ^2_{prop} (CSF)	CSF residual error	26.25	26.28	10.33

designs optimised and evaluated in Tables 3 and 4 show that the approach provides an opportunity to evaluate the ability of the different designs to estimate the parameters in the model with good precision. Design 1 was based on optimisation of five sampling time points per patient for joint sampling of plasma and CSF. This design with a total number of 250 plasma and CSF samples (125 each) showed that parameters, especially the fixed effect parameters, were well estimated. Design 2 is also similar to Design 1 in that they are both based on the same number of plasma and CSF samples but Design 2 was evaluated with a different dosage regimen (Table 2) assuming five subjects per regimen. It is therefore not surprising that the predicted RSE% is similar for the two designs. Design 3 is the final design that was proposed for the study, and was based on 15 time points for joint plasma and CSF sampling. This design will give a total of 750 samples (375 each) for plasma and CSF, which is three times the total number of samples in Design 1. The results in Table 3 show that this design improves on the performance of Design 2 as seen in the predicted RSE% especially for the random effect parameters. However despite an increase of 200 % in the total number of samples between Designs 2 and 3, Design 3 is only about 70 % more efficient relative to Design 2. This is because the sampling times in Design 2 have been selected by a process that allows the most informative 5 time points in the interval to be selected by using PopDes, although other time points in Design 3 contribute some information to the total information, but not to the same degree as sampling times in Design 2.

The predictive performance of the previous model by Gueorguieva et al. [5] show the model was able to predict

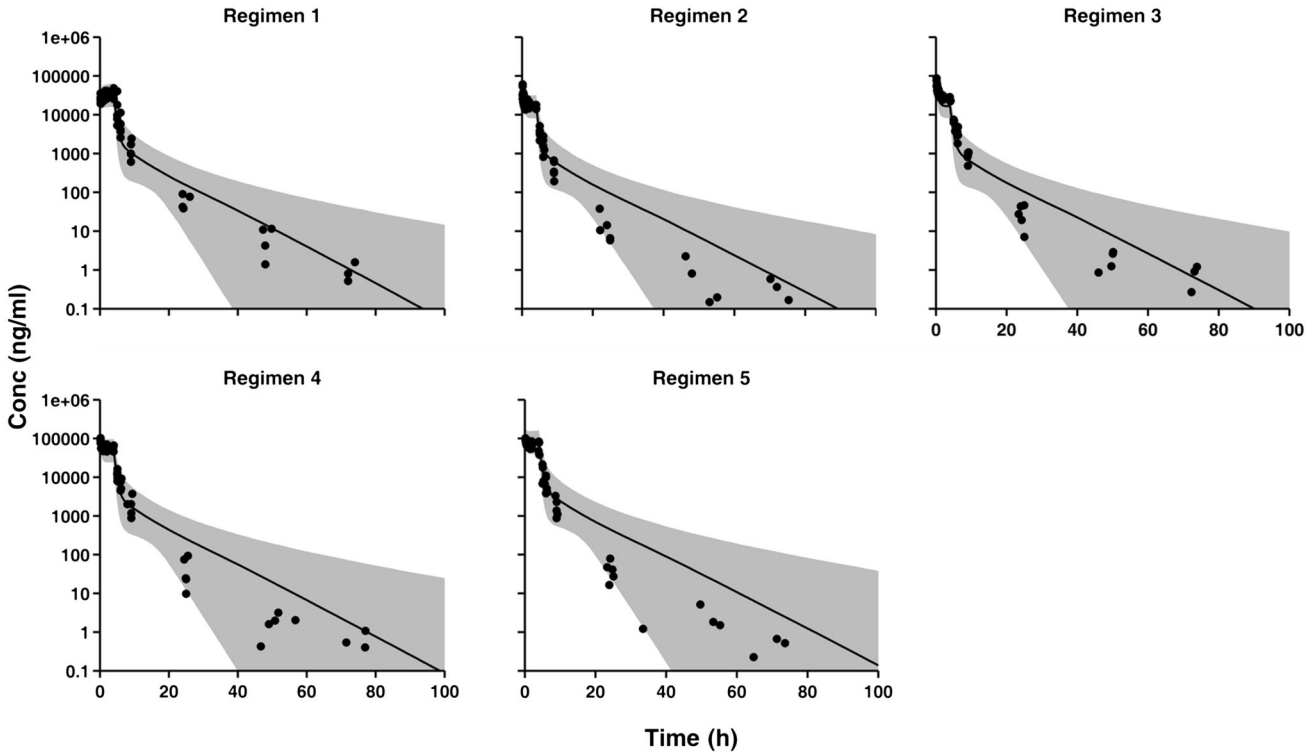

Fig. 2 Plots (plasma) of the 95 % prediction intervals (*grey areas*) and the median lines (*continuous lines*) obtained using the previous population PK model (Gueorguieva et al. [5]) and the observed plasma data (*filled circles*) for the five dosage regimen

