PHARMACOKINETICS

Population pharmacokinetic meta-analysis of ramucirumab in cancer patients

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AIMS

Ramucirumab is a human IgG1 monoclonal antibody that specifically binds vascular endothelial growth factor receptor-2 (VEGFR-2) and blocks binding of VEGF-A, VEGF-C and VEGF-D. The objective of the analysis was to characterize the clinical pharmacology profile of ramucirumab using a population pharmacokinetic approach.

METHODS

A total of 1639 patients with 6427 serum concentrations from 11 Phase 1b, 2 and 3 clinical trials in patients with various cancer indications were included in the analysis. Ramucirumab was administered as an intravenous infusion over 1 h at 8 mg kg^{-1} every 2 weeks or 10 mg kg^{-1} every 3 weeks. A series of pharmacostatistical models were developed to describe the concentration data. The best model was used to evaluate patient factors for their effect on ramucirumab pharmacokinetics.

RESULTS

The pharmacokinetics of ramucirumab were well characterized by a two-compartment model. Mean population estimates of clearance, volume of distribution and half-life for a typical 68-kg patient were 0.0148 l h^{-1}, 5.30 l and 13.4 days, respectively. A modest relationship was observed between body weight and ramucirumab disposition; clearance and central compartment volume increased with body weight. No other patient characteristics were shown to influence the disposition of ramucirumab in this patient population.

CONCLUSIONS

The final model adequately described the concentration–time profile of ramucirumab in patients with a range of cancer indications. The model confirmed that a weight-normalized dosing regimen is appropriate for ramucirumab therapy. Dose adjustment was not required for patients with mild to moderate renal impairment or mild hepatic impairment.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Ramucirumab is a human IgG1 monoclonal antibody vascular endothelial growth factor receptor-2 (VEGFR-2) antagonist that prevents binding of VEGF-A, -C and -D, and, therefore, results in blockade of VEGFR-2-mediated signalling and receptor-mediated pathway activation in endothelial cells.
- Ramucirumab is approved in the USA, European Union and Japan for the treatment of metastatic gastric and gastroesophageal adenocarcinoma, metastatic nonsmall cell lung cancer (in combination with docetaxel for platinum-resistant nonsmall cell lung cancer) and metastatic colorectal cancer (in combination with FOLFIRI).
- Ramucirumab pharmacokinetics (PK) were previously investigated in a noncompartmental manner based on a limited PK sampling schedule in patients with different solid tumours.

WHAT THIS STUDY ADDS

- This manuscript describes the development, qualification and application of a population PK model to provide a robust PK characterization for ramucirumab and to support statements in clinical pharmacology sections of ramucirumab prescribing information (drug label).
- This manuscript assesses the appropriateness of a body weight-based dosing regimen for ramucirumab in cancer patients.
- The current population PK model was used to derive exposure data for subsequent exposure-response analyses outside the scope of this manuscript.

Introduction

Kinase insert domain receptor [1] or vascular endothelial growth factor receptor-2 (**VEGFR-2**)-mediated signalling and angiogenesis can contribute to the pathogenesis and progression of cancer [2–4]. Ramucirumab (Cyramza™, IMC-1121B; Eli Lilly and Company, Indianapolis, IN, USA), a novel human immunoglobulin G, subclass 1 (IgG1) monoclonal antibody, specifically binds to the extracellular domain of VEGFR-2, thereby blocking the binding of VEGFR ligands **VEGF-A**, **VEGF-C** and **VEGF-D** and inhibiting receptor activation [5, 6]. VEGFR-2 appears to be primarily responsible for the mitogenic and angiogenic effects of VEGF-A, and experimental evidence suggests that the VEGF-A/VEGF-2 interactions play an important role in tumour angiogenesis, a process essential for tumour growth and metastasis [2–4].

Ramucirumab has demonstrated an overall survival benefit for patients with gastric cancer (REGARD and RAINBOW), nonsmall cell lung cancer (REVEL) and colorectal cancer (RAISE; Table 1) [7–10]. Ramucirumab has been approved in the USA, the European Union, Japan and many other jurisdictions for the treatment of advanced gastric cancer, nonsmall cell lung cancer and colorectal cancer [11–13]. In a Phase 3 trial in patients with hepatocellular carcinoma (HCC; REACH), ramucirumab demonstrated clinically meaningful improvement in overall survival (OS) with an acceptable safety profile in patient subgroups that had baseline α-fetoprotein $\geq 1.5 \times$ upper limit of normal or ≥ 400 ng ml^{-1} [14]. A confirmatory Phase 3 study (REACH-2) is currently ongoing to investigate the efficacy and safety of ramucirumab in HCC patients with elevated α-fetoprotein [15].

