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ARTICLE

Pharmacokinetics and safety of a novel influenza treatment (baloxavir marboxil) in Korean subjects compared with Japanese subjects

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Abstract

Baloxavir marboxil, a novel influenza therapeutic agent, is a prodrug rapidly metabolized into its active form, baloxavir acid, which inhibits cap-dependent endonuclease. This study evaluated the pharmacokinetics (PKs) and safety of baloxavir acid in healthy Korean subjects and compared them with published data in Japanese subjects. This open-label and single-ascending dose study was conducted in 30 Korean male subjects, with a single oral dose of baloxavir marboxil (20, 40, or 80 mg) administered to eight subjects each; additionally, 80 mg was administered to six subjects (body weight >80 kg). Noncompartmental and population PK analyses were performed, and results were compared with those of Japanese subjects. Appropriateness of the body weight-based dosing regimen was evaluated by simulation. PK profiles of baloxavir acid revealed multicompartment behavior with a long half-life (80.8–98.3 h), demonstrating a dose-proportional increase. Baloxavir acid reached peak plasma concentration from 3.5 to 4.0 h postdosing. Body weight was identified as a significant covariate of apparent oral clearance and apparent volume of distribution, which was similar to that observed in Japanese subjects. Body weight-adjusted analysis revealed that exposure to baloxavir acid did not significantly differ between Korean and Japanese subjects. Simulated exposures to baloxavir acid demonstrated that the body weight-based dosing regimen for baloxavir marboxil was appropriate. Based on a PK study, clinical data including dosing regimen developed in Japan were adequately extrapolated to Korea, supporting the approval of baloxavir marboxil in Korean as a new treatment option for influenza.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Baloxavir marboxil, a novel influenza therapeutic agent, has been approved in Japan (first global approval; February 2018) and in the United States (October 2018). The recommended dosage for patients depends on body weight: 40 mg (40–80 kg), 80 mg (≥80 kg). However, no clinical data was available for adequate clinical use in the Korean population.

WHAT QUESTION DID THIS STUDY ADDRESS?

What are the pharmacokinetic characteristics of baloxavir acid in Koreans, and will it show similar characteristics to those in Japanese?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Pharmacokinetics of baloxavir acid were similar to those of Japanese population. Simulated exposures to baloxavir acid demonstrated that the body weight-based dosing regimen for baloxavir marboxil was appropriate in Korean population. This study provided the pharmacokinetic data to support the approval of baloxavir marboxil in Korea (November 2019) as a new treatment option for influenza.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Based on this pharmacokinetic study, the efficacy, safety, and body weight-based dosing regimen data developed in foreign countries could be adequately extrapolated to Korea.

INTRODUCTION

Influenza viruses often threaten public health with seasonal outbreaks worldwide, resulting in considerable morbidity and mortality. Reportedly, up to 650,000 respiratory-related deaths occur annually according to an estimated global attack rate of 5–10% in adults and 20–30% in children.[1,2] Influenza infection is related to substantial economic burden owing to healthcare expenses, absence from work or education, and frequent complications, including bacterial pneumonia.[2,3] Typically, vaccination can prevent influenza but could be ineffective in the case of an antigenic drift or shift, resulting in public health completely unprotected against circulating viruses.[4,5] Antiviral agents are usually prescribed to treat newly surfaced or variant viruses owing to their ability to target stable viral parts.[5] Neuraminidase inhibitors, including oseltamivir, are mainstay antiviral treatment against influenza, but a considerable emergence of variants resistant to oseltamivir warrants the development of new antiviral agents with novel mechanisms of action.[6–8] Moreover, antiviral drug-resistant influenza viruses have been detected in South Korea.[9,10]

Baloxavir marboxil (Xofluza) is a novel influenza treatment that is rapidly transformed into the active moiety, baloxavir acid, which inhibits polymerase acidic endonuclease, thus suppressing viral replication of both influenza A and B viruses.[11] Baloxavir marboxil has been approved in Japan (first global approval; February 2018) and in the United States (October 2018).[12] The recommended dosage for patients (≥12 years of age) depends on body weight: 40 mg for patients weighing 40 to 80 kg, 80 mg for patients weighing at least 80 kg.[12] Following a single oral administration, baloxavir marboxil is rapidly metabolized by arylacetamide deacetylase (AADAC) in the intestine and liver into baloxavir acid, which reaches its maximum plasma concentration ~4 h after administration.[13] Baloxavir acid presents linear pharmacokinetics in a dose range from 6 to 80 mg and is eliminated from plasma mainly through hepatic metabolism by UDP-glucuronosyltransferase 1A3 (UGT1A3), with minor metabolism by cytochrome P450 3A4 (CYP3A4).[12] Elimination of baloxavir acid from plasma follows a multi-exponential decline, with a mean terminal elimination half-life of ~80 h.[12,13]

In an exposure-response analysis of baloxavir acid, a clear pharmacokinetic/pharmacodynamic relationship was not observed for the time to alleviation of symptoms (TTAS), although TTAS was shorter in the treatment group than in the placebo group.[14,15] However, a greater reduction in the influenza viral titer was observed with increasing plasma concentration of baloxavir acid 24 h after dosing (C_{24}).[16] The most significant covariates influencing clearance and volume of distribution were body weight and ethnicity (Asian or non-Asian).[14] Although body weight and ethnicity influence drug exposure, body weight-based dosing provides sufficient exposure to expect antiviral efficacy regardless of these covariates.[14] Furthermore, baloxavir acid has a favorable safety profile with minimal safety concerns, supporting the wide therapeutic window of baloxavir acid.[13]

However, limited clinical data regarding baloxavir acid is available for the Korean population. To extrapolate the above-mentioned characteristics of baloxavir acid in the Korean population, a pharmacokinetic study in Korean subjects is necessary for adequate clinical use. Therefore, the purpose of this study was to evaluate the pharmacokinetics, safety, and tolerability of baloxavir acid after a single oral administration in healthy Korean subjects and compare them with Japanese data.