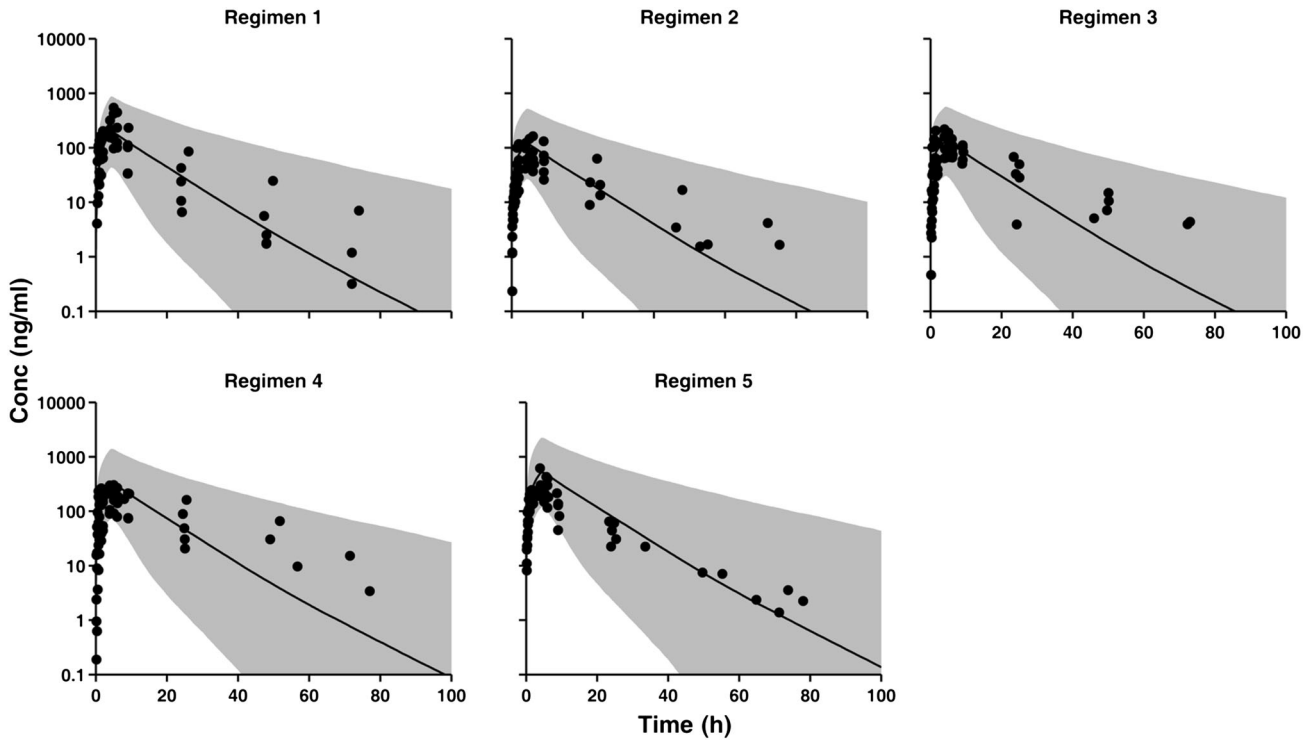

Fig. 3 Plots (CSF) of the 95 % prediction intervals (*grey areas*) and the median lines (*continuous lines*) obtained using the previous population PK model (Gueorguieva et al. [5]) and the observed CSF data (*filled circles*) for the five dosage regimen