Table 1

Summary of studies included in the PPK analysis

Study code	Phase of study	Cancer indication	Ramucirumab dose (mg kg^{-1})[a]	Number of patients with PK samples	Mean samples per patient
I4T-MC-JVBB (RAISE)	3	Colorectal	8	431	4
I4T-MC-JVBA (REVEL)	3	Nonsmall cell lung	10	399	3
I4T-IE-JVBF (REACH)	3	Hepatocellular	8	312	3
I4T-IE-JVBE (RAINBOW)	3	Gastric	8	321	4
I4T-IE-JVBD (REGARD)	3	Gastric	8	72	2
I4T-IE-JVCA	2	Solid tumours	8	36	12
I4T-IE-JVCC	2	Solid tumours	10	17	13
I4T-IE-JVBJ	2	Nonsmall cell lung	10	32	7
I4T-IE-JVBW	1b	Gastric	8	6	28
I4T-IE-JVBX	1b	Metastatic breast	10	7	27
I4T-IE-JVBY	1b	Colorectal	8	6	18

[a]Administered as an intravenous infusion over approximately 60 minutes, at either 8 mg kg^{-1} every 2 weeks (Q2W) on a 14- or 28-day cycle or 10 mg kg^{-1} every 3 weeks (Q3W) on a 21-day cycle.

Ramucirumab clinical pharmacology sections of the prescriber information, including Pharmacokinetics and Specific Populations, are primarily based on the population pharmacokinetic (PPK) analysis results reported here. This manuscript describes the development, qualification and application of a PPK model; presents PPK-derived PK parameters for ramucirumab; and assesses the potential effect of intrinsic factors on ramucirumab PK, including renal and hepatic impairment. The developed PPK model was used to determine the ramucirumab exposures of individual patients which were then used to characterize exposure–response relationships of ramucirumab efficacy and safety as presented in other manuscripts [16–18].

Methods

Data

A total of 1639 patients with 6427 ramucirumab serum concentrations from 11 Phase 1b, 2 and 3 clinical trials were included in the PPK analysis. A range of disease states were represented in the patient population: colorectal cancer (27%), nonsmall cell lung cancer (27%), gastric cancer (24%), hepatocellular cancer (19%), metastatic breast cancer (<1%) and other solid tumour types (2%). Patients participating in the clinical trials provided written informed consent prior to receiving treatment. Each centre's institutional review board or independent ethics committee approved the individual studies, and the studies were conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki. A summary of the studies included in the PPK analysis is provided in Table 1.

Ramucirumab was administered as an intravenous infusion over approximately 1 h, at either 8 mg kg^{-1} every 2 weeks (Q2W) or 10 mg kg^{-1} every 3 weeks (Q3W), per study protocol. Blood samples were collected according to predefined schedules for each study. Pharmacokinetic sampling was both sparse and intensive, varying across studies. Each patient contributed between one and 30 blood samples, with the majority providing three or four samples. Approximately 40% of the samples were collected on the first day of each collected cycle within 3 h following the start of infusion.

Ramucirumab serum concentrations were evaluated using a validated enzyme-linked immunosorbent assay method. The lower limit of quantification was either 1900 or 2500 ng ml^{-1} depending on the study, and the upper limit of quantification was 27 500 or 54 000 ng ml^{-1}. Interassay coefficient of variation was <20%. Samples above the upper limit of quantitation were diluted and re-assayed. Serum concentrations that were below the quantitation limit of the assay or that had missing corresponding dosing or sampling information were excluded from the analysis.

PPK model development

The PPK analysis was conducted using nonlinear mixed-effects modelling techniques, implemented in NONMEM® version 7.3 software (ICON Development Solutions, Ellicott City, MD, USA). First-order conditional estimation with interaction was used as the estimation method. Interindividual variability (including covariance between parameters) and

residual error were estimated. Graphical data visualization, evaluation of NONMEM® output, construction of goodness-of-fit plots, graphical model comparisons and simulations were conducted using TIBCO Spotfire S + Version 8.2 (TIBCO Software Inc., Palo Alto, CA, USA) or R Version 2.15.3 (R Core Team, Vienna, Austria).

A series of one-, two- and three-compartment models were evaluated to identify the model which best described the ramucirumab concentration data. Interpatient variability was assumed to be log-normally distributed, and variability terms were investigated for all PK model parameters. Covariance between parameters was assessed using an omega block. With each assessment of interpatient variability, proportional and combined additive/proportional residual error models were evaluated. Assessments of dose and time dependency were conducted using the two-compartment model. Dose dependency was evaluated by adding nonlinear (Michaelis–Menten) clearance (CL) components from either the central or peripheral compartments. The time invariance of ramucirumab CL was investigated by adding a CL component as a linear function of time from the central or peripheral compartments. Selection of the most appropriate base model structure was based on agreement between predicted and observed serum concentrations, lack of pattern (that is, randomness) in the weighted residuals vs. the predicted values, magnitude of unexplained interpatient variability, and significant decreases in the minimum objective function.

