Biomedicine & Pharmacotherapy 167 (2023) 115441

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Novel modeling approach integrating population pharmacokinetics and interspecies scaling to predict human pharmacokinetics of the new anti-tuberculosis agent telacebec (Q203)

Jeongjun Kim [a,b,1], Tae Hwan Kim [c,1], Jinho Choi [b], Kiyean Nam [b], Beom Soo Shin [a,*], Soyoung Shin [d,*]

[a] School of Pharmacy, Sungkyunkwan University, 2066 Seobu-ro, Jangan-gu, Suwon, Gyeonggi 16419, Republic of Korea
[b] Qurient Co., Ltd., C-dong-801, PDC, 242, Pangyo-ro, Bundang-gu, Seongnam, Gyeonggi 13487, Republic of Korea
[c] College of Pharmacy, Daegu Catholic University, 13-13 Hayang-ro, Hayang-eup, Gyeongsan, Gyeongbuk 38430, Republic of Korea
[d] College of Pharmacy, Wonkwang University, 460 Iksan-daero, Iksan, Jeonbuk 54538, Republic of Korea

ARTICLE INFO

Keywords:
Telacebec
Tuberculosis
Pharmacokinetics
Interspecies scaling
Population pharmacokinetic model

ABSTRACT

Telacebec is a new anti-tuberculosis agent with promising therapeutic activity and a favorable safety profile. This study aimed to characterize the pharmacokinetics of telacebec via interspecies scaling and population pharmacokinetic modeling for the prediction of human pharmacokinetics. Preclinical pharmacokinetic data were obtained from mice, rats, and dogs following intravenous and oral doses of telacebec. A population pharmacokinetic model was developed to describe the pharmacokinetic data from all three species. The disposition parameters were well correlated with the body weight for all species using an allometric equation. Thus, the allometric scaling was incorporated into the population pharmacokinetic model, which could simultaneously describe the plasma concentration vs. time data from all preclinical studies as well as the Phase 1A clinical study. The developed model was used to predict the pharmacokinetics of telacebec after IV injection, including the clearance (CL) of 168.58 [118.86 – 238.73] mL/min and volume of distribution (V_{ss}) of 968.84 [396.87 – 2831.31] L for 80-kg human. The absolute bioavailability of telacebec in humans in the fed state was estimated as 70.34 ± 9.91%. Finally, the population pharmacokinetic model with allometric scaling was utilized to simulate the plasma concentration vs. time profiles of telacebec after multiple oral doses in humans. The model-predicted profiles well agreed with the observed data in Phase 1B clinical trial. The present pharmacokinetic model may help better understand the activity of telacebec, leading to the design of optimal dosing regimens and new formulation development.

1. Introduction

Telacebec (Q203) is a novel anti-tuberculosis agent under clinical development, which has shown its safety and efficacy in vitro and in vivo, including in humans [1,2]. The primary mode of action of telacebec is the inhibition of mycobacterial cytochrome *bc1* complex, which contributes to the electron transport required for adenosine triphosphate (ATP) synthesis of *M. tuberculosis* [1–3]. Thus, telacebec causes immediate depletion of intracellular ATP in *M. tuberculosis*, leading to bacterial cell death. In particular, telacebec has shown its potential as an effective treatment option against multidrug-resistant tuberculosis [1, 4], which is an emerging challenge globally. The minimum inhibitory concentration required for 90% inhibition of growth (MIC90) of *M. tuberculosis* was conserved against clinical isolates of multidrug-resistant and extensively drug-resistant *M. tuberculosis* strains [1]. It was also shown that the MIC of telacebec was in low nanomolar ranges (3.0 – 7.4 nM) against isoniazid, rifampicin, and fluoroquinolone drug-resistant *M. tuberculosis* strains [4].

So far, three clinical trials of telacebec, including the first-in-human Phase 1A single ascending dose trial (NCT02530710), Phase 1B multiple ascending dose trial (NCT02858973), and Phase 2A efficacy trial (NCT03563599), have been successfully completed [2, 5–7]. The Phase

* Corresponding authors.
E-mail addresses: bsshin@skku.edu (B.S. Shin), shins@wku.ac.kr (S. Shin).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.biopha.2023.115441
Received 3 July 2023; Received in revised form 25 August 2023; Accepted 4 September 2023
Available online 9 September 2023

1A trial evaluated the safety, tolerability, and pharmacokinetics of telacebec following a single oral dose of telacebec from 10 mg to 800 mg in healthy volunteers. Phase 1B trial assessed the safety, tolerability, and pharmacokinetics of telacebec following multiple oral doses of telacebec from 20 mg to 320 mg once daily for 14 days in healthy volunteers. The recent Phase 2A study was conducted in patients with newly diagnosed rifampin- and isoniazid-susceptible pulmonary tuberculosis to evaluate the early bactericidal activity of telacebec at doses of 100 – 300 mg within a 14-day treatment period [2].

In all three clinical trials, no significant or serious adverse events related to telacebec doses were observed, consistent with preclinical safety studies [1,2,5,6]. In both Phase 1A (16.7%) and Phase 1B (19%) studies, headache was the most common adverse event, except mild contact dermatitis due to ECG lead adhesive, which was not correlated with telacebec doses [5,6]. In particular, there were no clinically significant ECG-related adverse events after telacebec administration in any of the clinical trials. The low risk of potential cardiotoxicity of telacebec is especially encouraging as potential cardiotoxicity due to prolonged QT interval is the major limitation of other recently approved drugs for treating drug-resistant tuberculosis [8–10].

The pharmacokinetics of telacebec after oral administration in healthy human subjects has been characterized in Phase 1 studies [5,6]. It was found that telacebec was rapidly absorbed after oral doses and eliminated from the plasma in a multiexponential manner. Systemic drug exposure was approximately dose-proportional and substantially increased by the food [5,6]. Following multiple oral doses for 14 days, approximately 2- to 3-fold accumulation was observed [5]. The effective half-life ($t_{1/2}$) of telacebec based on the steady-state accumulation was 21.9 – 41.9 h [5]. As the plasma concentration of telacebec showed a multiexponential decline, a significantly prolonged terminal half-life ($t_{1/2,z}$) was observed, which also showed significant variability.

Although descriptive pharmacokinetic information following oral administrations has been obtained from clinical trials, more quantitative pharmacokinetic analyses are required to guide the development of optimal dosing formulations. Since the intravenous (IV) formulations of telacebec are not available, the pharmacokinetic disposition of telacebec after IV injection is unknown. Thus, primary pharmacokinetic parameters, including clearance (CL), the volume of distribution (V_{ss}), and absolute oral bioavailability, could not be determined for telacebec. Potential factors associated with the pharmacokinetic variability, including food effects, also need to be identified. The development of a pharmacokinetic model would allow the integration of the results from various preclinical and clinical studies and help to predict the pharmacokinetics in humans. The model-based knowledge and insights in pharmacokinetics are essential to ensure treatment success as well as to develop new dosage forms with optimized pharmacokinetics.

During the preclinical development process, the pharmacokinetics of telacebec have been evaluated in mice, rats, and dogs. Preliminary pharmacokinetic results in a mouse model have been reported, which indicated promising pharmacokinetics of telacebec with sufficient half-life and bioavailability [1]. However, complete preclinical pharmacokinetic study results have never been released. Besides the significance of preclinical pharmacokinetics itself, the pharmacokinetics in animals could also be extrapolated to predict pharmacokinetics in humans based on the allometric relationship between physiological processes and the body size or mass of animal species [11–13]. In the absence of intravenous pharmacokinetic data, the disposition kinetics of telacebec in humans may be predicted by allometric scaling, which can predict the accurate pharmacokinetic disposition and absolute oral bioavailability of telacebec in humans.

