

ARTICLE

Pharmacokinetics, safety, and simulated efficacy of an influenza treatment, baloxavir marboxil, in Chinese individuals

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Abstract

Baloxavir marboxil is an endonuclease inhibitor indicated for the treatment of influenza in patients ≥ 12 years. No data exist for Chinese patients in global studies. This randomized, open-label, phase I study evaluated the pharmacokinetics (PK) and safety of baloxavir marboxil in healthy Chinese volunteers and was used to anticipate efficacy in Chinese patients. Patients received a single oral dose of baloxavir marboxil (40 or 80 mg [1:1]). Serial blood samples were collected pre-dose and at various timepoints up to 14 days postdose. Baloxavir marboxil and acid plasma concentrations were determined by liquid chromatography tandem mass spectrometry. PK parameters of baloxavir acid were estimated by noncompartmental analysis. Adverse events (AEs) were recorded. Time to alleviation of symptoms (TTAS) was simulated for otherwise healthy (OwH) and high-risk (HR) Chinese and Asian patients. Thirty-two male patients received baloxavir marboxil. Baloxavir acid plasma concentration peaked 4 h postdose. Mean maximum concentration (C_{max}) was 107.6 and 206.9 ng/ml, and mean area under the plasma concentration-time curve from zero to infinity (AUC_{0-inf}) was 6955 and 9643 ng·h/ml in the 40 and 80 mg cohorts, respectively. AEs were mild and transient; no new safety signals were identified. Simulated median TTAS for OwH and HR Chinese patients agreed with simulated values in Asian patients. PK parameters were similar to Asian populations in other studies. The globally adopted baloxavir marboxil dosing strategy was consistent with the established safety profile of baloxavir marboxil in this population. Simulated efficacy indicated Chinese patients could benefit from similar efficacy to Asian patients.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Baloxavir marboxil, the prodrug of baloxavir acid, is indicated for the treatment of influenza virus infection and is to be administered within 48 h of symptom onset. At the time of this study, baloxavir marboxil was not approved for the

treatment of influenza in China, and there were no clinical data available in Chinese populations.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study characterized baloxavir acid pharmacokinetics (PK) and safety in healthy Chinese volunteers, and simulated efficacy (time to alleviation of symptoms) in Chinese patients. The aim of this study was to determine if the PK, safety, and efficacy of baloxavir marboxil would be similar between a Chinese population and other Asian patients from global phase III studies.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study indicates that no meaningful differences in the safety and efficacy of baloxavir marboxil are anticipated between Chinese patients and other Asian patients.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Findings from this investigation were used to support a new drug application in China, which was subsequently approved.

INTRODUCTION

Influenza virus outbreaks incur a significant public health and economic burden.^{1,2} Although annual vaccination programs and nonpharmaceutical interventions mitigate the burden of influenza infections to some degree, antiviral therapies are critical for treatment of acutely ill patients and in outbreak management.^{2,3} In China, almost 1.2 million cases of influenza were reported between 2005 and 2015, with regional variances observed.⁴ A recent large-scale epidemiological study investigating the distribution of influenza in mainland China demonstrated that the mean influenza case incidence was ~ 1–21 cases of 100,000 people in 31 provinces and areas.⁴ Mortality due to influenza was higher among elderly versus non-elderly patients, with rates of excess mortality of up to 30.35 and 0.91 per 100,000 people, respectively.⁵

Baloxavir marboxil is an oral influenza virus-specific antiviral which, upon metabolism to its active form baloxavir acid, inhibits the cap-dependent endonuclease and prevents viral transcription.^{6,7} Baloxavir marboxil is indicated for the treatment of influenza A and B virus infections within 48 h of symptom onset in patients aged 12 years and over.^{7–11} The globally adopted dosing strategy is weight dependent, with a single 40 mg dose recommended for those who weigh 40 to <80 kg, and a single 80 mg dose for those weighing at least 80 kg.⁷

Prior pharmacokinetic (PK) analyses demonstrated that baloxavir marboxil is rapidly metabolized, with baloxavir acid achieving peak plasma concentration 4 h after administration.¹² Baloxavir acid exhibited linear PK characteristics in patients in a fasted state who received doses

of 6–80 mg.¹² The terminal elimination half-life of baloxavir acid was 85.9 h and 75.9 h for baloxavir marboxil doses of 40 and 80 mg, respectively.¹²

Subgroup analyses of Asian patients (mostly Japanese) in pivotal phase III studies show that, compared with placebo, baloxavir marboxil results in significantly shorter time to alleviation of symptoms (TTAS; CAPSTONE-1: 80.2 h vs. 53.7 h and CAPSTONE-2: 102.8 h vs. 77.0 h, respectively) and time to cessation of viral shedding (CAPSTONE-1: 96 h vs. 24 h and CAPSTONE-2: 96 h vs. 48 h, respectively) in otherwise healthy (OwH) and high-risk (HR) patients.^{9,11,13} Moreover, postmarketing surveillance of over 3000 patients across 688 hospitals in Japan indicate that baloxavir marboxil, administered per recommended dosing, is well-tolerated and efficacious in the treatment of influenza A and B.¹⁴ However, there are no clinical data in Chinese populations.