Once a structural and statistical base model was established, potentially significant patient factors (demographics, laboratory data, and measures of tumour burden) were evaluated for their influence on the disposition of ramucirumab. A summary of the baseline patient characteristics and laboratory data is provided in Table 2 [19]. Baseline measures of tumour burden [lactate dehydrogenase, Eastern Cooperative Oncology Group performance status, number of metastatic sites, and sum of the longest diameter tumour lesions (SLD)] are summarized in Table 3. Continuous covariates (e.g. age) were tested for relationships with relevant PK parameters, CL, and central compartment volume (V_1) using linear, exponential and power models. Categorical covariates (e.g. sex, cancer indication) were tested using a proportional model. Given that ramucirumab was administered as a weight-based regimen and body weight was shown to be correlated with several patient factors (e.g. Cockcroft–Gault creatinine clearance, race), weight was evaluated a priori on the base model and included in the model using a power function on both CL and V_1 for individual covariate evaluation. Covariates were tested using a univariate screening procedure. Those that resulted in a significant decrease in the objective function value (OFV; ≥6.635 points for 1 degree of freedom, $P < 0.01$, based on χ^2 distribution), decreased the relative interpatient variability estimate for the PK parameter on which it was tested by at least 10% [20], and demonstrated clinical relevance by influencing the PK model parameter by at least 20%, when tested individually on the base model were then combined. Covariates retained in the final model were those resulting in a significant increase in OFV (≥10.828 points for 1 degree of freedom, $P < 0.001$, based on χ^2 distribution) when removed from this combined model using backward elimination.

Table 2

Summary of baseline demographics and laboratory covariates

Continuous	Mean (CV%)	Range
Age (years)	60.7 (18)	19–87
Body weight (kg)	70.5 (23)	31.9–143
Serum albumin (g l^{-1})	37.0 (14)	16.0–64.8
Alanine transaminase (IU l^{-1})	31.2 (105)	3–742
Aspartate transaminase (IU l^{-1})	39.1 (91)	2–567
Alkaline phosphatase (IU l^{-1})	176 (113)	25–2210
Total bilirubin (μmol l^{-1})	9.55 (66)	1.4–49.6
Total protein (g l^{-1})	70.5 (10)	29–140
Serum creatinine (μmol l^{-1})	76.4 (28)	23.0–182
Cockcroft–Gault creatinine clearance (ml min^{-1})	89.8 (35)	25.3–303
Lactate dehydrogenase (IU l^{-1})[a]	298 (99)	80–5034

Categorical	N (%)
Sex	
Male	1052 (64)
Female	587 (36)
Race	
White	1125 (69)
Asian	433 (26)
Other	81 (5)
Cancer indication	
Colorectal	439 (27)
Nonsmall cell lung	440 (27)
Gastric	400 (24)
Hepatocellular carcinoma	312 (19)
Other	48 (3)
Hepatic function[b]	
Normal: TBI ≤ ULN and AST ≤ ULN	1055 (64)
Mild Impairment: (TBI ≤1.5 x ULN and AST > ULN) or (TBI ≤1.5 x ULN and TBI > ULN)	525 (32)
Moderate impairment: (TBI >1.5 x ULN and TBI ≤3 x ULN)	23 (1)
Missing	36 (2)
AFP[c]	
<1.5 * AFP ULN	75 (24)
≥1.5 * AFP ULN	232 (74)
Missing	5 (2)
Child–Pugh Score[c]	
A	273 (88)
B	39 (12)

(continues)

Table 2

(Continued)

Categorical	N (%)
Calculated creatinine clearance (estimated by Cockcroft–Gault formulae)	
Normal: >90 ml min^{-1}	697 (42)
Mild impairment: ≥60 and <90 ml min^{-1}	687 (42)
Moderate impairment: ≥30 and <60 ml min^{-1}	244 (15)
Severe impairment: ≥15 and <30 ml min^{-1}	6 (<1)
Missing	5 (<1)

Abbreviations: AFP = α-fetoprotein; AST = aspartate transaminase; CV% = percentage coefficient of variation; N = number of patients included in the PPK analysis with baseline demographic and laboratory data; TBI = total bilirubin; ULN = upper limit of normal.
[a]Modelled using log-transformed values.
[b]National Cancer Institute Organ Dysfunction Working Group classification [19].
[c]Data available for patients in Study I4T-IE-JVBF (REACH) only.

PPK model evaluation

The PPK models were evaluated using diagnostic plots, nonparametric bootstrap, and visual predictive check (VPC). Model fit was evaluated by visual inspection using goodness-of-fit plots (observations vs. population or individual predictions) and plots of the conditional weighted residual vs. population predictions or time after dose. A nonparametric bootstrap was performed using PsN version 4.4.0 (University of Uppsala, Sweden) to assess the accuracy and robustness of the final population model and to provide information on parameter uncertainty. Additionally, VPCs were performed to ensure that the models maintained fidelity with the observed data. The VPC approach entailed simulating PK data (1000 replicates) with the model, taking into account variability in all parameters as given by the interpatient variability and residual error terms. The distributions (5th, 50th and 95th percentiles) of simulated concentrations, conditional on the posterior distribution of model parameters, were then visually compared to the actual concentration distributions to ensure concordance.

PPK model application

Individual empirical Bayes posthoc estimates were generated from the PPK model and these estimates of CL were used to calculate average concentration at steady state (C$_{ave,ss}$) for each patient. The relationship between exposure and patient factors of interest (e.g. body weight, renal function, and hepatic status) was examined graphically.