Therefore, the objectives of this study were to characterize the pharmacokinetics of telacebec in different species via interspecies scaling and to develop a population pharmacokinetic model for the prediction of human pharmacokinetics. The population pharmacokinetic model, which adopted the disposition parameters from allometric scaling, allowed to fit the clinical pharmacokinetic data from Phase 1A clinical trial and preclinical data in different species simultaneously. The utility of the model was demonstrated by predicting the time course of plasma drug concentrations following IV injection and oral doses of telacebec with various dose regimens.

2. Methods

2.1. Materials

Telacebec (6-chloro-2-ethyl-N-(4-(4-(4-(trifluoromethoxy)phenyl) piperidin-1-yl)benzyl)imidazo[1,2-*a*]pyridine-3-carboxamide) was provided by Qurient Co., Ltd. (Seongnam, Korea). Diclofenac sodium, formic acid, ammonium acetate, D-α tocopherol polyethylene glycol 1000 succinate, and Kolliphor® HS 15 were purchased from Sigma Aldrich Chemical Co. (Milwaukee, WI). Dimethyl sulfoxide was obtained from Kanto Chemical Co. (Tokyo, Japan). High-performance liquid chromatography (HPLC) grade acetonitrile, methanol, and water were purchased from J.T. Baker Co. (Philipsburg, NJ).

2.2. Animal studies

The animal studies were approved by the Ethics Committee for the Treatment of Laboratory Animals at Sungkyunkwan University (SKKUIACUC 2018–07–27–1), KNOTUS (19-KE-576), and WuXi AppTec (QI-20130411, QI-20130701A, QI-20130627) and conducted following standard operating procedures. The animals were maintained at 22 – 24 °C with a 12 h light-dark cycle and relative humidity of 50 ± 10%.

2.2.1. Mouse study

For an intravenous injection (IV) study, female Balb/c mice (20 – 21 g; Vital River Laboratories, Beijing, China) were fasted overnight and given telacebec dissolved in 20% Solutol via tail vein injection at 1 mg/kg (n = 9). Approximately 30 μL of blood samples were collected from submandibular or saphenous vein from 3 animals at each time point, i.e., 0, 0.083, 0.25, 0.5, 1, 2, 4, 6, 8, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, and 336 h, after drug administration.

For oral administration (PO) studies, male ICR mice (26 – 30 g; DBL Co., Ltd, Eumseong, Korea) were divided into two groups, i.e., fasted and fed groups (n = 12 each). Food and water were available ad libitum for the fed group while the food was removed from the cages of the fasted group 12 h before drug administration. Mice were orally administered telacebec prepared in 20% D-α tocopherol polyethylene glycol 1000 succinate (20% TPGS) at a dose of 5 mg/kg by oral gavage. Approximately 100 μL of blood samples were collected via retro-orbital plexus from 3 to 4 animals per group at each time point, i.e., 0, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 h, after drug administration. Plasma samples were harvested by centrifugation of the blood samples at 3,220g for 10 min. All samples were stored at − 70 °C until analysis.

2.2.2. Rat study

For an IV study, male Sprague-Dawley rats (218 – 262 g; DBL Co., Ltd, Eumseong, Korea) were fasted overnight, and telacebec dissolved in 30% Solutol was administered via penile vein injection at 2 mg/kg (n = 6). Approximately 0.3 mL of blood samples were collected via jugular vein at 0, 0.083, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 h after IV injection.

For PO studies, male Spraque-Dawley rats (230 – 252 g; DBL Co., Ltd, Eumseong, Korea) were divided into two groups, i.e., fasted and fed groups (n = 5 each). While food and water were available ad libitum for the fed group, the food was removed from the cages of the fasted group 12 h before drug administration. Rats were orally administered telacebec prepared in 20% TPGS at a dose of 5 mg/kg by oral gavage. Blood samples (approximately 0.3 mL) were collected at 0, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 h after drug administration. Plasma samples were harvested by centrifugation of the blood samples at 3,220g for 10 min. All samples were stored at − 70 °C until analysis.

2.2.3. Dog study

For an IV study, male beagle dogs (11.0 – 11.7 kg; Marshall Bioresources, Beijing, China) were fasted overnight, and telacebec dissolved in 10% EtOH/ 60% PEG400/ 30% saline was administered via cephalic vein injection at 1 mg/kg (n = 3). Approximately 1 mL of blood samples were collected via jugular vein at 0, 0.083, 0.25, 0.5, 1, 2, 4, 6, 8, 24, 48, 72, 96, 120, 144, and 168 h after IV injection.

For PO studies, eight male beagle dogs (9.9 – 10.6 kg; Orient Bio Inc., Jeongeup, Korea) were divided into fasted and fed groups. A two-treatment, randomized crossover study was conducted with a two-week washout period between treatments (n = 8). While dogs in the fasted group were fasted for 14 h with free access to water before the experiment, dog food was provided to each dog in the fed group 30 min before drug administration. Both groups were orally administered with a telacebec tablet (100 mg, Supplementary Material S1). Blood samples (approximately 1 mL) were collected at 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 20, 24, 28, 32, 36, 48, 72, 96, 120, 144, and 168 h after drug administration. Plasma samples were harvested by centrifugation of the blood samples at 3,220g for 10 min and stored at − 70 °C until analysis.

2.3. LC-MS/MS

Telacebec concentrations in the mouse, rat, and dog plasma were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) analyses. Briefly, plasma samples (30 μL) were mixed with 30 μL of internal standard (IS1; diclofenac) and 300 μL of 0.1% formic acid in acetonitrile. After vortexed for 10 min, the mixture was centrifuged at 3,220g for 30 min at 4 °C. The supernatant 50 μL was mixed with 450 μL of 0.1% formic acid in acetonitrile/water (50:50, v/v), and 2 μL was injected into the LC-MS/MS.

The LC-MS/MS was performed by an Agilent 6430 triple-quadrupole mass spectrometer coupled with an Agilent 1200 HPLC system (Agilent Technologies, Santa Clara, CA). Telacebec was separated on a Kinetex C_{18} 100Å (2.1 ×50 mm i.d., 2.6 μm, Phenomenex, Torrence, CA) with a SecurityGuard AJ0–9000 (Phenomenex). For mouse and rat plasma samples, chromatographic separations were performed by using a binary gradient mobile phase composed of mobile phase A (0.1% formic acid and 2 mM ammonium acetate in distilled water/acetonitrile (95:5, v/v) and mobile phase B (0.1% formic acid and 2 mM ammonium acetate in acetonitrile/distilled water (95:5, v/v). The total run time was 7.5 min, and the column oven temperature was 50 °C. For beagle dog plasma samples, dutasteride (IS2) was used as an IS, and telacebec was eluted by isocratic elution with A:B = 50:50 (v/v) for 6 min. Other LC-MS/MS conditions were identical for mouse, rat, and dog plasma samples.

The electrospray ionization (ESI) source was operated in positive mode, and the mass spectrometer was operated in the multiple reaction monitoring (MRM) mode with a dwell time of 100 ms. The selected precursor/product ion pairs were *m/z* 557.2 → 334.1 for telacebec, 296 → 213 for IS1, and 529.2 → 461.3 for IS2. The mass spectrometric data were processed by Mass Hunter Quantitative Analysis (Agilent Technologies, Santa Clara, CA). The lower limit of quantification (LLOQ) and the upper limit of quantification (ULOQ) of telacebec was 5 and 5000 ng/mL, respectively, and the calibration range was 5 – 5000 ng/mL for all plasma samples. Intra- and inter-day accuracy and precision were assessed by using the matrix-matched quality control samples (n = 3, each). For mouse and rat plasma samples, the intra- and inter-day accuracy was 96.3 – 106.7%, and precision was within 9.9%. For dog plasma samples, the intra- and inter-day accuracy was 93.7 – 108.3%, and precision was within 8.1%. Plasma samples from the IV injection studies of mouse and dog were analyzed at WuXi AppTec, which was described in Supplementary Material S2.