METHODS

This study was performed in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice and was approved by the Institutional Review Board of Seoul National University Hospital, as well as registered in the Korean Clinical Research Information Service (KCT0003535). All subjects provided written informed consent before performing any study-related procedures.

Study subjects and design

This single-center, open-label, and single-ascending dose study was performed in 30 healthy Korean male subjects to evaluate the pharmacokinetics, safety, and tolerability of baloxavir marboxil. Healthy Korean male subjects aged between 19 and 45 years, with body weight greater than or equal to 50 to less than or equal to 80 kg (body mass index ≥18.5 to <25.0 kg/m^2) and greater than 80 kg for an additional 80 mg dose group, were screened for eligibility by evaluating physical examinations, vital signs, electrocardiograms (ECGs), and laboratory test results. Subjects were excluded if they presented (i) any clinically significant history of gastrointestinal disease or surgery, (ii) history or a positive screening result for drug abuse or alcohol, (iii) use of any drugs, including prescribed or nonprescribed drugs, herbal medicine, dietary supplements, and vitamins, within 3 days before screening or 14 days before the first drug administration, (iv) consumption of alcohol-, caffeine-, grapefruit-, or St. John's wort-containing products within 72 h before administration, and (v) use of tobacco or nicotine-containing products within 24 weeks before screening.

Subjects were assigned to one of the following dose groups: 20, 40, and 80 mg of baloxavir marboxil (Xofluxa). Each dose group consisted of eight subjects, and an additional 80 mg dose group consisted of six subjects with body weight greater than 80 kg. All subjects received an assigned single-dose of baloxavir marboxil in the fasted state (≥8 h) with 200 ml of water, and food intake was prohibited until 4 h after administration. The administered dose was increased in ascending order after the safety and tolerability of the previous dose were confirmed.

Serial blood samples for pharmacokinetic evaluation of baloxavir marboxil and baloxavir acid were collected at predose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, 48, 60, 72, 168, 264, and 336 h postdose. Two milliliters of blood were collected in heparin lithium tubes at each point and then centrifuged (2000 g and 4°C for 10 min) to separate 0.4 ml plasma aliquots into polypropylene tubes, containing 20 μl of dichlorvos solution (60 mmol/L). The separated samples were well mixed, and 0.2 ml of each plasma sample was transferred into cryotubes and stored at less than −70°C until analysis.

Measurement of baloxavir marboxil and its active form, baloxavir acid

Plasma concentrations of baloxavir marboxil and active form baloxavir acid were analyzed by a validated liquid chromatography tandem-mass spectrometry (LC-MS/MS) method at Sumika Chemical Analysis Service, Ltd. (Osaka, Japan). Dichlorvos was added to plasma samples to inhibit metabolism from baloxavir marboxil to baloxavir acid by esterase. Determination of baloxavir marboxil and baloxavir acid was performed by deproteinization with acetonitrile/formic acid (1000:1, v/v), followed by separation using liquid chromatography (L-column 2 ODS metal-free; Chemicals Evaluation and Research Institute). The MS/MS system (API5000; AB Sciex Pte. Ltd.) was operated with a turbo ion spray in positive ion detection mode. The lower limit of quantification for the analytical results was 0.500 ng/ml, with linear calibration curves in the concentration range of 0.500–300 ng/ml ($r^2 > 0.99$).

Noncompartmental pharmacokinetic analysis

Pharmacokinetic parameters of baloxavir marboxil and baloxavir acid were determined by a noncompartmental method using the Phoenix WinNonlin software (version 8.1; Certara USA, Inc.). The following parameters were included: the maximum plasma concentration (C_{max}) and time at which the peak plasma drug concentration (T_{max}) based on observed concentrations and actual times, the area under plasma concentration-time curve (AUC) from 0 to certain time points (AUC_{0-72h}, to 72 h; AUC_{last}, to the last measurable time point; AUC_{inf}, to infinity) calculated using the linear up/log down trapezoidal rule, terminal elimination half-life ($t_{1/2}$) derived by $\ln 2/\lambda_z$ (λ_z, terminal elimination rate constant), apparent oral clearance (CL/F), and plasma concentration at 24 h after dosing (C_{24}).

Population pharmacokinetic analysis

A population pharmacokinetic analysis for baloxavir acid was performed using the nonlinear mixed-effects method with NONMEM (version 7.4.3, Icon Development Solutions). First-order conditional estimation with the interaction estimation method was used to estimate pharmacokinetic parameters and variabilities. The population

pharmacokinetic model of baloxavir acid was developed using the Korean population data and some corresponding Japanese population data with the same clinical design ($n = 18$; 20, 40, and 80 mg).[13]

The pharmacokinetic structural models of baloxavir acid were investigated with one-, two-, or three-compartment models using zero-order, first-order, or zero- and first-order absorption and linear elimination. Interindividual variabilities were evaluated with exponential error models, and residual unexplained variabilities were evaluated with additive, proportional, and combined error models:

$$Y_{ij} = C_{ij} + \omega_{ij} \bullet \varepsilon_{ij}$$

$$\omega_{ij} = \sqrt{C_{ij}^2\sigma_1^2 + \sigma_2^2}$$

where Y_{ij} represents the observed concentration at time t_j for the ith individual, C_{ij} represents the corresponding predicted concentration from the pharmacokinetic model, ε_{ij} represents the intra-individual variability, and ω_{ij} represents the residual SD with proportional and additive variance components (σ_1^2 and σ_2^2).