To assess time to achieve steady state, estimates of the fixed and random effects from the final PPK model were used to simulate the time course of ramucirumab concentration following an 8-mg kg^{-1} Q2W dosing regimen or a 10-mg kg^{-1} Q3W dosing regimen in 1000 virtual patients. Individual body weights were obtained by resampling from the body weights available from patients in the pooled dataset. The

Table 3

Summary of baseline measures of tumour burden

Study Cancer type	Phase 3 Studies				
	I4T-IE-JVBD (REGARD) + I4T-IE-JVBE (RAINBOW) Gastric	I4T-IE-JVBF (REACH) Hepatic	I4T-MC-JVBA (REVEL) NSCLC	I4T-MC-JVBB (RAISE) Colorectal	All Available Data Phase 1b, 2, 3
Continuous					
Number of metastatic sites[a]					
Mean (CV%)		1.26 (80)	3.08 (57)	2.10 (48)	2.21 (68)
Range		0–5	0–12	1–6	0–12
Sum of the longest diameter					
Tumour lesions (mm)					
Mean (CV%)	74.1 (78)	105 (58)	76.8 (64)	82.4 (71)	84.0 (69)
Range	10.0–362	10.0–357	10.0–276	10.0–438	10.0–438
Categorical					
ECOG PS Grade					
0 N (%)	139 (35)	164 (53)	154 (39)	226 (52)	730 (44)
1 N (%)	254 (65)	148 (47)	245 (61)	204 (47)	904 (55)
2 N (%)					4 (<1)
Missing N (%)				1 (<1)	1 (<1)
Number of metastatic sites[a]					
0–2 N (%)	257 (66)	277 (89)	178 (45)	303 (70)	1015 (62)
≥ 3 N (%)	136 (34)	35 (11)	221 (55)	128 (30)	520 (32)

CV% = percentage coefficient of variation; ECOG PS = Eastern Cooperative Oncology Group performance status; N = number of patients included in the PPK analysis with baseline measurement; NSCLC = Nonsmall cell lung cancer.
[a]Number of metastatic sites was captured categorically in Studies JVBD and JVBE.

5th, 50th and 95th percentiles of the ramucirumab concentrations over time were plotted.

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 [21], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [1].

Results

PPK model development

The ramucirumab concentration–time data were best described by a linear two-compartment structural model with zero order intravenous infusion and first order elimination. The model was parameterized in terms of CL, V_1, peripheral compartment volume (V_2), and intercompartmental clearance (Q). Exponential interindividual variability (IIV) terms were included for CL, V_1, V_2, and Q, with covariance between CL and V_1. Residual variability was accounted for by a combined additive and proportional error structure. VPCs of the linear two-compartment model with and without nonlinear or time-varying clearance components were compared. No improvement in model fit was observed with the more complex models.

Body weight and sex were found to influence the PK of ramucirumab based on the predefined criteria; both statistical significance ($P > 0.001$) and a relative reduction in IIV of ≥10% in the relevant parameter. The addition of body weight on CL and V_1 resulted in a decrease in the minimum OFV of 247 points and a relative reduction in IIV of 13% and 27%, respectively. Patients with higher body weights exhibited higher CL and V_1. Sex was found to influence V_1 (reduction in OFV = 43 points and IIV = 14%) with males achieving higher volume of distribution (10%) than females. Due to the small effect and the minimal impact on ramucirumab exposure, sex was not found to be clinically relevant and therefore not retained in the final model.

Parameter estimates for the final PK model are provided in Table 4. The estimated population mean (typical value) of CL, volume of distribution at steady-state and terminal half-life for a 68-kg patient (population median) were 0.0148 l h^{-1}, 5.30 l, and 13.4 days, respectively. The mean individual *posthoc* estimates (CV%) were 0.0148 l h^{-1} (30%), 5.36 l

Table 4

Final PPK parameter estimates and summary of bootstrap

Parameter description	Population estimate (% SEE)	Bootstrap results	
		Mean[a]	95% confidence interval
Clearance (CL), l h^{-1}	0.0148 (1.97)	0.0148	0.0139–0.0155
Effect of body weight on CL[b]	0.499 (7.64)	0.500	0.422–0.571
Central volume of distribution (V_1), l	3.26 (0.880)	3.26	3.21–3.32
Effect of body weight on V_1[c]	0.556 (6.26)	0.556	0.482–0.628
Intercompartmental clearance (Q), l h^{-1}	0.0102 (17.8)	0.0108	0.00554–0.0174
Peripheral volume of distribution (V_2), l	2.04 (5.20)	2.06	1.80–2.30
Interpatient variability			
Clearance (CL)	32.3% (5.97)	32.3%	30.3–34.3%
Central volume of distribution (V_1)	22.9% (9.33)	22.1%	20.3–24.1%
Covariance (CL and V_1)	0.0478 (8.79)	0.0507	0.0423–0.0606
Intercompartmental clearance (Q)	82.0% (26.3)	81.0%	45.1–115%
Peripheral volume of distribution (V_2)	54.0% (21.1)	55.1%	41.6–71.6%
Residual error			
Additive (μg ml^{-1})	4.80 (9.39)	4.77	3.69–5.94
Proportional	22.5% (5.25)	22.6%	21.4–23.8%

SEE, standard error of the estimate.
[a]Mean parameter values calculated from 1000 bootstrap replicates.
[b]CL = 0.0148 * (body weight/68)$^{0.499}$ where 68 is the median baseline body weight.
[c]V_1 = 3.26 * (body weight/68)$^{0.556}$ where 68 is the median baseline body weight.