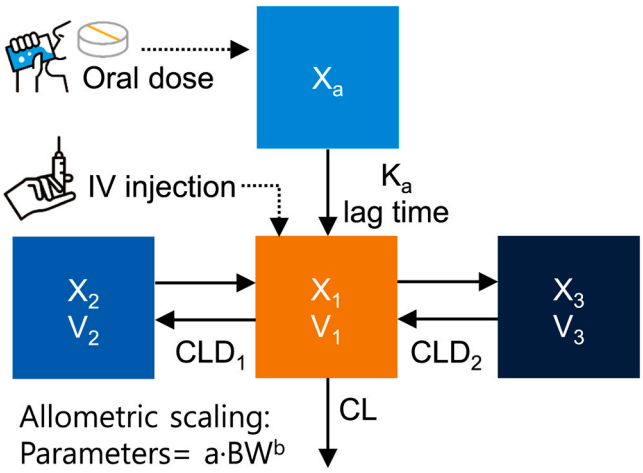

Fig. 1. Structure of the population pharmacokinetic model of telacebec.

2.4. Pharmacokinetic modeling

2.4.1. Noncompartmental analysis

The plasma concentration vs. time data of telacebec after IV and PO administration in each species were analyzed by noncompartmental analysis (Phoenix WinNonlin, Certara, Princeton, NJ). Absolute oral bioavailability (BA %) was calculated by the ratio of the dose-normalized area under the plasma concentration vs. time curves (AUC) from time zero to infinity (AUC_{inf}) after single oral dose or AUC during dosing interval at steady-state ($AUC_{n\rightarrow n+1,ss}$) after multiple oral doses in Phase 1B study to that after IV injection.

2.4.2. Population pharmacokinetic modeling

A three-compartment model (Fig. 1) was used to characterize the concentration vs. time profiles following IV bolus injection of telacebec in mice, rats, and dogs. For oral administration of telacebec in humans, a gut compartment was added in the population pharmacokinetic model. The amount of telacebec in the gut compartment (X_a) was assumed to transfer to the central compartment with the first-order absorption rate constant K_a after a lag time (T_{lag}). Thus, K_a was set to zero at any time prior to T_{lag}. F is the oral bioavailability of telacebec in humans. Telacebec in the central compartment (X_1) was assumed to distribute to the shallow (X_2) and deep (X_3) peripheral compartments and to be eliminated from the central compartment. The differential equations to describe the drug disposition are as follows:

$$\frac{dX_a}{dt} = -K_a \cdot X_a \quad (1)$$

$$\frac{dX_1}{dt} = K_a \cdot F \cdot X_a - \frac{CLD_1}{V_1} \cdot X_1 + \frac{CLD_1}{V_2} \cdot X_2 - \frac{CLD_2}{V_1} \cdot X_1 + \frac{CLD_2}{V_3} \cdot X_3 - \frac{CL}{V_1} \cdot X_1 \quad (2)$$

$$\frac{dX_2}{dt} = \frac{CLD_1}{V_1} \cdot X_1 - \frac{CLD_1}{V_2} \cdot X_2 \quad (3)$$

$$\frac{dX_3}{dt} = \frac{CLD_2}{V_1} \cdot X_1 - \frac{CLD_2}{V_3} \cdot X_3 \quad (4)$$

V_1, V_2, and V_3 are the volumes of distribution in the respective compartments. CLD_1 and CLD_2 are the distribution clearances to each peripheral compartment, while CL is the systemic clearance of telacebec. The population pharmacokinetic model was developed using S-ADAPT (version 1.57, Biomedical Simulations Resource, Los Angeles, CA).

2.4.3. Allometric scaling

Allometric scaling was applied to the pharmacokinetic parameters obtained from IV plasma concentration vs. time data. Allometric scaling assumes anatomical, physiological, and biochemical similarities among

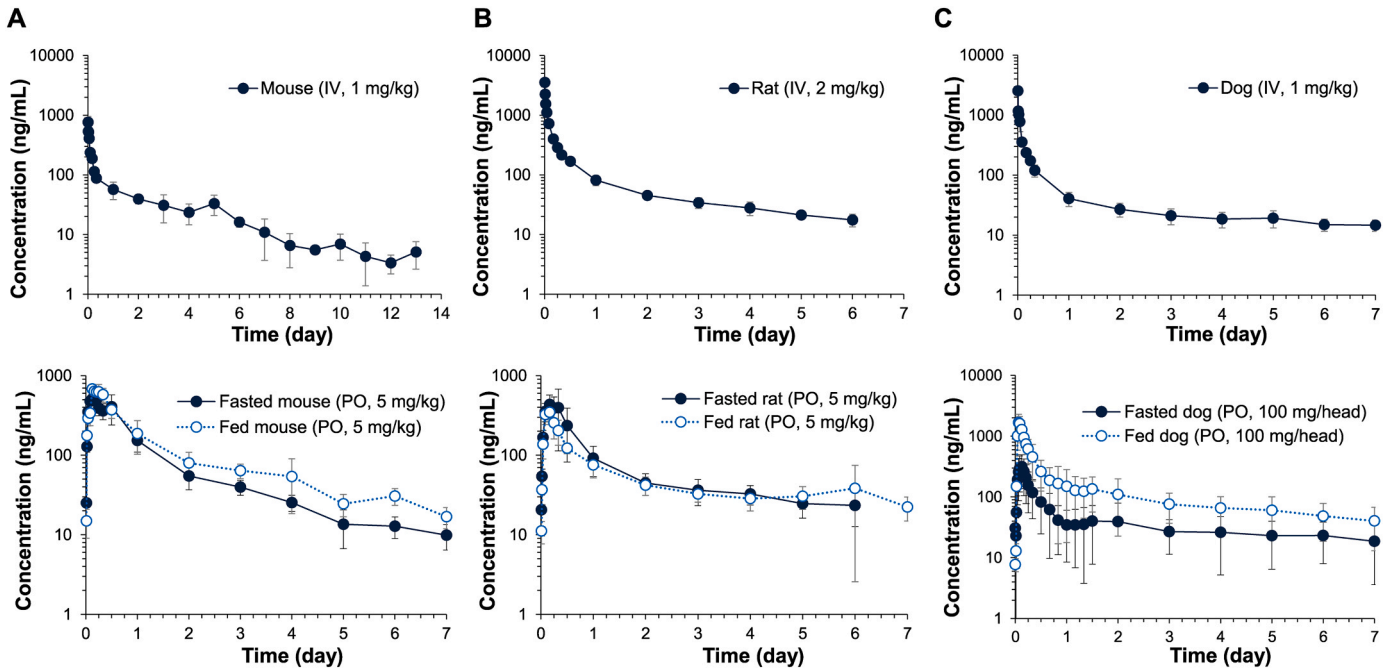

Fig. 2. Average plasma concentration vs. time profiles of telacebec following intravenous (IV) injection (upper panels) and oral (PO) administration (lower panels) in (A) mice, (B) rats, and (C) dogs (n = 3 – 12).

animals [11]. Thus, many physiological processes may display an allometric relationship with the body size or body mass of various animal species, which can be expressed mathematically through the power function:

$$P = a \cdot BW^{b} \quad (5)$$

where P is a parameter of interest, which is the PK parameter in the present study, including V_1, V_2, V_3, CL, CLD_1, and CLD_2, BW is the body weight of the animal species, a is the allometric coefficient, and b is the allometric exponent [11,14]. The pharmacokinetic parameters of telacebec obtained from different animal species were plotted against the body weights (BW) of the animal on a log-log scale. Based on the power-based allometric relationship (Eq. 5), the allometric coefficient (a) and exponent (b) for each pharmacokinetic parameter were estimated. Thus, all pharmacokinetic parameters for drug disposition, i.e., V_1, V_2, V_3, CL, CLD_1, and CLD_2, in the three-compartment model (Fig. 1) were expressed as $a \cdot BW^{b}$ with the estimated allometric coefficient (a) and exponent (b) values specific to each pharmacokinetic parameter. The derived allometric equation was used to predict the disposition pharmacokinetic parameters for an 80-kg human subject. The body weight of 80 kg for humans was chosen because the average body weight of the subjects enrolled in the Phase 1 study was 79.65 kg.