Effects of potential covariates, including ethnicity (Korean or Japanese), age, height, body weight, body mass index, aspartate aminotransferase, alanine aminotransferase, total bilirubin, and creatinine, on the pharmacokinetics of baloxavir acid were investigated via graphical and statistical analysis using a generalized additive model. Stepwise forward selection and backward elimination were implemented to determine statistical significance from screened covariates at significance levels of 0.05 (forward selection) and 0.01 (backward elimination). Continuous covariates were modeled with power functions centralized to the median values, and the categorical covariate was modeled with an exponential function as given by the following equations:

$$\text{TV} = \theta_1 \times (\text{Covariate}/\text{median of Covariate})^{\theta_2} \text{ (Power functions)}$$

$$\text{TV} = \theta_{cat=0} \times e^{\theta_{cat\_i}} \text{ (Exponential function)}$$

where TV represents the typical pharmacokinetic parameter, and θ_1, θ_2, $\theta_{cat=0}$, and θ_{cat_i} (0 or 1) are the estimated parameters.

Only biologically plausible relationships between covariates and parameters were considered for the final model. Basic goodness-of-fit plots, individual plots, prediction-corrected visual predictive checks (pcVPCs), and nonparametric bootstrap resampling were used to evaluate the stability, adequacy, and robustness of the final pharmacokinetic model.

Based on the developed final population pharmacokinetic model, pharmacokinetic simulations were performed to evaluate the appropriateness of the body weight-based dosing regimen of baloxavir marboxil with the previously approved doses (40 mg dose group with <80 kg and 80 mg dose group with ≥80 kg). Using the estimated C_{max}, AUC, and C_{24} of baloxavir acid, the achievement of the observed effective pharmacokinetic target was investigated.

Safety and tolerability

Safety and tolerability were evaluated through vital signs, physical examinations, clinical laboratory tests, 12-lead ECGs, and treatment-emergent adverse events (TEAEs). TEAEs were classified by the Medical Dictionary for Regulatory Activities (version 21.1), and investigators reviewed the results in terms of the relationship between baloxavir marboxil and clinical significance.

Statistical data analysis

The sample size was based on previous pharmacokinetic studies, with no power-based calculation performed. Demographic and pharmacokinetic characteristics were described as arithmetic means and SDs. Safety and tolerability profiles were analyzed using frequency and percentages. To evaluate the dose proportionality, a comparison of dose-normalized pharmacokinetic parameters (C_{max}/dose and AUC/dose) across dose groups was performed using the Kruskal-Wallis method and linear regression analysis with a power model (log-transformed C_{max} and AUCs). Statistically significant dose-proportionality was considered if the 95% confidence interval (CI) of the gradient of the regression line included. Comparison of pharmacokinetic characteristics by ethnicity was performed with geometric mean ratios and the analysis of covariance when the adjusted analysis was needed. All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc.). Values of p less than 0.05 were considered statistically significant.

RESULTS

Study subjects

In total, 30 Korean subjects were enrolled, randomized, and completed the study with no withdrawal. Safety evaluations were performed for the 30 subjects who received baloxavir marboxil. In the 40 mg dose group, one subject was excluded from the pharmacokinetic analysis owing to the violation of exclusion criteria, which was

a positive result (0.02%) for the alcohol expiratory test. Baseline demographic characteristics are presented in Table S1.

Pharmacokinetic analysis

Most plasma baloxavir marboxil concentrations were below the lower limit of quantification (0.5 ng/ml), except for two measurements from one subject (0.617 and 0.592 ng/ml at 4 and 5 h after dosing, respectively; 80 mg dose group). This reflected the rapid metabolism of baloxavir marboxil into baloxavir acid, as expected.

The pharmacokinetic profile of baloxavir acid showed a multicompartmental behavior in the dose range of 20–80 mg (Figure 1). Baloxavir acid reached its peak plasma concentration from 3.5 to 4.0 h (median) postdose, presenting a multicompartmental elimination phase with an average half-life ranging from 80.8 to 98.3 h (Table 1 and Figure 1). The average apparent oral clearance of baloxavir acid ranged from 7.6 to 10.1 L/h (Table 1). For subjects weighing greater than 80 kg, the general