(15%), and 13.9 days (20%), respectively. Interindividual variability for CL, V_1, and V_2 was moderate (32.3%, 22.9% and 54.0%, respectively), while variability in Q was high (82.0%).

PPK model evaluation

Diagnostic plots indicated that the model described the observed data well, based on the agreement between model-predicted concentration–time profiles of ramucirumab and the observed concentration data (not shown). Results of the nonparametric bootstrap analysis are provided in Table 4 and the VPC is shown in Figure 1. All model parameters were well estimated, with mean values of the bootstrap parameters nearly equivalent to those of the model parameter estimates. Agreement between the distributions of observed and predicted concentration data was also seen in the VPC. Both model evaluation techniques confirmed the suitability of the model to describe the ramucirumab concentration data.

PPK model application

To assess time to steady state, the ramucirumab concentration vs. time profiles for patients on the 8-mg kg^{-1} Q2W or 10-mg kg^{-1} Q3W dosing regimens were simulated using the final model parameter estimates. Dose amounts were calculated by sampling from the body weight distribution for each dose group in the PPK patient population. Based on the simulation results, steady-state conditions were achieved around Week 9–10, approximately following the fifth dose

of the 8-mg kg^{-1} Q2W regimen (Figure 2) and the third dose of the 10-mg kg^{-1} Q3W regimen.

To provide guidance in the label for usage of ramucirumab in renal or hepatic impaired patients, the relationship between predicted $C_{ave,ss}$ (calculated from post hoc CL estimates) and renal or hepatic function was evaluated graphically to determine if dose adjustment is necessary in these special populations. Results are shown in Figure 3 and Figure 4. No clinically meaningful difference in $C_{ave,ss}$ was observed in patients with mild or moderate renal impairment compared to patients with normal renal function. Additionally, no differences were observed in patients with mild or moderate hepatic impairment compared to patients with normal hepatic function. Data were only available from 23 patients with moderate hepatic impairment, however. Both observations are consistent with the population analysis, which found that renal and hepatic status had no significant influence on CL or V_1. No dose adjustment is therefore necessary for patients with pre-existing mild hepatic impairment, or mild-to-moderate renal impairment.

Discussion

This manuscript provides a comprehensive assessment of ramucirumab PK properties using a PPK approach. Previous noncompartmental analysis (NCA)-based ramucirumab PK
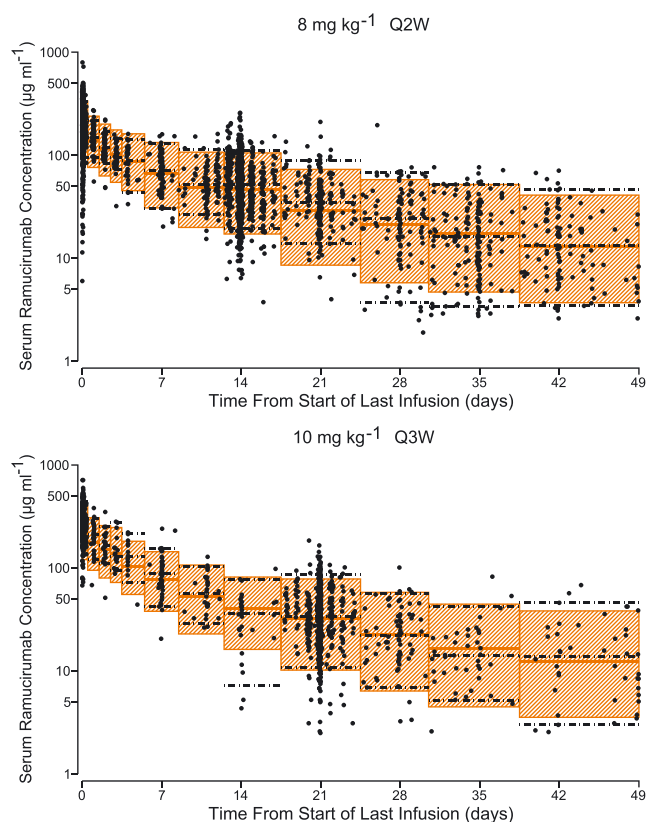
Figure 1

Visual predictive check. Dashed lines represent the 5th, 50th and 95th percentiles of the observed concentration data. Solid lines and shaded regions represent the 5th, 50th and 95th percentiles of model predictions. A total of 14 data points from the 8-mg kg^{-1} every 2 weeks (Q2W) group and 28 data points from the 10-mg kg^{-1} every 3 weeks (Q3W) group are omitted from the plots (time from start of last infusion >49 days)