Table 1
Noncompartmental pharmacokinetic parameters of telacebec following intravenous (IV) and oral (PO) administration in mice, rats, and dogs.

	Mouse			Rat			Dog		
	IV	PO		IV	PO		IV	PO	
		Fasted	Fed		Fasted	Fed		Fasted	Fed
Dose	1 mg/kg	5 mg/kg	5 mg/kg	2 mg/kg	5 mg/kg	5 mg/kg	1 mg/kg	100 mg	100 mg
n	9	12	12	6	5	5	3	8	8
Body weight (kg)	0.0201 ± 0.0005	0.0257 ± 0.0008	0.0273 ± 0.0013	0.24 ± 0.01	0.24 ± 0.01	0.24 ± 0.01	11.39 ± 0.37	10.11 ± 0.31	10.11 ± 0.31
$t_{1/2}$ (h)	82.99	50.68	47.44	70.73 ± 11.42	86.87 ± 30.75	131.34 ± 84.17	138.06 ± 16.01	103.03 ± 44.74	84.61 ± 27.86
T_{lag} (h)	–	0.00	0.00	–	0.10 ± 0.14	0.00 ± 0.00	–	0.19 ± 0.35	0.06 ± 0.12
T_{max} (h)	–	4.00	3.00	–	4.40 ± 2.19	4.00 ± 1.63	–	2.56 ± 0.62	1.69 ± 0.26 *
C_0 or C_{max} (ng/mL)	912.41	510.82	682.28	4522.75 ± 906.02	513.13 ± 243.82	336.21 ± 51.24	3738.46 ± 534.53	331.23 ± 179.20	1734.69 ± 624.99 *
AUC_{all} (ng·h/mL)	8170.10	13,658.75	17,881.30	11,756.17 ± 854.85	10,672.48 ± 4136.74	9166.25 ± 1941.63	7535.57 ± 1625.96	6191.23 ± 4703.50	22,183.12 ± 10,226.36 *
AUC_{inf} (ng·h/mL)	8681.96	14,383.85	19,038.86	13,601.80 ± 1502.51	13,930.41 ± 5878.21	13,776.31 ± 1949.06	10,426.22 ± 2022.53	8884.65 ± 7651.09	27,490.12 ± 12,999.09 *
V_{ss} (L)	0.22	–	–	2.01 ± 0.30	–	–	146.97 ± 43.62	–	–
CL (mL/min)	0.04	–	–	0.59 ± 0.08	–	–	18.70 ± 3.88	–	–
BA (%)	–	33.14	43.86	–	40.97	40.51	–	8.61	26.64

Data represent the arithmetic mean ± SD; BA, bioavailability; * , $p < 0.05$ vs. fasted by t-test.

2.4.4. Population pharmacokinetic model with allometric scaling

The allometric equations were incorporated into the population pharmacokinetic model, which depicted the pharmacokinetic profiles of telacebec in each species from the body weights. The pharmacokinetic parameters of telacebec across species were estimated by simultaneously fitting the obtained plasma concentration-time profile data of telacebec in mice, rats, and dogs after IV injection as well as in humans after oral administration at 10 – 800 mg using S-ADAPT (version 1.57). The human data were obtained from Phase 1A trial, which was a randomized, double-blind, placebo-controlled, and single escalating dose study of telacebec in normal, healthy human subjects [6]. The doses of telacebec in the Phase 1A trial were 10, 30, 50, 100, 200, 400, and 800 mg in the fasted state and 100 mg in a fed state [6].

All parameter estimation was performed by using the importance sampling algorithm (pmethod = 4) in parallelized S-ADAPT (version 1.57) via the SADAPT-TRAN facilitator [15]. The between subject variability (BSV) was described by a log-normal distribution for all parameters. Residual error was represented by an additive plus proportional model. Models were compared using the objective function (−1·log-likelihood in S-ADAPT), the plausibility of parameter estimates, standard diagnostic plots, visual predictive checks (VPCs), and normalized prediction distribution error (NPDE).

One thousand individual plasma concentration vs. time profiles of telacebec for each species were simulated via Monte Carlo simulations using Berkeley Madonna (version 8.3.18, Berkeley Madonna, Berkeley, CA). The predictability of the final model was assessed by comparing the model-predicted values vs. observations.

2.5. Statistical analysis

The data were presented as the mean ± standard deviation (SD). The statistical analyses were performed using IBM® SPSS® Statistics (IBM, Chicago, IL). Comparisons between the means of the two groups, i.e., fasted vs. fed noncompartmental parameters for each species, were performed by t-test. The statistical significance level was set at $p < 0.05$. Since the food effect study in dogs was designed as a crossover study, the significance of the food effect was further tested by a linear mixed effects model with fixed effects terms for treatment condition, i.e., fasted or fed, as described previously [6]. An absence of food effect was concluded if the 90% confidence interval (CI) for all comparisons was contained within the interval [0.8, 1.25].

3. Results and discussion

3.1. Pharmacokinetics of telacebec in animals

Fig. 2 shows the observed pharmacokinetic profiles after IV and oral doses of telacebec in mice, rats, and dogs. The pharmacokinetic profiles for 24 h or 12 h after oral administration were highlighted in Supplementary Material S3. Table 1 summarizes the non-compartmental pharmacokinetic parameters of telacebec. Telacebec was well tolerated in all animals without any death or severe abnormality in physiological conditions during the study period. The plasma concentration-time profiles of telacebec following IV injection exhibited a multi-exponential decline in all three species. Prolonged terminal half-life ($t_{1/2}$) of telacebec, i.e., 82.99 h, 70.73 ± 11.42 h, and 138.06 ± 16.01 h in mice, rats, and dogs, respectively, was observed. Following oral administration in the fasted condition, the plasma concentration of telacebec reached the maximum concentration (C_{max}) at 4.0, 4.4, and 2.6 h in mice, rats, and dogs, respectively. While the oral absorption began immediately after administration in mice, slight delays in absorption represented by T_{lag} of 0.10 h and 0.19 h were observed in rats and dogs, respectively. The oral bioavailability of telacebec in the fasted state was 33.14% in mice, 40.97% in rats, and 8.61% in dogs.

The pharmacokinetics of telacebec after oral administration in healthy human subjects, which has been characterized in Phase 1A and Phase 1B clinical trials, have been recently reported [5,6]. The prolonged and variable $t_{1/2,z}$ was also observed in humans, although the effective half-life based on the accumulation at steady state was much shorter, i.e., 21.9 – 41.9 h [5]. Potential risks associated with extended subtherapeutic exposure after the treatment of telacebec may need to be carefully monitored in terms of drug resistance [7]. Optimized treatment regimens potentially in combination with other drugs are also of particular importance for successful treatment.

3.2. Food effect on the pharmacokinetics of telacebec

Another distinct feature found in the clinical pharmacokinetics of telacebec was the substantial food effect on the drug exposure [6]. In the present study, it was observed that the food effect on the pharmacokinetics of telacebec was highly dependent on species. Telacebec plasma concentrations following oral administration in fed conditions were higher in mice, but comparable in rats, compared to those in fasted conditions (Fig. 2). In dogs, however, the absorption was faster in the fed condition, represented by the shorter time to C_{max} (T_{max}). Significantly higher C_{max}, AUC_{all}, and AUC_{inf} of telacebec were also observed in the fed state compared to the fasted state ($p < 0.05$). Since the food effect study in dogs was designed as a crossover study, 90% confidence interval (CI) for the geometric mean ratios of fed and fasted conditions could be calculated. Compared with the fasted state, the geometric mean ratio for C_{max} in the fed state was 5.61 [90% CI; 4.12 – 7.64]. The geometric mean ratio was 4.33 [90% CI; 2.86 – 6.57] for AUC_{all} and 3.76 [90% CI; 2.60 – 5.44] for AUC_{inf}, indicating the significant food effect on the oral bioavailability of telacebec in dogs. The extent of food effect on telacebec exposure in dogs is comparable with that in humans [6].