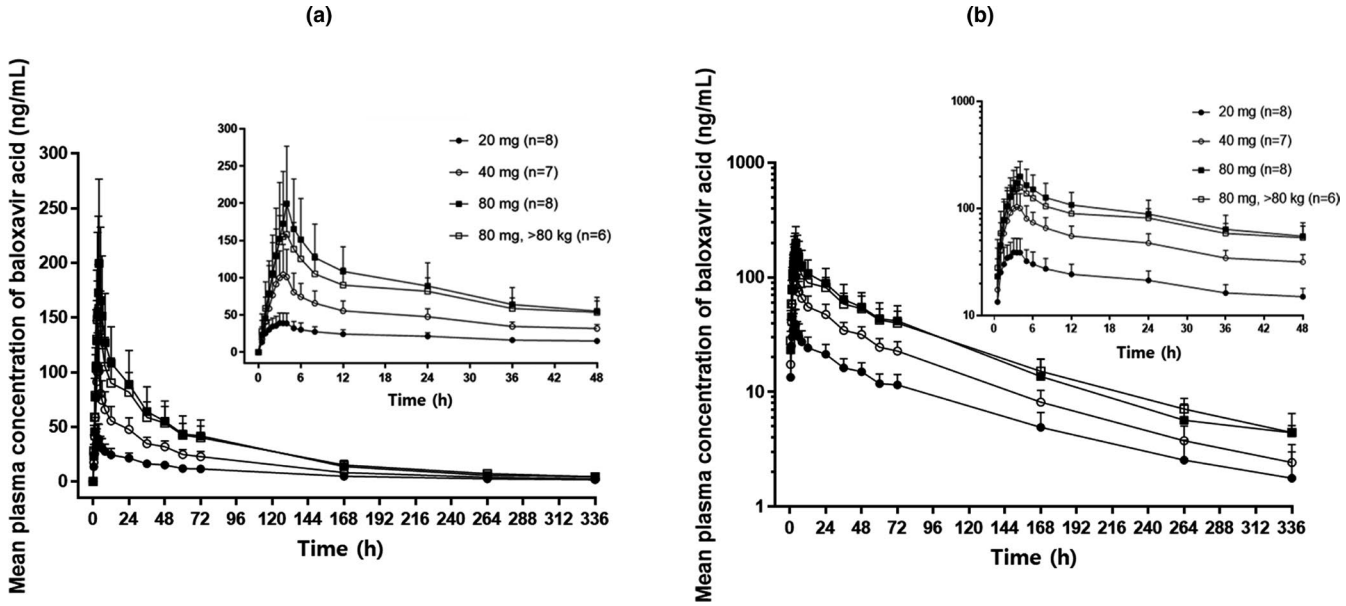

FIGURE 1 Mean plasma concentration-time profiles of baloxavir acid after a single oral administration of baloxavir marboxil. (a) Linear scale and (b) semilogarithmic scale. Inserted graphs show the plots from 0 to 48 h

Parameters	Baloxavir marboxil			
	20 mg ($n = 8$)	40 mg ($n = 7$)	80 mg ($n = 8$)	80 mg, >80 kg ($n = 6$)
T_{max} (h)	3.50 [1.50–4.00]	3.50 [3.02–5.00]	4.00 [3.00–4.00]	4.00 [3.00–5.00]
C_{max} (ng/ml)	41.4 ± 12.9	106.9 ± 40.1	206.2 ± 78.3	163.7 ± 37.5
AUC_{0-72h} (ng·h/ml)	1334 ± 295	2940 ± 635	5393 ± 1776	4896 ± 1146
AUC_{last} (ng·h/ml)	2580 ± 663	5066 ± 973	8928 ± 2969	8903 ± 2124
AUC_{inf} (ng·h/ml)	2864 ± 887	5385 ± 1019	9447 ± 3178	9503 ± 2198
$t_{1/2}$ (h)	98.3 ± 23.5	87.7 ± 15.1	80.8 ± 6.9	93.4 ± 15.6
CL/F (L/h)	7.6 ± 2.3	7.7 ± 1.5	10.1 ± 6.1	8.7 ± 1.6
C_{24} (ng/ml)	11.6 ± 2.6	22.8 ± 4.8	41.8 ± 14.7	40.1 ± 10.7

TABLE 1 Summary of pharmacokinetic parameters of baloxavir acid after a single oral administration of baloxavir marboxil

Abbreviations: AUC_{0-72h}, the area under concentration-time curve from 0 to 72 h point; AUC_{inf}, AUC from 0 to infinity; AUC_{last}, the AUC from 0 to the last measurable time point; C_{24}, the observed plasma concentration at 24 h after dosing; CL/F, apparent oral clearance; C_{max}, the maximum plasma concentration; $t_{1/2}$, half-life; T_{max}, the time at which the peak plasma drug concentration.

Data were presented as mean ± SD except for T_{max}, which was presented as median [min–max].

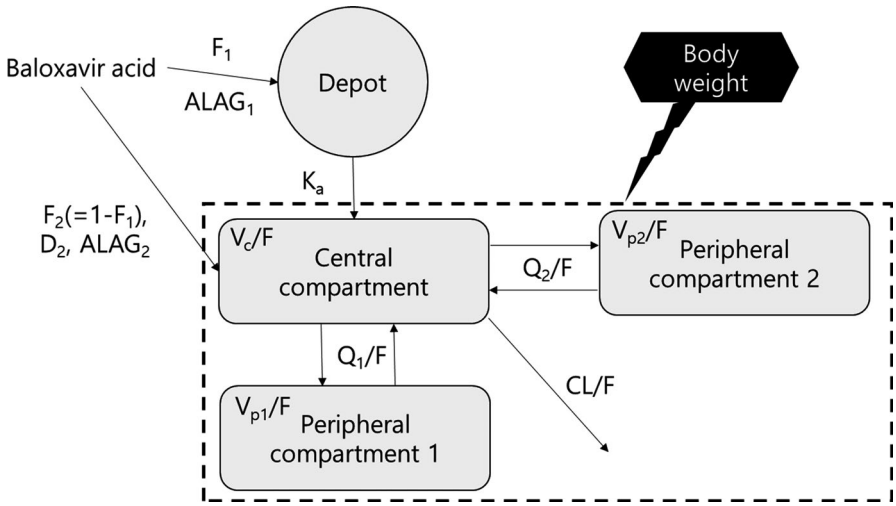

FIGURE 2 Schematic representation of the final population pharmacokinetic model for baloxavir acid and significant covariate of body weight. F_1, fraction of bioavailable dose of baloxavir acid for first-order absorption; F_2, fraction of bioavailable dose of baloxavir acid for zero-order absorption; D_2, duration of zero-order absorption; K_a, absorption rate constant of first-order absorption; V_c/F, apparent volume of central compartment; V_{p1}/F, apparent volume of peripheral compartment 1; V_{p2}/F, apparent volume of peripheral compartment 2; Q_1/F, apparent intercompartmental clearance 1; Q_2/F, apparent intercompartmental clearance 2; CL/F, apparent oral clearance