Here, we present PK data from a phase I study of baloxavir marboxil in healthy Chinese volunteers and use an established PK–time to symptom alleviation model to predict efficacy in Chinese patients treated at the globally adopted dosing strategy.¹⁵

METHODS

Study design and population

YP40902 (NCT03959332) was an open-label, single-center, randomized phase I study evaluating the PK, safety, and tolerability of baloxavir marboxil in healthy Chinese patients.

Healthy Chinese volunteers aged 20–59 years with a bodyweight of ≥ 50 to < 80 kg (body mass index ≥ 18.5 to < 26 kg/m²) were enrolled in this study. All parents and grandparents of patients must have been Chinese and born in China. Patients underwent a detailed medical and surgical history and a complete physical examination as part of the screening procedure; patients with a history of disease with clinical manifestations, chronic infection, or laboratory results or vital signs outside of the normal range were excluded. Furthermore, patients were excluded from the study if they had received drugs of any kind (including prescribed, over-the-counter, and herbal and dietary supplements) within 3 days prior to screening or within 2 weeks prior to day -1 , or if they had consumed products containing alcohol, caffeine, grapefruit, or St. John's wort within 72 h prior to day -1 .

Volunteers were randomized 1:1 to receive a single oral dose of 40 mg or 80 mg baloxavir marboxil. Patients received baloxavir marboxil in a fasted state (~ 10 h overnight) with 250 ml of water, which was followed by a 4-h fasting period.

The study protocol along with participants' informed consent documents were approved by the study center's institutional review board and independent ethics committee. The study was performed in accordance with the principles of the Declaration of Helsinki and in compliance with International Council for Harmonization Good Clinical Practices.

Study outcomes

The primary outcome was to assess the PK profile of baloxavir acid; evaluated PK parameters included maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the plasma concentration-time curve (AUC_{0-last} , AUC_{0-inf} , AUC_{0-t}), terminal elimination half-life ($t_{1/2}$), apparent total oral clearance (CL/F), apparent volume of distribution based on the terminal phase (V_z/F), and plasma concentration at 24, 48, and 72 h postdose (C_{24} , C_{48} , and C_{72} , respectively). Serial blood samples for PK evaluation were collected at pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, 120, 168, 216, 264, and 336 h post-dose. Plasma concentrations of baloxavir marboxil and baloxavir acid were analyzed by liquid chromatography tandem mass spectrometry, and analyses were performed by Sumika Chemical Analysis Service, Ltd., Japan. Secondary endpoints included the incidence, severity, and frequency of adverse events (AEs), serious AEs (SAEs), vital signs, and clinical laboratory tests. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA central coding dictionary, version 22.0).

Simulations of efficacy in Chinese and Asian patients

TTAS was defined as the time at which all seven influenza symptoms (cough, sore throat, headache, nasal congestion,