The exact mechanism of the food effect on telacebec pharmacokinetics is still unknown. Studies have indicated that the improved dissolution and solubility of telacebec in the presence of food may result in increased absorption [6]. Telacebec has a high LogP of 7.64 and is poorly water-soluble, with a water solubility of 0.079 mg/mL at pH 2.0 [16]. Food may change the pH or stimulate the bile flow in the gastrointestinal tract, which may affect the solubility of telacebec. The food effect is likely dependent on the gastrointestinal physiology of animal species. It is interesting that there was no food effect in rats in which the gallbladder is absent [17], while significant food effect was observed in dogs, and to a lesser extent in mice. It should also be noted that telacebec was administered as a solution for mice and rats, while the same tablet formulation was administered for dogs and humans. The dissolution process of the telacebec tablet may also be affected by the food. Thus, dogs may provide a useful animal model for further studies to examine the food effect on telacebec pharmacokinetics and to test new dosage forms of telacebec.

3.3. Interspecies scaling

Interspecies scaling was performed on the disposition parameters of central and peripheral volumes of distribution, i.e., V_1, V_2, and V_3, and systemic and distributional clearances, i.e., CL, CLD_1, and CLD_2 to predict human pharmacokinetic disposition. Each of the pharmacokinetic parameters was well correlated with the body weights of all species. The average body weight was 0.020, 0.238, and 11.39 kg for a mouse, rat, and dog, respectively. The allometric scaling relationships were derived as follows:

$$V_1 = 0.5543 \cdot BW^{0.7942} \quad (6)$$

$$V_2 = 1.0000 \cdot BW^{0.8882} \quad (7)$$

$$V_3 = 8.5223 \cdot BW^{1.0589} \quad (8)$$

$$CL = 3.0839 \cdot BW^{0.9988} \quad (9)$$

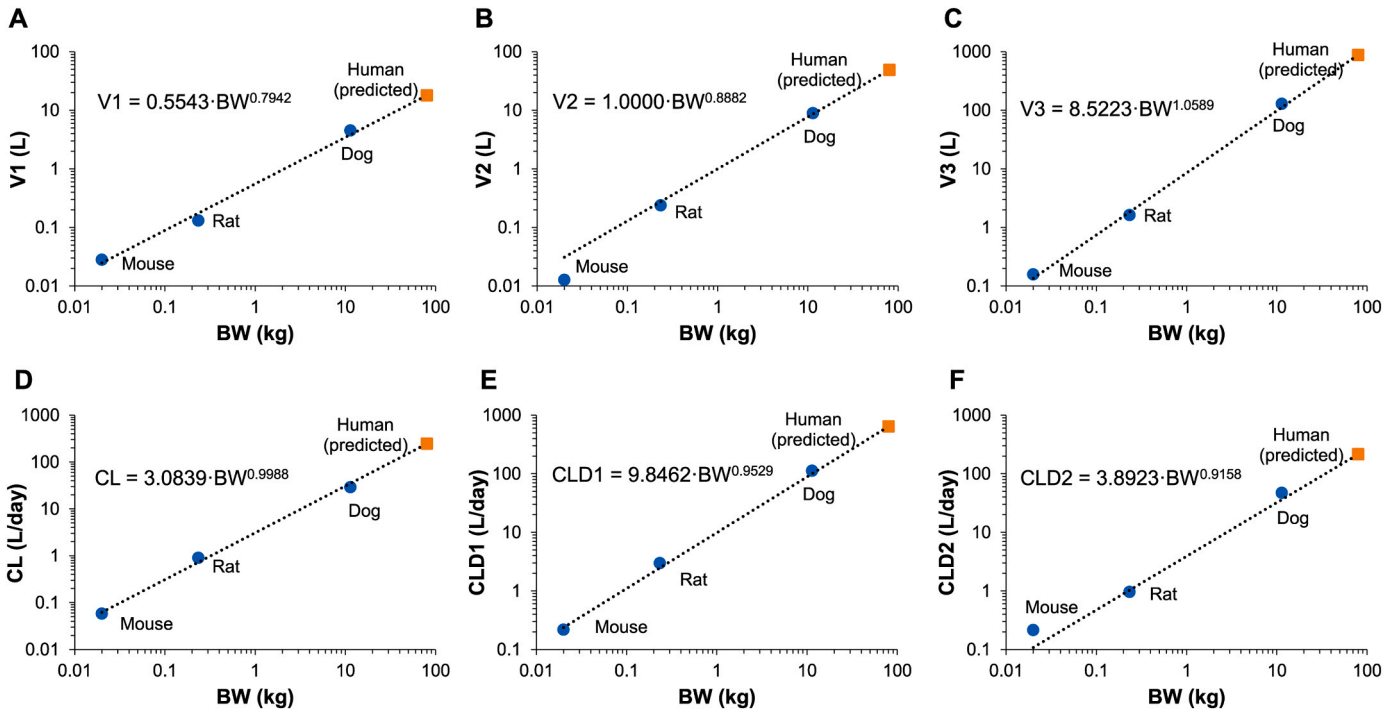

Fig. 3. Log-log representation of the allometric relationship in various pharmacokinetic parameters: (A) V_1, (B) V_2, (C) V_3, (D) CL, (E) CLD_1, and (F) CLD_2. Symbols represent the initial parameter estimates of mice, rats, and dogs, while lines represent the final allometric equation.

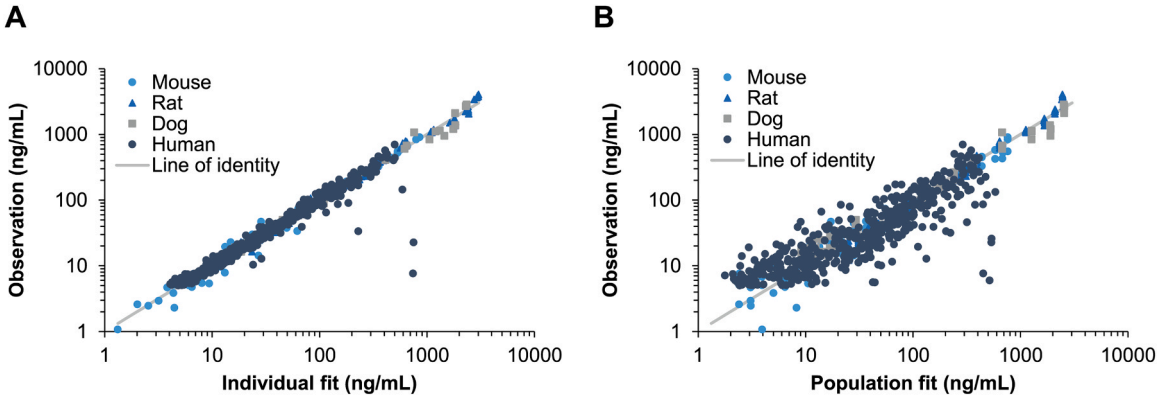

Fig. 4. Goodness of fit plots for the comparison between observed plasma concentrations of telacebec with the (A) individual and (B) population fit for all species.

$$CLD_1 = 9.8462 \cdot BW^{0.9529} \quad (10)$$

$$CLD_2 = 3.8923 \cdot BW^{0.9158} \quad (11)$$

Fig. 3 shows the final allometric relationships between the pharmacokinetic parameters and body weights. Based on these relationships, the pharmacokinetic parameters, i.e., V_1, V_2, V_3, CL, CLD_1, and CLD_2, could be predicted from the body weight (BW) across the different species. While the dotted lines represent the allometric equation derived from the final population model with allometric scaling, the symbols are the observations, i.e., mean initial parameters estimated separately for each species. The pharmacokinetic parameters were finally extrapolated for an 80-kg human subject (Fig. 3), as the average body weight of the subjects enrolled in Phase 1 study was 79.65 kg.