pharmacokinetic profile was similar, and C_{max}, $AUC_{0\text{-}72h}$, and CL/F were decreased by 20%, 9.2%, and 14%, respectively, when compared with subjects in the same dose group (Table 1).

Dose-normalized systemic exposure parameters (C_{max}/dose and AUCs/dose) and power model analysis of baloxavir acid showed the dose-proportionality of baloxavir acid across 20 to 80 mg (Figure 1). The dose-normalized exposure parameters (C_{max}/dose and $AUC_{0\text{–}72h}$/dose) were lower in Korean than those in Japanese subjects (geometric mean ratios with 90% CIs: 0.84 [0.68–1.03] and 0.81 [0.70–0.74], respectively) after a single oral administration of baloxavir marboxil 20, 40, and 80 mg (Table S2). This could be explained by the fact that the body weights of Korean subjects were significantly higher than those of Japanese subjects (arithmetic mean ± SD [*p* value]: 67.8 ± 7.6 for Korean and 62.7 ± 6.5 for Japanese [0.0252], respectively; Table S1). Following body weight-adjusted analysis, no significant difference was observed between Korean and Japanese subjects in exposure to baloxavir acid (C_{max}/dose, $p = 0.4754$; $AUC_{0\text{–}72h}$/dose, $p = 0.0544$), although a decreasing tendency was still observed among Koreans (Table S2).

Population pharmacokinetic analysis

A population pharmacokinetic model for baloxavir acid was developed using 966 plasma concentrations from 48 subjects (29 Korean and 18 Japanese subjects). A three-compartment model with a simultaneous zero- and first-order absorption model along with each lag time adequately described the time-concentration profiles of baloxavir acid (Figure 2). Typical values of CL/F and apparent intercompartmental clearances (Q_1/F and Q_2/F) were 7.43, 51.0, and 2.69 L/h, respectively (Table 2). The absorption process of baloxavir acid was described by a first-order absorption rate constant (k_a, 0.917/h) with lag time (0.233 h), and duration of zero-order absorption (D_2, 2.49 h) with lag time (1.42 h). The pharmacokinetic model revealed that 62.5% of the administered baloxavir dose was absorbed by the first-order process, with the remaining 37.5% absorbed by the zero-order process. Body weight was identified as the only covariate on apparent oral clearance (CL/F, Q_1/F, and Q_2/F) and volume of distributions (V_c/F, V_p/F, and V_{p2}/F), supporting the current dosing regimen based on body weight regardless of ethnicity. Their ethnicity (Korean or Japanese) was not a significant covariate for clearances or volume of distributions after the body weight was incorporated into the model. Goodness-of-fit plots showed good adequacy between observed and predicted pharmacokinetic data (Figure S1), and model evaluation by pcVPCs and bootstrap indicated that the developed model was adequate, precise, and robust (Figure 3 and Table 2).

Comparison of simulated C_{max}, AUC, and C_{24} of baloxavir acid in Korean and Japanese subjects, stratified by body weight categories (<80 kg and ≥80 kg), showed that all of the exposure parameters were higher than the mean values at 10 mg (C_{max}, 27.8 ng/ml; AUC, 2105 ng·h/ml; C_{24}, 15.1 ng/ml) in the phase II study,[16] which was revealed as the minimum effective dose for both type A and B influenza viruses (Figure 4). Furthermore, the simulated C_{max},

TABLE 2 Summary of final parameter estimates of the pharmacokinetic model for baloxavir acid

		Final model		Bootstrap	
Parameters	**Description**	**Estimates**	**RSE (%)**	**Median**	**95% CIs[a]**
Fixed effect					
CL/F (L/h)	Apparent oral clearance	7.43	4.5	7.36	6.76–8.12
Q_1/F (L/h)	Apparent inter-compartmental clearances	51.0	9.8	52.8	43.8–75.8
Q_2/F (L/h)		2.69	10.0	2.86	2.24–4.04
Effect of body weight on CL/F, Q_1/F, Q_2/F		0.542	74	0.617	−0.325 to 1.718
V_c/F (L)	Apparent volume of central compartment	251	9.0	241	192–287
V_{p1}/F (L)	Apparent volume of peripheral compartments	309	4.7	305	269–343
V_{p2}/F (L)		224	7.5	228	196–266
Effect of body weight on V_c/F, V_{p1}/F, V_{p2}/F		0.844	29.3	0.854	0.161–1.354
F_1	Fraction of bioavailable dose of Baloxavir acid for first-order absorption	0.625	9.6	0.624	0.50–0.71
K_a (1/h)	Absorption rate constant of first-order absorption	0.917	11.3	0.878	0.684–1.116
ALAG1 (h)	Absorption lag time for first-order absorption	0.233	12.7	0.232	0.175–0.291
D_2 (h)	Duration of zero-order absorption	2.49	8.3	2.48	2.11–2.95
ALAG2 (h)	Absorption lag time for zero-order absorption	1.42	8.7	1.37	1.25–1.74
Random effect					
$\omega_{CL/F}$ (CV%)	Interindividual variability of CL/F	30.3	18.3	29.8	20.8–45.0
$\omega_{Vc/F}$ (CV%)	Inter-individual variability of V_c/F	60.3	14.8	61.4	41.3–82.5
$\omega_{Vp1/F}$ (CV%)	Interindividual variability of V_{p1}/F	28.2	13.5	28.9	20.9–50.0
ω_{ka} (CV%)	Interindividual variability of ka	152	14.4	156	106–257
ω_{ALAG1} (CV%)	Interindividual variability of ALAG1	70.4	15.6	69.3	42.5–105
$\rho_{CL/F\text{-}Vc/F}$	Correlation coefficient between CL/F and V_c/F	0.0912	47.8	0.0822	0.0157–0.192
$\rho_{CL/F\text{-}Vp1/F}$	Correlation coefficient between CL/F and V_{p1}/F	0.0526	40.3	0.0513	0.0195–0.1075
$\rho_{Vp1/F\text{-}Vp2/F}$	Correlation coefficient between V_{p1}/F and V_{p2}/F	0.0648	49.7	0.0679	0.0064–0.1655
Residual error					
σ_{prop} (%)	Proportional error	11.9	8.1	11.5	9.82–13.3