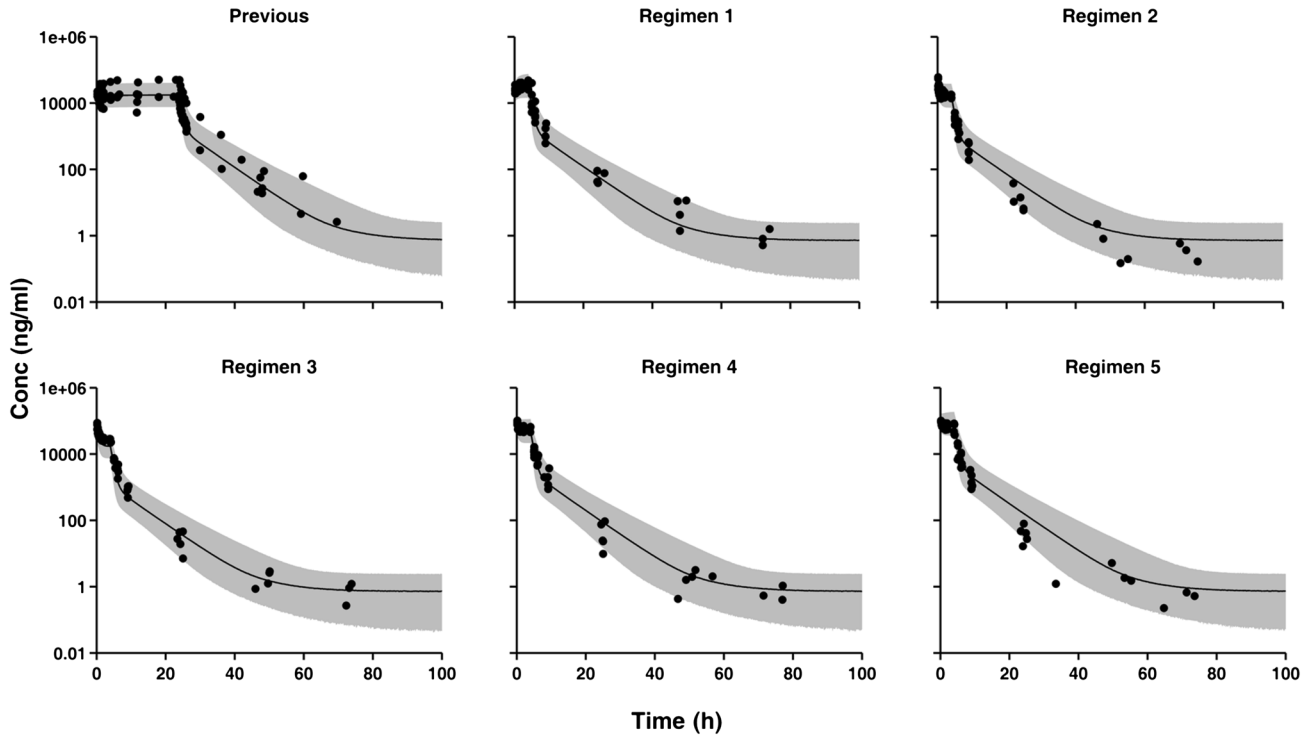

Fig. 4 Plots (plasma) of the 95 % prediction intervals (visual predictive check) (*grey areas*) and the median lines (*continuous lines*) obtained using the updated population PK model and the observed plasma data (*filled circles*) for the previous data and the five dosage regimen