3.4. Population pharmacokinetic model with allometric scaling

The population pharmacokinetic model with allometric scaling adequately described the observed data in all animal species after IV injection and humans after oral doses. Fig. 4 shows the goodness of fit plots, i.e., observed data vs. individual and population fits in mice, rats, dogs, and humans. Normalized prediction distribution error (NPDE) plots are shown in Supplementary Material S4. The estimates of the population pharmacokinetic parameters of telacebec, including the oral bioavailability in each dose cohort in Phase 1A trial, are shown in Table 2.

Fig. 5 is the visual predictive check (VPC) plots for the model predictions after IV injection in animals and after oral administration in humans, respectively. VPC plots highlighting the absorption phase are shown in Supplementary Material S5. The profiles of drug concentrations, which were predicted by Monte Carlo simulation, well agreed with the observed data following IV injection in mice, rats, and dogs (Fig. 5A-C). The predicted human pharmacokinetic profiles after oral dose of telacebec were also well comparable with the observations in Phase 1A clinical trial. Table 3 summarizes the predicted AUC values and CL, and V_{ss} of telacebec in each species compared with the observations, i.e., those obtained by noncompartmental analysis. The model predicted ranges [5^{th} - 95^{th} percentile] of each parameter were well

Table 2
Pharmacokinetic parameters of telacebec across species using the population pharmacokinetic model with allometric scaling.

Parameter		Definition	Population mean	BSV (%)
V_1	a_1	allometric coefficient for V_1	0.5543	11.25
	b_1	allometric exponent for V_1	0.7942	16.23
V_2	a_2	allometric coefficient for V_2	1.0000	0.14
	b_2	allometric exponent for V_2	0.8882	18.43
V_3	a_3	allometric coefficient for V_3	8.5223	10.89
	b_3	allometric exponent for V_3	1.0589	13.48
CL	a_4	allometric coefficient for CL	3.0839	22.12
	b_4	allometric exponent for CL	0.9988	0.98
CLD_1	a_5	allometric coefficient for CLD_1	9.8462	11.19
	b_5	allometric exponent for CLD_1	0.9529	3.29
CLD_2	a_6	allometric coefficient for CLD_2	3.8923	12.38
	b_6	allometric exponent for CLD_2	0.9158	8.09
K_a (day^{-1})		absorption rate constant	11.39	7.02
T_{lag} (day)		lag time before absorption	0.04	33.59
F_10mg		bioavailability after oral administration of 10 mg (%)	20.78	35.67
F_30mg		bioavailability after oral administration of 30 mg (%)	24.74	41.81
F_50mg		bioavailability after oral administration of 50 mg (%)	18.91	42.80
F_100mg		bioavailability after oral administration of 100 mg (%)	15.42	36.68
F_200mg		bioavailability after oral administration of 200 mg (%)	8.59	14.64
F_400mg		bioavailability after oral administration of 400 mg (%)	5.55	34.17
F_800mg		bioavailability after oral administration of 800 mg (%)	6.25	33.40
F_100mg_Fed		bioavailability after oral administration of 100 mg in the fed state (%)	67.87	58.54

BSV, between subject variability.

comparable with the results from noncompartmental analysis, demonstrating the predictability of the population pharmacokinetic model with allometric scaling across species.

The model estimated oral bioavailability in humans was higher at lower doses, i.e., approximately 20%, but decreased at higher doses in the fasted state (Table 2). The lowest oral bioavailability was observed at 400 mg and 800 mg dose cohorts, i.e., 5.55% and 6.25%, respectively. The dose-dependent oral bioavailability may be attributed to the low

Table 3
Comparison between observed and model-predicted pharmacokinetic parameters of telacebec following intravenous injection of telacebec in mice, rats, dogs, and humans.

Species		AUC_{all} (μg·h/L)	AUC_{inf} (μg·h/L)	CL (mL/min)	V_{ss} (L)
Mouse (1 mg/kg)	Observed	8170.10	8681.96	0.039	0.220
	Predicted*	7289.34 [5273.77, 10,302.61]	7729.55 [5390.61, 11,411.45]	0.040 [0.03, 0.06]	0.200 [0.11, 0.38]
Rat (2 mg/kg)	Observed	11,756.17 ± 854.85	13,601.80 ± 1502.51	0.59 ± 0.08	2.01 ± 0.30
	Predicted*	12,510.25 [9253.74, 16,383.03]	15,341 [10641.75, 22,577.66]	0.52 [0.35, 0.75]	2.34 [1.65, 3.14]
Dog (1 mg/kg)	Observed	7535.57 ± 1625.96	104,26.22 ± 2022.53	18.70 ± 3.88	146.97 ± 43.62
	Predicted*	6264.85 [4603.4, 8565.44]	7762.64 [5469.63, 11,191.64]	24.45 [16.96, 34.7]	127.71 [80.36, 229.31]
Human (1 mg/kg)	Observed	–	–	–	–
	Predicted*	6981.76 [4903.04, 10,077.64]	7847.75 [5499.11, 11,157.92]	168.58 [118.86, 238.73]	968.84 [396.87, 2831.31]

*Predicted parameters are presented as the median [5th percentile, 95th percentile]; –, not available.