Abbreviations: CI, confidence interval; CV, coefficient of variation RSE, relative standard error.

[a]95% CIs were derived by the bootstrap method of 500 resampled data sets.

simulated AUCs, and observed C_{24} were comparable with corresponding values in Asian patients from both phase III studies.[15]

Safety and tolerability

A single oral administration of baloxavir marboxil was generally well-tolerated in Korean subjects (Table 3). In total, six TEAEs were reported by 6 (20%) of the 30 subjects. Among the TEAEs, two adverse drug reactions (dyspepsia, 20 mg dose group; headache, 80 mg dose group [≥80 kg]) were observed. All TEAEs were mild in severity, resolved without any treatment, with no serious events or deaths observed during the study. There were no clinically significant changes in vital signs, physical examinations, laboratory tests, and ECGs.

DISCUSSION

This is the first clinical study in Korean subjects assessing the pharmacokinetics, safety, and tolerability of baloxavir acid after a single oral administration of baloxavir marboxil. Baloxavir acid demonstrated rapid metabolism into the active drug, dose-proportionality ranging from 20 to 80 mg, and multicompartmental behavior with a long elimination half-life, which is consistent with previously reported data.13 Although a lower tendency of exposure to baloxavir acid was observed in Koreans than in the Japanese population, no significant difference in drug exposure was observed after the impact of body weight was adjusted. This was a consistent result that a significant influence of body weight was previously identified in other ethnic populations.[14,15] Moreover, population pharmacokinetic analysis revealed that ethnicity (Korean or

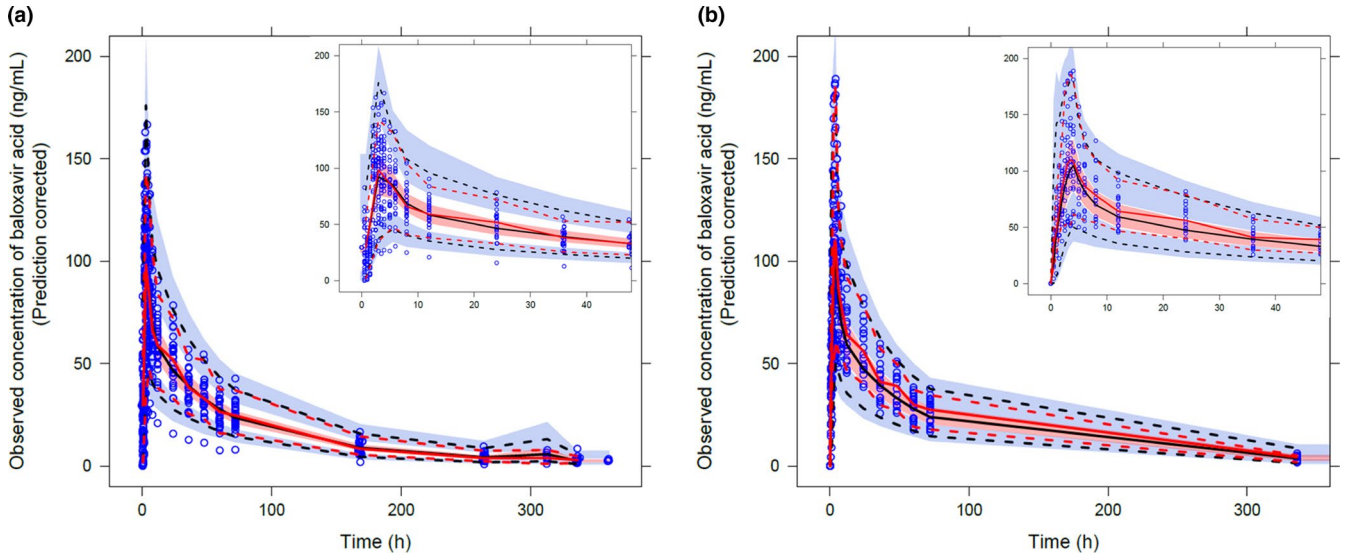

FIGURE 3 Prediction-corrected visual predictive check plots of the final pharmacokinetic model according to (a) Korean and (b) Japanese subjects.[13] Inserted graphs show the plots from 0 to 48 h. Blue circles represent the observed concentrations of baloxavir acid. The red lines represent the median (solid) and the 5th and 95th percentiles (dashed) of the observed concentration. The black lines represent the median (solid) and 5th and 95th percentiles (dashed) of the simulated concentrations. The areas represent the 95% confidence intervals for the median (red) and for the prediction percentiles (blue)