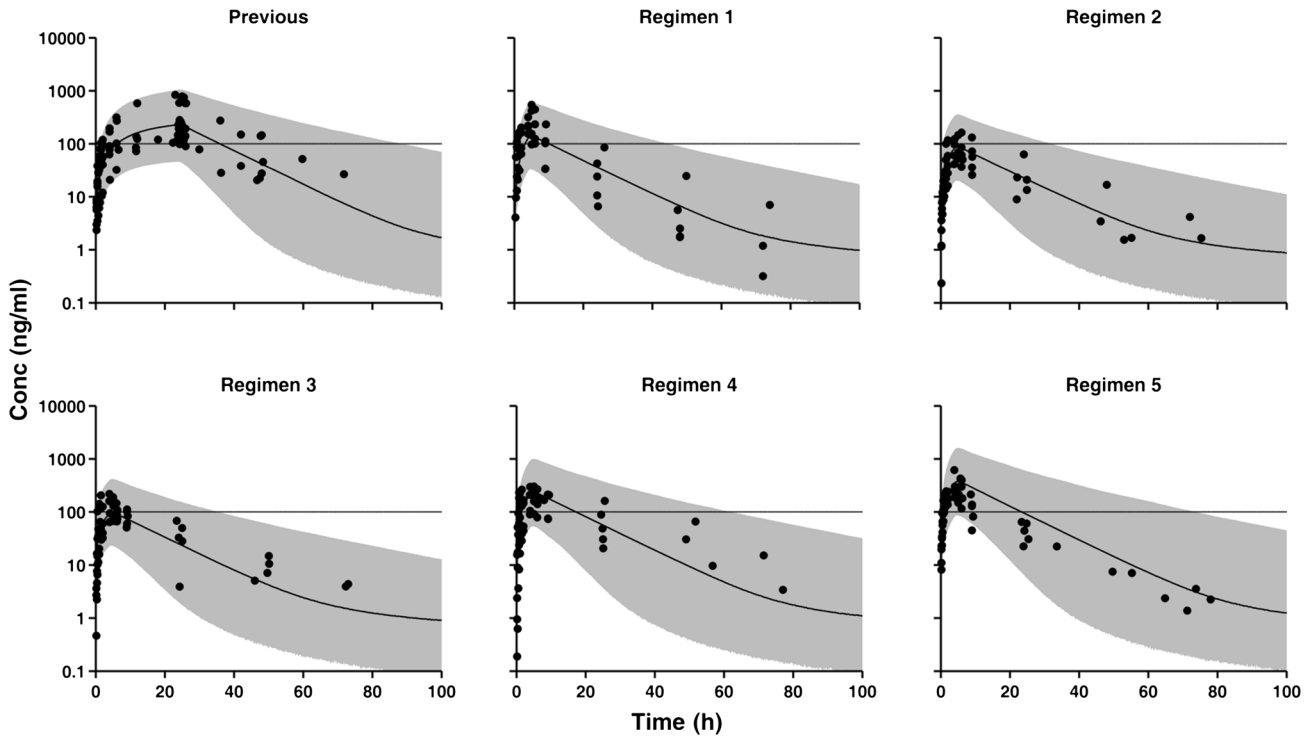

Fig. 5 Plots (CSF) of the 95 % prediction intervals (visual predictive check) (*grey areas*) and the median lines (*continuous lines*) obtained using the updated population PK model and the observed plasma data (*filled circles*) for the previous data and the five dosage regimen (the horizontal line represents 100 ng/ml)