Figure 2

Predicted ramucirumab concentration over an 8-mg kg^{-1} (top panel) or 10-mg kg^{-1} (bottom panel) dosing regimen to predicted steady-state. Shaded regions represent the 5th and 95th percentile ramucirumab concentrations calculated from 1000 simulation iterations. Simulations were performed for patients in the 8-mg kg^{-1} and 10-mg kg^{-1} groups

characterization in Phase 1 studies had little multiple dose data and PK parameters were estimated using inadequate PK sampling duration. These caveats limited the PK characterization and parameter estimation. The population estimates of CL and volume of distribution at steady-state are consistent with those obtained from prior NCAs of Phase 1 and 2 ramucirumab studies [22, 23]. The terminal half-life estimate obtained from the final model (approximately 2 weeks), however, appeared to be longer than that obtained from the NCA (6–9 days). This may be due to limitations in the PK sampling schedules in studies for which NCA was applied – the longest intensive PK duration was either 2 or 3 weeks, dependent on dose regimens – and therefore, the true terminal half-life may not have been accurately captured. Time to achieve steady state was also not well characterized in previous studies due to the nature of rapid disease progression in cancer patients. The simulation results indicate that it takes 9–10 weeks to achieve steady state following ramucirumab administration, consistent with the estimated 2-week half-life.

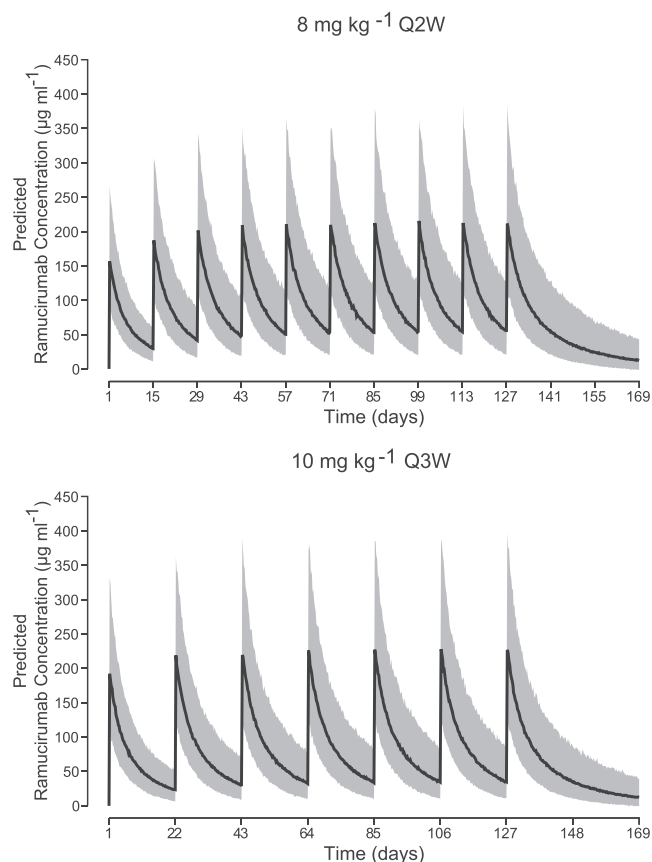As with other human IgG1 monoclonal antibodies targeting cell membrane-expressed antigens, target mediated drug disposition is expected to play a role in ramucirumab clearance. PK results from an early multiple ascending dose study suggested that ramucirumab exhibited nonlinear PK characteristics [24]. While apparent nonlinear PK profiles were observed between 2 and 8 mg kg^{-1}, PK profiles appeared to be linear at doses of 8 mg kg^{-1} and above [24, 25]. This is consistent with the current PPK finding that ramucirumab PK is dose-independent between 8 and 10 mg kg^{-1}. PK data generated from early clinical development were not included in this PPK analysis due to change in the bioanalytical assay [25]. Because the PK data included in the PPK analysis were limited to a dose range of 8 to 10 mg kg^{-1}, the robustness of the dose dependency assessment was constrained by the available data. Time dependency was also assessed using two-compartment models with constant and time varying clearance components in either the central or peripheral compartments. Since the majority (76%) of the single- and multiple-dose concentration data available for analysis were collected within 12 weeks from the start of therapy, the ability to make this assessment was limited. Based on available data however, no PK time-dependency was observed for ramucirumab. Taken together, the data suggest that target-