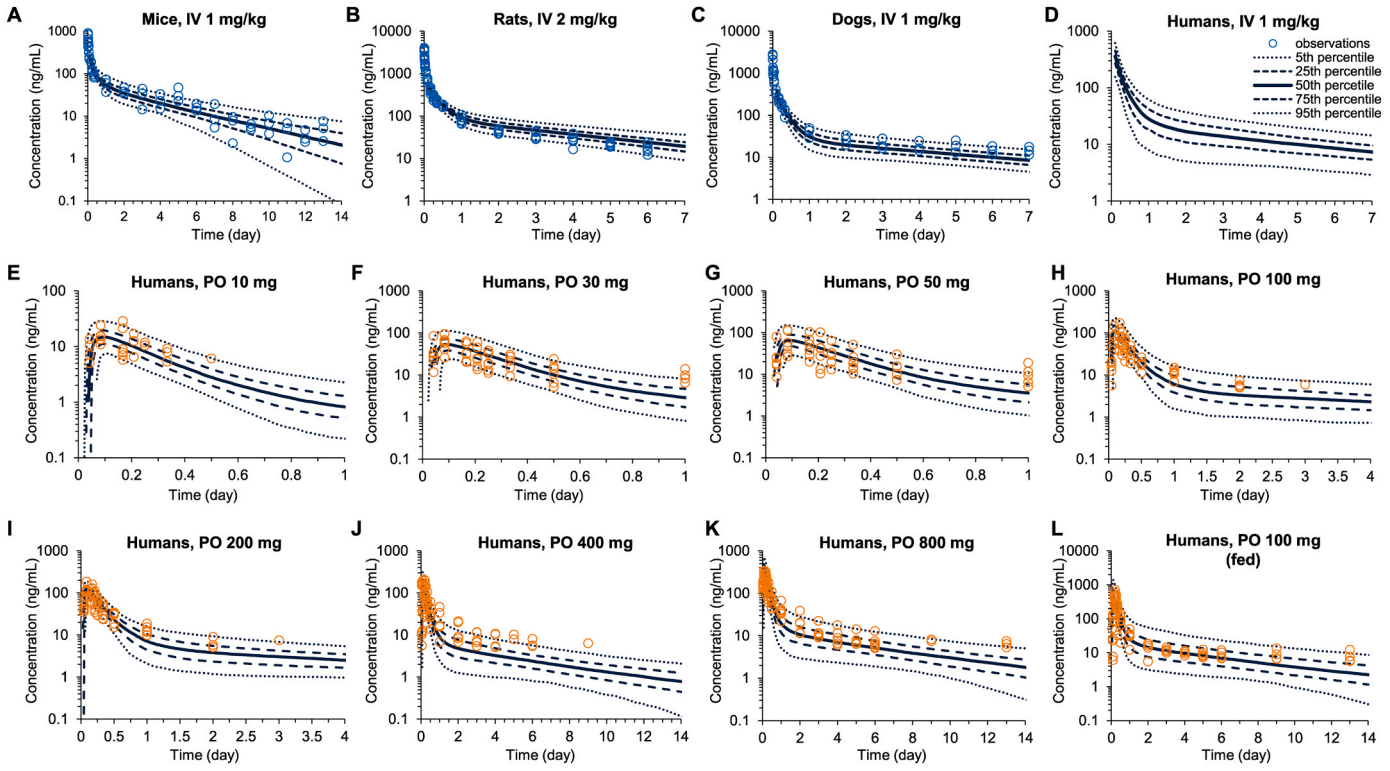

Fig. 5. Visual predictive check plots for the population pharmacokinetic model with allometric scaling using data obtained after intravenous (IV) injection in (A) mice (1 mg/kg), (B) rats (2 mg/kg), (C) dogs (1 mg/kg), and (D) humans (1 mg/kg) and oral administration (PO) in humans at (E) 10 mg, (F) 30 mg, (G) 50 mg, (H) 100 mg, (I) 200 mg, (J) 400 mg, (K) 800 mg in the fasted state and (L) 100 mg in the fed state. Since IV data in humans are not available, only predicted profiles are presented for an 80-kg human (D).

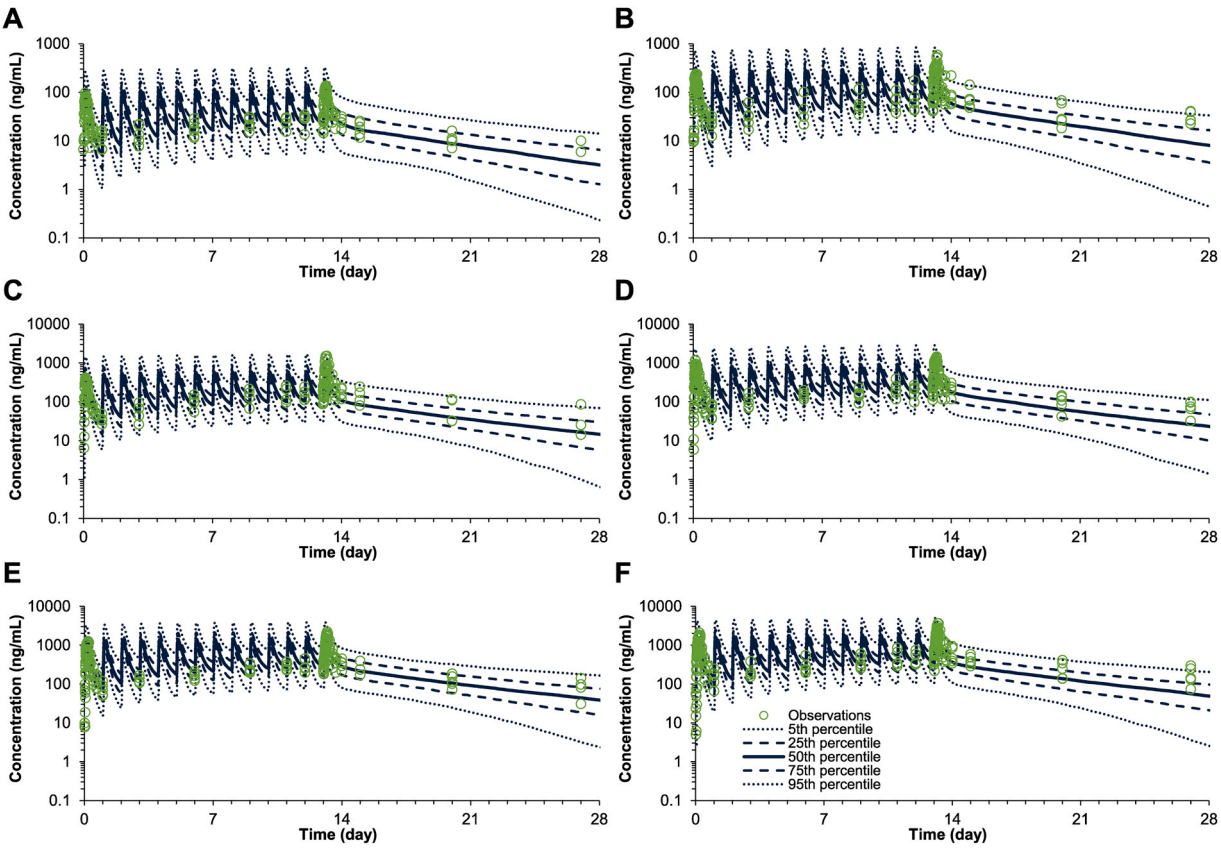

Fig. 6. Model-predicted plasma concentration vs. time profiles of telacebec following multiple oral administrations of telacebec at (A) 20 mg, (B) 50 mg, (C) 100 mg, (D) 160 mg, (E) 250 mg, and (F) 320 mg once daily for 14 days overlayed with the observed concentrations from the Phase 1B trial.

solubility of telacebec in the fasted state. Lower doses of telacebec are likely more completely solubilized and absorbed in the gastrointestinal tract, the limited solubility at higher doses may lead to the less absorption. It is also noted that the model estimated bioavailability increased to 67.87% after oral administration of 100 mg telacebec in the fed state (vs. 15.42% in the fasted state), which is postulated to be associated with the increased solubility of telacebec in the gastrointestinal contents in the fed state.

3.5. Prediction of human pharmacokinetics

The population pharmacokinetic model with allometric scaling also allowed to predict the pharmacokinetic profiles after IV injection of 1 mg/kg for 80-kg human subjects (Fig. 5D). The predicted AUC values and CL, and V_{ss} of telacebec in humans are shown in Table 3. The model predicted median CL of telacebec in humans was 168.58 [118.86 – 238.73] mL/min, while V_{ss} was 968.84 [396.87 – 2831.31] L (Table 3). The predicted AUC values after IV injection were also applied to predict the absolute oral bioavailability of telacebec in humans by using the data obtained after multiple oral doses in Phase 1B trial [5]. After oral administration of telacebec at 20 – 320 mg once daily for 14 days, the average oral bioavailability was calculated as 70.34 ± 9.91%. The predicted bioavailability of telacebec using the Phase 1B trial and predicted IV profile is consistent with the model estimated bioavailability in the fed state (67.87%) by the population pharmacokinetic model.

Finally, the population pharmacokinetic model with allometric scaling was utilized to predict the pharmacokinetic profiles of telacebec following multiple oral doses of telacebec. Fig. 6 depicts the simulated plasma concentration vs. time profiles after multiple oral doses of telacebec once daily for 14 days. When overlayed with the observations in Phase 1B trial [5], the predicted pharmacokinetic profiles were in excellent agreement with the observed ones, indicating the high predictive accuracy of the model.