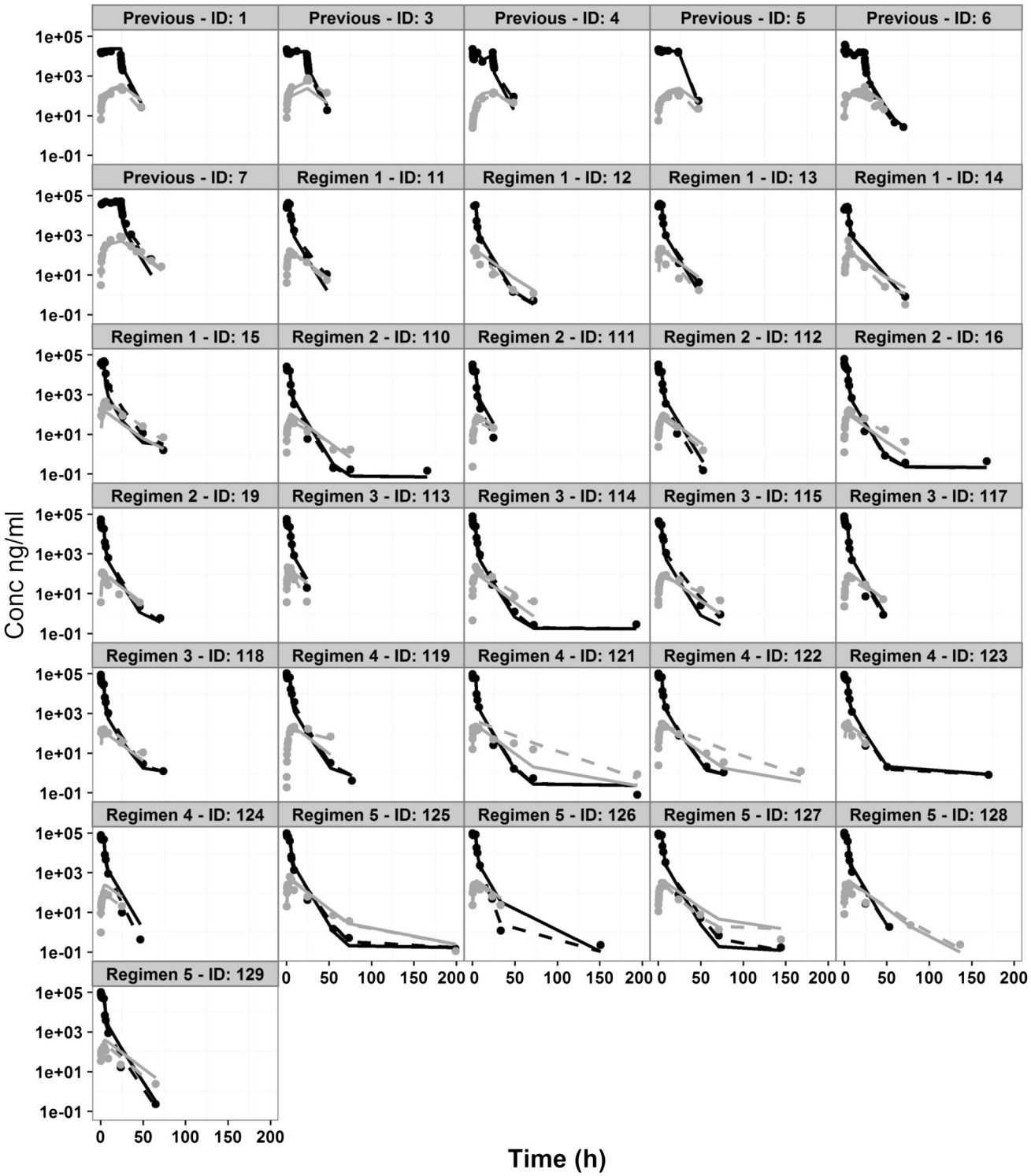

Fig. 6 Plots of observed individual plasma (*filled circles*) and CSF (*grey circles*) IL-1Ra concentrations and the population (*black and grey continuous lines*) and individual (*black and grey broken lines*) predicted IL-1Ra concentrations using the updated population PK model

the trend (median) of the data for both plasma and CSF especially within the first 20 h of dosing. However the variability in the data appears to be over-estimated by the previous model as the prediction intervals are wide and covered the whole plasma and CSF data. Also the model prediction did not follow the same trend as the data obtained after 50 h, especially for plasma data. This is because the previous model did not have plasma or CSF