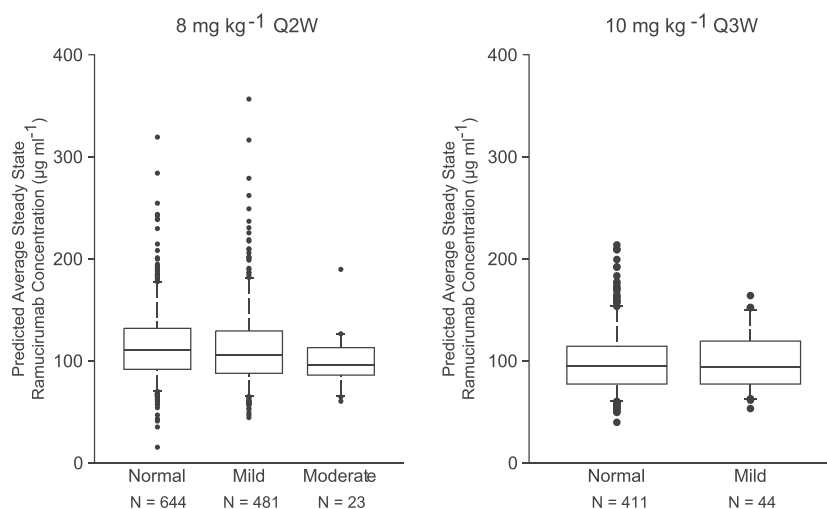## 8 mg kg⁻¹ Q2W / 10 mg kg⁻¹ Q3W

Figure 3

Box plots of predicted average steady-state ramucirumab concentration stratified by baseline hepatic function based on NCI-ODWG (normal, or mild and moderate hepatic dysfunction) for the 8-mg kg^{-1} and 10-mg kg^{-1} dose groups. Box plots depict the 5th, 25th, 50th, 75th and 95th percentiles. TBI = total bilirubin; AST = aspartate transaminase; ULN = upper limit of normal. Normal = (TBI ≤ ULN and AST ≤ ULN). Mild = (TBI ≤ 1.5 x ULN and AST > ULN) or (TBI ≤ 1.5 x ULN and TBI > ULN). Hepatic function classification was missing for 36 patients
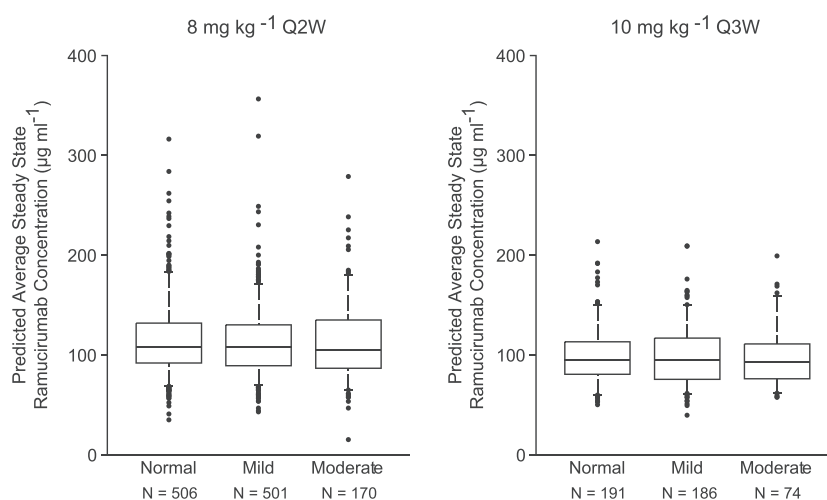
Figure 4

Box plots of predicted average steady-state ramucirumab concentration stratified by baseline renal function (normal, or mild and moderate dysfunction) for the 8-mg kg^{-1} and 10-mg kg^{-1} dose groups. Box plots depict the 5th, 25th, 50th, 75th and 95th percentiles. CLcr = Cockcroft–Gault creatinine clearance. Normal = CLcr ≥ 90 ml min^{-1}. Mild = 60 ml min^{-1} ≤ CLcr ≤ 89 ml min^{-1}. Moderate = 30 ml min^{-1} ≤ CLcr ≤ 59 ml min^{-1}. Five patients in the 8-mg kg^{-1} group and 1 patient in the 10-mg kg^{-1} group were classified as severely impaired (15 ml min^{-1} ≤ CLcr ≤ 29 ml min^{-1}). Renal impairment function was missing for five patients

mediated drug disposition may be saturated at a dose range of 8–10 mg kg^{-1}.

The identification of patient factors having significant influence on ramucirumab disposition was another important objective of this PPK analysis. Patient factors shown to significantly decrease the OFV (≥6.635 points for 1 degree of freedom, $P < 0.01$, based on χ^2 distribution), decrease the relative value of the interpatient variability in the relevant PK parameter by at least 10%, and influence the PK model parameter by at least 20% were retained in the final model. Among the variables listed in Table 2 and Table 3, body weight (range 31.9 to 143 kg) was found to be the only covariate meeting these predefined criteria, with a positive correlation between body weight and ramucirumab CL and V_1. This relationship was described using a power model with estimated exponents of 0.499 and 0.556 for CL and V_1, respectively. This result is consistent with previous findings from other biologics [26] and supports a body weight-based dosing

regimen for ramucirumab. Of note, significant overlap was observed when comparing the distributions of ramucirumab exposure ($C_{ave,ss}$) among the four body weight quartile groups (Figure 5).

Although sex was found to have a statistically significant effect on V_1, the effect on the parameter value was small, with females having 10% lower V_1 than males. Additionally, sex was found to influence CL, with females having approximately 10% lower CL than males, although the relative reduction in IIV was only 7%. Taken together, these differences would have minimal influence on overall exposure and are unlikely to have any clinical impact. Similar findings have been reported for bevacizumab [27].