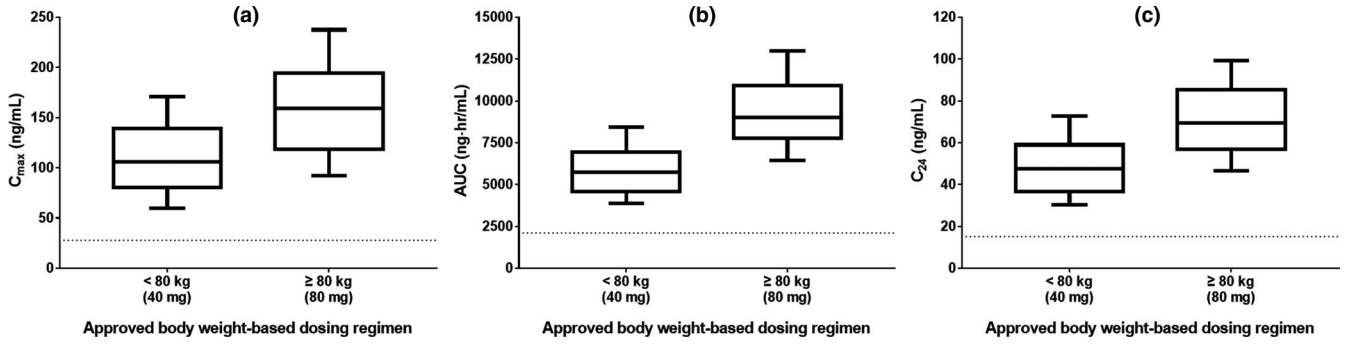

FIGURE 4 Model-based simulation of (a) C_{max}, (b) AUC, and (c) C_{24} for baloxavir acid based on final pharmacokinetic model in Korean and Japanese subjects stratified by the approved body weight-based dosing regimen of baloxavir marboxil. The horizontal dashed line corresponds to the observed mean C_{max} (27.8 ng/ml), AUC (2105 ng·h/ml), and C_{24} (15.1 ng/ml) at the minimum effective dose of 10 mg in phase II study.[16] The horizontal lines within each box represent the median, and the box edges show lower (25th) and upper (75th) quartiles, respectively. The whiskers represent the 10th/90th percentile. AUC, area under plasma concentration-time curve; C_{24}, plasma concentration 24 h after dosing; C_{max}, maximum plasma concentration

Japanese) was not a significant covariate for pharmacokinetic parameters after body weight was incorporated into the model. Meanwhile, baloxavir marboxil was generally well-tolerated in Korean subjects at a single-dose of up to 80 mg. Accordingly, this study could provide a rationale for extrapolating foreign clinical data to the Korean population, to enable the approval of baloxavir marboxil in Korea (November 2019) as an influenza treatment.

There are several scientific reasons for performing a pharmacokinetic study to obtain marketing approval for baloxavir marboxil in Korea, with a reasonable assessment of ethnic sensitivity and minimal potential for clinically significant impact by intrinsic and extrinsic ethnic factors. An adequate pharmacokinetic comparison between Korean and Japanese populations could allow rational consideration of what kinds of bridging studies are needed in the new region.[17,18] Considering several points to be mentioned, the Ministry of Food and Drug Safety in Korea decided that if the pharmacokinetics was not significantly different between Korean and Japanese populations, the data on clinical efficacy and dose-response in Korea may not have been needed. First, the ethnic sensitivity to baloxavir marboxil was less likely due to following factors: linear pharmacokinetics,[13] a flat or non-steep pharmacodynamic curve over a wide dose and exposure range,[14–16] metabolism/elimination among multiple

TABLE 3 Summary of adverse events after single oral administration of baloxavir marboxil in Korean subjects

	Baloxavir marboxil			
	20 mg (*n* = 8)	**40 mg (*n* = 8)**	**80 mg (*n* = 8)**	**80 mg, >80 kg (*n* = 6)**
Subjects with TEAEs	3 (37.5)	0	2 (25.0)	1 (16.7)
TEAEs				
Dyspepsia	1 (12.5)	0	0	0
Catheter site bruise	1 (12.5)	0	0	0
Fatigue	1 (12.5)	0	0	0
Pharyngeal erythema	0	0	1 (12.5)	0
Hyperkeratosis	0	0	1 (12.5)	0
Headache	0	0	0	1 (16.7)
Treatment-related TEAEs				
Dyspepsia	1 (12.5)	0	0	0
Headache	0	0	0	1 (16.7)

Abbreviation: TEAEs, treatment emergent adverse events.