4. Conclusions

In this study, the pharmacokinetics of the new anti-tuberculosis agent telacebec was characterized via interspecies scaling and the population pharmacokinetic model for the prediction of human pharmacokinetics was developed. We provided the first pharmacokinetic model for the new anti-tuberculosis agent telacebec that simultaneously described the pharmacokinetic profiles of telacebec in mice, rats, dogs, and humans. In the absence of IV formulations in humans, the population pharmacokinetic model incorporating allometric scaling allowed the prediction of the time course of plasma concentration after IV injection and estimates of the CL, V_{ss}, and absolute bioavailability in humans. Finally, the predictability of the present model was validated by simulating the pharmacokinetics of telacebec after multiple oral doses in humans, which was in good agreement with the observations from the Phase 1B clinical trial. The present findings and modeling approach may help with predicting human pharmacokinetics toward a better design of optimal dosing regimens and new formulation development.

Funding

This research was supported in part by the National Research Foundation of Korea (Grant Nos. NRF-2021R1A2B5B01001970 and NRF-2023R1A2C1007013).

CRediT authorship contribution statement

Jeongjun Kim: Methodology, Investigation, Formal analysis. **Tae Hwan Kim:** Methodology, Investigation, Formal analysis. **Jinho Choi:**

Investigation. **Kiyean Nam:** Invesgitation. **Beom Soo Shin:** Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **Soyoung Shin:** Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

J.K., J.C., and K.N. are employees of Qurient Co., Ltd.

Data Availability

Data will be made available on request.

Acknowledgements

We thank Dean Hickman (Bill & Melinda Gates Foundation) for the helpful comments on the manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2023.115441.

References

[1] K. Pethe, P. Bifani, J. Jang, S. Kang, S. Park, S. Ahn, J. Jiricek, J. Jung, H.K. Jeon, J. Cechetto, T. Christophe, H. Lee, M. Kempf, M. Jackson, A.J. Lenaerts, H. Pham, V. Jones, M.J. Seo, Y.M. Kim, M. Seo, J.J. Seo, D. Park, Y. Ko, I. Choi, R. Kim, S. Y. Kim, S. Lim, S.A. Yim, J. Nam, H. Kang, H. Kwon, C.T. Oh, Y. Cho, Y. Jang, J. Kim, A. Chua, B.H. Tan, M.B. Nanjundappa, S.P. Rao, W.S. Barnes, R. Wintjens, J. R. Walker, S. Alonso, S. Lee, J. Kim, S. Oh, T. Oh, U. Nehrbass, S.J. Han, Z. No, J. Lee, P. Brodin, S.N. Cho, K. Nam, J. Kim, Discovery of Q203, a potent clinical candidate for the treatment of tuberculosis, Nat. Med 19 (9) (2013) 1157–1160.

[2] V.R. de Jager, R. Dawson, C. van Niekerk, J. Hutchings, J. Kim, N. Vanker, L. van der Merwe, J. Choi, K. Nam, A.H. Diacon, Telacebec (Q203), a new antituberculosis agent, N. Engl. J. Med. 382 (13) (2020) 1280–1281.

[3] L.G. Matsoso, B.D. Kana, P.K. Crellin, D.J. Lea-Smith, A. Pelosi, D. Powell, S. S. Dawes, H. Rubin, R.L. Coppel, V. Mizrahi, Function of the cytochrome bc1-aa3 branch of the respiratory network in mycobacteria and network adaptation occurring in response to its disruption, J. Bacteriol. 187 (18) (2005) 6300–6308.

[4] G.C. Moraski, N. Deboosere, K.L. Marshall, H.A. Weaver, A. Vandeputte, C. Hastings, L. Woolhiser, A.J. Lenaerts, P. Brodin, M.J. Miller, Intracellular and in vivo evaluation of imidazo[2,1-b]thiazole-5-carboxamide anti-tuberculosis compounds, PLoS One 15 (1) (2020), e0227224.

[5] J. Kim, J. Choi, H. Kang, J. Ahn, J. Hutchings, C.V. Niekerk, J. Kim, Y. Jeon, K. Nam, T.H. Kim, B.S. Shin, S. Shin, Safety, Tolerability, Pharmacokinetics, and Metabolism of Telacebec (Q203) for the treatment of tuberculosis: a randomized, placebo-controlled, multiple ascending dose phase 1B Trial, Antimicrob. Agents Chemother. 67 (1) (2023), e0112322.

[6] J. Kim, J. Choi, H. Kang, J. Ahn, J. Hutchings, C. van Niekerk, D. Park, J. Kim, Y. Jeon, K. Nam, S. Shin, B.S. Shin, Safety, tolerability, and pharmacokinetics of telacebec (Q203), a new antituberculosis agent, in healthy subjects, Antimicrob. Agents Chemother. 66 (1) (2022), e0143621.

[7] B.S. Lee, K. Pethe, Telacebec: an investigational antibacterial for the treatment of tuberculosis (TB), Expert Opin. Invest. Drugs 31 (2) (2022) 139–144.

[8] A.H. Diacon, A. Pym, M.P. Grobusch, J.M. de los Rios, E. Gotuzzo, I. Vasilyeva, V. Leimane, K. Andries, N. Bakare, T. De Marez, M. Haxaire-Theeuwes, N. Lounis, P. Meyvisch, E. De Paepe, R.P.G. van Heeswijk, B. Dannemann, Multidrug-resistant tuberculosis and culture conversion with bedaquiline, N. Engl. J. Med. 371 (8) (2014) 723–732.

[9] M.T. Gler, V. Skripconoka, E. Sanchez-Garavito, H. Xiao, J.L. Cabrera-Rivero, D. E. Vargas-Vasquez, M. Gao, M. Awad, S.-K. Park, T.S. Shim, G.Y. Suh, M. Danilovits, H. Ogata, A. Kurve, J. Chang, K. Suzuki, T. Tupasi, W.-J. Koh, B. Seaworth, L.J. Geiter, C.D. Wells, Delamanid for multidrug-resistant pulmonary tuberculosis, N. Engl. J. Med. 366 (23) (2012) 2151–2160.

[10] E. Pontali, G. Sotgiu, S. Tiberi, L. D'Ambrosio, R. Centis, G.B. Migliori, Cardiac safety of bedaquiline: a systematic and critical analysis of the evidence, Eur. Respir. J. 50 (5) (2017).

[11] Q. Huang, J.E. Riviere, The application of allometric scaling principles to predict pharmacokinetic parameters across species, Expert Opin. Drug Metab. Toxicol. 10 (9) (2014) 1241–1253.

[12] T.H. Kim, S. Shin, B.S. Shin, Model-based drug development: application of modeling and simulation in drug development, J. Pharm. Investig. 48 (4) (2018) 431–441.

[13] I. Mahmood, J.D. Balian, The pharmacokinetic principles behind scaling from preclinical results to phase I protocols, Clin. Pharmacokinet. 36 (1) (1999) 1–11.

[14] A. Sharma, D.M. Benbrook, S. Woo, Pharmacokinetics and interspecies scaling of a novel, orally-bioavailable anti-cancer drug, SHetA2, PLoS One 13 (4) (2018), e0194046.

[15] J.B. Bulitta, A. Bingolbali, B.S. Shin, C.B. Landersdorfer, Development of a new pre- and post-processing tool (SADAPT-TRAN) for nonlinear mixed-effects modeling in S-ADAPT, AAPS J. 13 (2) (2011) 201–211.

[16] A. Wang, H. Wang, Y. Geng, L. Fu, J. Gu, B. Wang, K. Lv, M. Liu, Z. Tao, C. Ma, Y. Lu, Design, synthesis and antimycobacterial activity of less lipophilic Q203 derivatives containing alkaline fused ring moieties, Bioorg. Med Chem. 27 (5) (2019) 813–821.

[17] H. Higashiyama, M. Uemura, H. Igarashi, M. Kurohmaru, M. Kanai-Azuma, Y. Kanai, Anatomy and development of the extrahepatic biliary system in mouse and rat: a perspective on the evolutionary loss of the gallbladder, J. Anat. 232 (1) (2018) 134–145.