Emerging evidence indicates that homeostasis of albumin and IgG is regulated by the same factor, the neonatal crystallisable fragment receptor (FcRn). Therefore, albumin is a potential covariate of interest for monoclonal antibodies. For example, it has been reported that albumin has a significant effect on the disposition of infliximab [28] and vedolizumab [29]. While this analysis found that the inclusion of albumin (range 16.0–64.8 g l^{-1}) on CL led to a statistically significant decrease in OFV, the relative IIV of CL was decreased by only 5%. Furthermore, a patient with an albumin value of 28 g l^{-1} (5th percentile of the population) would be predicted to have 17% greater CL than a patient with the same body weight and an albumin value of 37 g l^{-1} (population median). This indicates that while a weak relationship exists between albumin and these PK parameters, it is unlikely to be clinically relevant.

Review papers [30, 31] have illustrated the potential effect of tumour burden and other disease factors on mAb PK variability. For example, lactate dehydrogenase has been found to influence the PK of ipilimumab [32], number of metastatic sites has been shown to impact trastuzumab clearance [33], and Eastern Cooperative Oncology Group performance status has been found to influence the PK of nivolumab PK [34]. In this analysis, SLD (range 10–438 mm) was found to have a weak effect on the clearance of ramucirumab. Inclusion of the covariate in the model reduced the OFV 56 points, but only resulted in a lowering of relative IIV of 4%. Furthermore, a patient with a large tumour burden (95th percentile of the population, SLD value of 198 mm) would be predicted to have 15% greater CL than a patient with the same body weight and a typical tumour burden (population median SLD of 71 mm). This difference is unlikely to be clinically relevant across the range of SLD values in this patient population.

It is generally very challenging to conduct special population clinical pharmacology studies (e.g. renal or hepatic impairment) in oncology. However, potential changes in PK due to varying extents of renal or hepatic impairment is a critical piece of information for the label. Therefore, a PPK approach was taken for this assessment. This analysis demonstrates that patients with differing extents (normal, mild and moderate) of renal or hepatic function showed similar exposure distributions. This supports a lack of dose adjustment for patients with mild-to-moderate renal impairment or mild hepatic impairment.
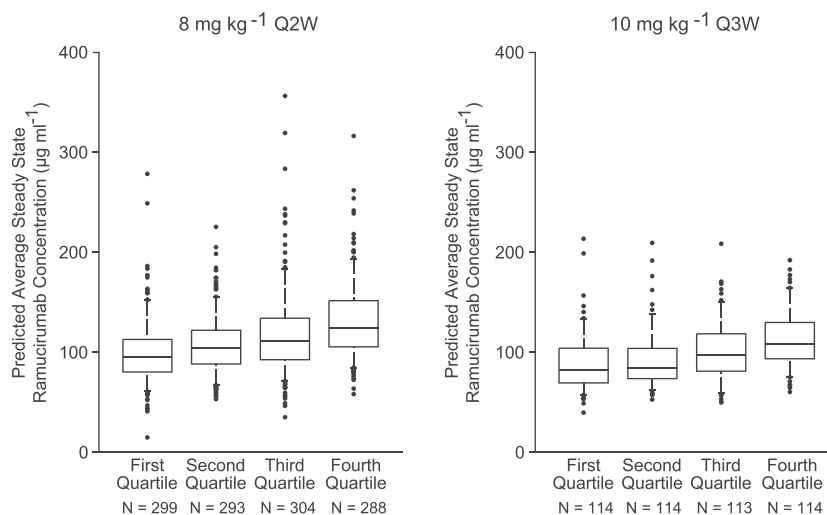

Figure 5

Box plots of predicted average steady-state ramucirumab concentration (μg ml^{-1}) stratified by baseline body weight (quartile). Box plots depict the 5th, 25th, 50th, 75th, and 95th percentiles

8-mg kg^{-1} Q2W group:	10-mg kg^{-1} Q3W group:
First quartile: ≤57.4 kg	First quartile: ≤63.7 kg
Second quartile: >57.4 – ≤66.4 kg	Second quartile: >63.7 – ≤73.5 kg
Third quartile: >66.4 – ≤78.0 kg	Third quartile: >73.5 – ≤84.4 kg
Fourth quartile: >78.0 kg	Fourth quartile: >84.4 kg

Biological drugs have the potential to induce immunogenicity, thereby altering the PK of a compound. Assessment of this effect is generally a requirement of health authorities and was of consideration in the present analysis. Due to the very low immunogenicity rate observed in ramucirumab (screening assay 3.0%; neutralized Ab <1%) [11], the effect of immunogenicity on ramucirumab PK was not evaluated. Based on assessment at an individual study level, exposure in patients with positive anti-drug antibody was within the range observed in patients with negative anti-drug antibody.

Conclusion

In conclusion, the PPK model adequately described PK data in patients with colorectal, nonsmall cell lung, gastric, hepatocellular, metastatic breast cancer and solid tumours randomized to receive ramucirumab. The PPK analysis demonstrated that a body weight-normalized dosing regimen is appropriate for ramucirumab and dose adjustments are not required for mild-to-moderate renal impairment or mild hepatic impairment. Data were not available to extend these findings to severe renal impairment or moderate-to-severe hepatic impairment.

The PPK model was applied to predict exposure parameters for individual patients in several Phase 3 studies to support exposure–response (efficacy and safety) analyses for these studies [8–10]. Manuscripts for these exposure–response analyses are under preparation.

Competing Interests

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