Data are represented as number of subjects (%).

pathways (major in UGT1A3, minor in CYP3A, and biliary secretion[11]), medium bioavailability, relatively low potential for protein binding (93–94%) and drug-drug interactions,[12] and little potential for inappropriate use (e.g., drug abuse, misdose, and incompliance) as this drug is a single-use drug. Second, baloxavir marboxil has a wide therapeutic dose range (10–80 mg), with good tolerability.[13] Third, the relationship between exposure to baloxavir acid and reduction in the influenza viral titer has been identified.[14,16] Last, extrinsic factors including medical practice, therapeutic approach, and regulatory practice were similar across Japan and the United States. As predominant types of influenza viruses are similar across global regions,[19] the diagnosis and therapeutic approach of influenza in Korea is aligned with Japan and is also broadly comparable with other regions, including the United States. Furthermore, the Ministry of Food and Drug Safety in Korea has extensive experience in the domestic application of safety and efficacy data obtained in foreign countries (Japan and the United States), conducting clinical confirmation studies. Meanwhile, even if the lowest recommended dose (40 mg) of baloxavir marboxil is administered in Korea, this study established that exposure to baloxavir acid would easily exceed the minimum effective exposure at 10 mg (C_{max}, 27.8 ng/ml; AUC, 2105 ng·h/ml; C_{24}, 15.1 ng/ml) and 5.88 ng/ml of the C_{24}, achieving 50% of the maximal response.[16] Based on the above-mentioned characteristics, it is estimated that the pharmacokinetics/pharmacodynamics of baloxavir acid do not significantly differ between the Korean population and other populations. Therefore, an adequate pharmacokinetic study in the Korean population could confirm the ability to extrapolate data from foreign regions, without the need to provide clinical data for efficacy, by characterizing the pharmacokinetic profile of baloxavir marboxil between Korean and Japanese populations. As confirmed by results in this study, the pharmacokinetic profile between Korean and Japanese populations was comparable.

The pharmacokinetic variability of baloxavir acid can be explained by the following possible reasons. The most plausible reason is the decreased metabolic activity of AADAC, which mainly metabolizes baloxavir marboxil into baloxavir acid by hydrolysis. In terms of genetic polymorphism, AADAC*3 (g.13651G>A/g.14008T>C) yields decreased enzyme activity when compared with AADAC*1 (wild-type), whereas AADAC*2 showed moderately lower or similar activity.[20] This explanation is supported by the two observed concentrations of baloxavir marboxil (0.617 and 0.592 ng/ml) in the subject with lower exposure to baloxavir acid, which can be attributed to decreased AADAC activity. However, allele frequencies of AADAC*3 are low in any ethnic population (~2%); hence, these minor polymorphisms are not considered to demonstrate a clinically significant impact on drug exposure in the Korean population.[20] Moreover, the variability of drug exposure can be explained by a genetic polymorphism of UGT1A3, which mainly metabolizes baloxavir acid. The enzyme activity of UGT1A3*2 (c.140T>C) was increased when compared with that of the wild-type allele, and UGT1A3*2 reportedly increases the metabolism of several drugs (montelukast, atorvastatin, telmisartan, and febuxostat), which are UGT1A3 substrates.[21–24] The allele frequencies of UGT1A3*2 are relatively lower in Asian populations (0.14, Korean; 0.125, Japanese; and 0.104, Chinese Han) and higher in Whites (0.580, German-White).[25,26] This ethnic difference in the UGT1A3 polymorphism implies that Asian patients may demonstrate a lower elimination capacity of baloxavir acid than non-Asian

patients, which supports high exposure to baloxavir acid in Asians regardless of body weight.[14,15] One Korean subject, administered 80 mg of baloxavir marboxil (<80 kg), showed substantially lower exposure to baloxavir acid (C_{max}, 57.2 ng/ml; C_{24}, 30.6 ng/ml; AUC_{last}, 3124 ng·h/ml; and AUC_{inf}, 3242 ng·h/ml). Unfortunately, genotyping was not conducted; however, it seems more plausible that this Korean subject could be a poor AADAC metabolizer rather than a rapid UGT1A3*2 metabolizer due to lower baloxavir acid exposure and detectable baloxavir marboxil concentrations.

As the impact of body weight on exposure to baloxavir acid was identified in early clinical studies, a single body weight-based dosing regimen (40 mg for patients <80 kg; and 80 mg for patients ≥80 kg) was implemented in phase III studies.[27,28] The body weight-based dosing regimen can provide sufficient exposure to baloxavir acid regardless of ethnicity and is also applicable to the Korean population. Population pharmacokinetic analysis in Korean subjects revealed that body weight was a significant covariate impacting the pharmacokinetics of baloxavir acid. Furthermore, the observed exposure to baloxavir acid in Korean subjects (40 mg dose group with <80 kg and 80 mg dose group with ≥80 kg) was higher than the mean effective concentration at 10 mg in the phase II study, and no relevant difference was observed when compared with those in Asian patients from phase III studies.[15] Therefore, when considering that baloxavir marboxil has a wide therapeutic window with safe and good tolerability up to 80 mg regardless of ethnicity, the body weight-based dosing regimen would successfully attain a therapeutic target in the Korean population without safety concerns.

In conclusion, baloxavir marboxil was well tolerated at doses up to 80 mg after single-dose administration in healthy Korean subjects. Pharmacokinetic characteristics of baloxavir acid were similar to those of the Japanese population. Regarding the contribution of body weight to pharmacokinetics, the body weight-based dosing regimen of baloxavir marboxil can be successfully applied to the Korean population. This study provides support for the extrapolation of efficacy, safety, and dosing regimen data developed in Japan to the Korean population.

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CONFLICT OF INTEREST

All authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

Y.K. wrote the manuscript. S.L., Y.K., I.J.J., and S.H.L. designed the research. Y.K., I.J.J., and S.H.L. performed the research. Y.K. analyzed the data.

ETHICAL APPROVAL

This study was performed in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice and was approved by the Institutional Review Board of Seoul National University Hospital, as well as registered in the Korean Clinical Research Information Service (KCT0003535). All subjects provided written informed consent before performing any study-related procedures.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of the article at the publisher's website.

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