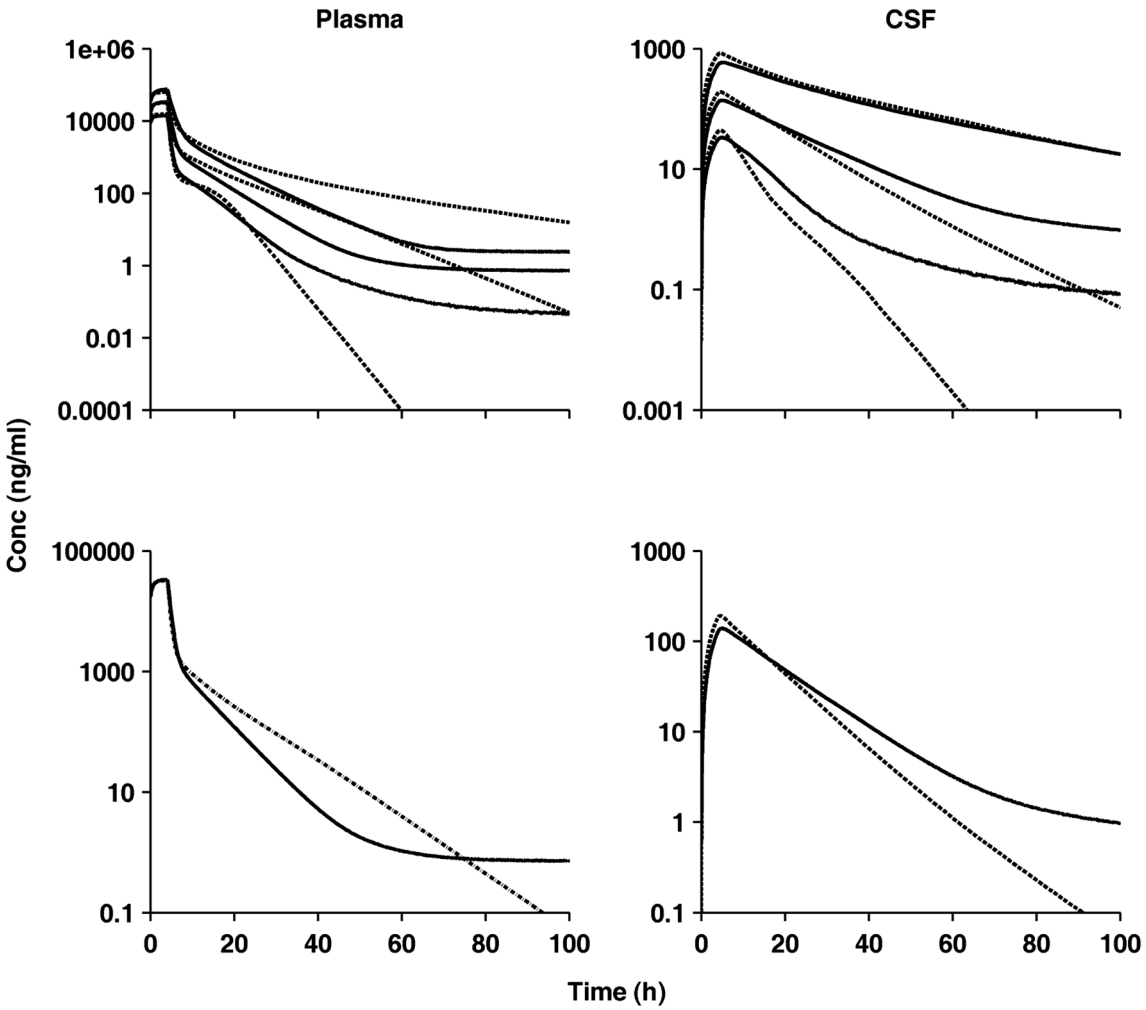

Fig. 7 Plots of 5th, 50th (median) and 97.5th percentiles (95 % prediction intervals) (*upper panels*) and median lines (*lower panels*) only for plasma and CSF obtained from the previous (*broken lines*) and updated (*continuous lines*) models

data beyond 50 h during which the profiles in individuals appear to return to baseline, and therefore not taken into account in the development of the model. This was corrected in this work as the measured baseline IL-1Ra concentration in plasma and CSF from individuals was incorporated in the development of the model. The data used in the previous model and the data obtained from this dose-ranging study were combined and analysed jointly. The total number of samples from the previous study was 256 (124 plasma and 132 CSF) and from the present study 699 (358 plasma and 341 CSF). As shown in Figs. 4 and 5 the use of individual baseline concentrations in the development of the model improves the predictive performance of the model. The variability in the data is much better estimated compared to the previous model, the prediction intervals are narrower and provided adequate coverage of the data and the trends of the intervals are the same as the observed data. The observed adequate performance of the model can also be seen with the plots of population and individual prediction and the observed IL-1Ra plasma and CSF data plotted for all the individuals (Fig. 6). The model adequately predicts the data in almost all cases and the trends in the profiles especially when it returns to baseline after 50 h (e.g. ID-16 and ID-114).

The plots of observed and population prediction and observed and individual prediction for plasma and CSF (Supplementary Material) using the updated model show considerable variability in the data and almost equal number of points are distributed on either side of the line of unity. The plots of CWRES versus population prediction and CWRES versus time (Supplementary Material) also show adequate prediction of the data as they did not reveal any systematic bias in the model prediction. The updated model obtained from this analysis and the previous model were compared using simulation (Fig. 7), the plots show that the predictions from the two models are comparable

for the first 10 h, however beyond this time the two models tend to diverge. This is due to the use of the baseline concentration in plasma and CSF in the development of the new model which allows the predictions to return to baseline rather than go toward infinite concentration as expected by the previous model. IL-1Ra is known to be neuroprotective in various models of brain injuries and there is emerging evidence that high baseline IL-1Ra: IL-1B levels are clinically associated with better outcome in central nervous system diseases [18]. Control levels of IL-1Ra have been reported to be as low as 40 pg/ml. After SAH, levels of IL-1Ra increase to levels up to 3000 pg/mL in patients with severe disease and poor outcome but do not exceed 5000 pg/mL and are typically much lower in patients with better outcome [19]. This six fold fluctuation observed in this patient cohort may be a response to curtail the deleterious effect of activation of IL-1 but more importantly introduces a significant baseline variation that may affect the concentration of exogenously administered IL-1Ra particularly during trough concentrations [20, 21]. Also in Table 2 is the proportion of subjects in each regimen that achieved the target concentration of 100 ng/ml in CSF and the time each subject achieved it. This was obtained from simulation using individual POSTHOC parameter estimates.

The results obtained from this study showed that a dose-ranging study was successfully designed using techniques in modelling and simulation using prior information to select dosage regimen and informative time points for sampling. The results of the data analysis of the combined data have also provided further information towards a good understanding of the PK of IL-1Ra and represent an important step in dose optimisation and will also help to design future efficacy studies.

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Compliance with ethical standards

Conflict of Interest NJR is a non-executive director of AstraZeneca plc, but this has no relation with the present study.

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