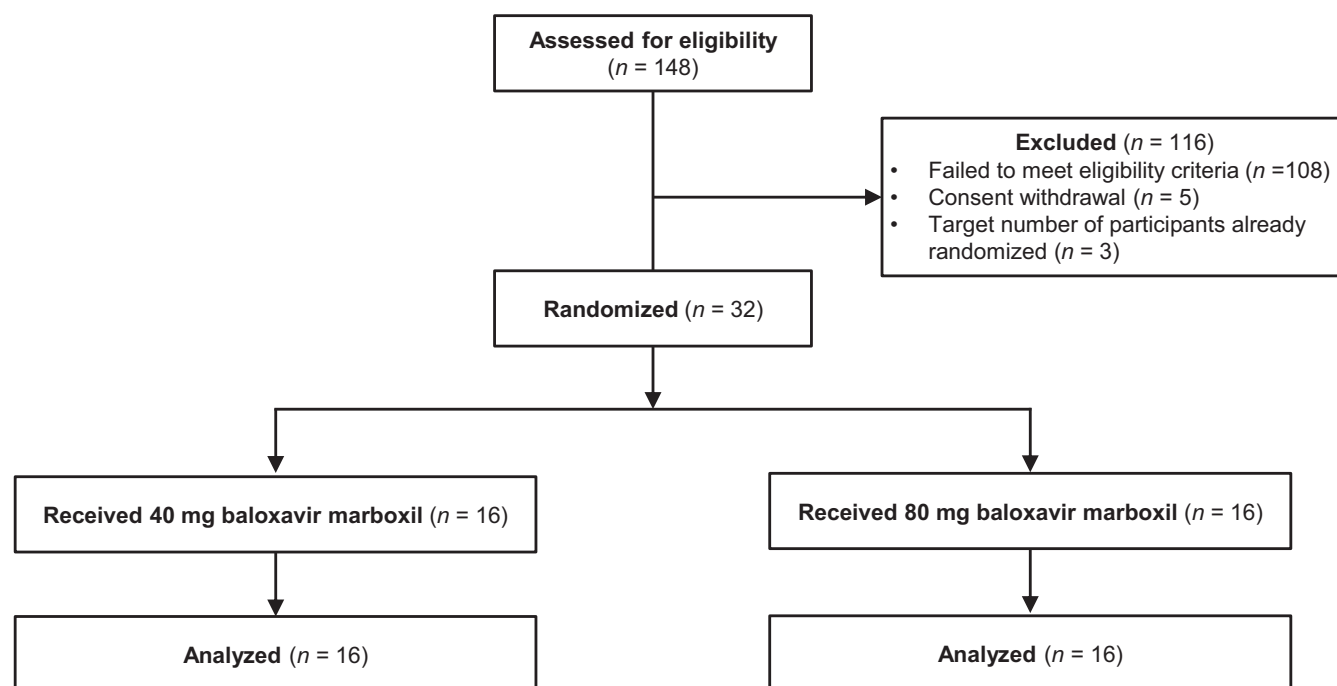


FIGURE 1 Patient disposition

feverishness or chills, muscle or joint pain, and fatigue) were graded as 0 or 1 by the participant, on a 4-point scale (0 indicated no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms) for at least 21.5 h. The composite symptom score at baseline was the total score attributed to the seven influenza symptoms upon study entry. Thus, the composite symptom score ranged from 0 to 21, with higher scores indicating more severe illness.

Using an established PK-efficacy model,¹⁵ simulations were conducted to compare TTAS for Chinese (50 to <80 kg) and Asian patients (40 to <80 kg) treated with 40 mg baloxavir marboxil who were classified as OwH or HR. Details of the PK-TTAS model and simulation method have been reported elsewhere.¹⁵ Briefly, model-based PK parameters of each Chinese subject included in the phase I trial were determined from a Bayesian analysis, using an existing baloxavir population PK model.¹⁶ Virtual Chinese patients ($N = 1400$), 50% men, were then simulated with PK model parameters sampled in the set of Bayesian estimated parameters of the Chinese healthy subjects. Only patients with a composite symptom score at baseline greater than 10 were considered to avoid, including very mildly affected patients. These virtual Chinese patients were compared with 1400 simulated Asian patients based on the model-based PK parameters from the Asian patients included in the OwH (NCT02954354 [CAPSTONE-1]) and HR (NCT02949011 [CAPSTONE-2]) phase III studies,^{9,11,17} with similar gender distributions and symptom scores at baseline conditions.

Statistical analysis

A total of 32 healthy Chinese patients were enrolled in the study, with the sample size based on prior PK studies of baloxavir marboxil; no power-based assessments were performed. Summary statistics for all plasma PK parameters (except for T_{\max}) include: geometric mean, geometric coefficient of variation (CV%), arithmetic mean, standard deviation (SD), median, minimum, and maximum. No statistical tests were performed. All derivations, summaries, and listings were generated using SAS version 9.4 (SAS Institute, Inc., Cary, NC). PK parameters were estimated by noncompartmental analysis and were performed using Phoenix WinNonlin 8.0 (Certara, L.P., Princeton, NJ).

RESULTS

In total, 32 healthy Chinese patients were randomized to receive either 40 mg or 80 mg baloxavir marboxil

($n = 16$ each; Figure 1; Table 1). All patients were male, with a mean age of 28.2 (range = 20–40) and 29.5 (range = 20–43) years and a mean (SD) body-weight of 66.26 (6.38) and 65.59 (7.17) kg for the 40 and 80 mg cohorts, respectively. There were no prior

TABLE 1 Patient baseline characteristics

	Baloxavir marboxil	
	40 mg ($n = 16$)	80 mg ($n = 16$)
Median age (range), years	27.5 (20–40)	30.5 (20–43)
Male, n (%)	16 (100%)	16 (100%)
Mean baseline weight (SD), kg	66.26 (6.38)	65.8 (7.17)
Median baseline BMI (range), kg/m^2	23.98 (20.7–26.1)	23.46 (19.2–26.0)

Abbreviations: BMI, body mass index; SD, standard deviation

TABLE 2 Baloxavir acid plasma PK parameters

Parameter, geometric mean (GCV%)	Baloxavir marboxil ^a	
	40 mg ($n = 16$)	80 mg ($n = 16$)
$\text{AUC}_{0-\infty}$ (ng·h/ml)	6955 (25.5)	9643 (29.4)
$\text{AUC}_{0-\text{last}}$ (ng·h/ml)	6442 (24.3)	9218 (29.2)
C_{\max} (ng/ml)	107.6 (24.2)	206.9 (38.3)
T_{\max} (h) ^b	4.00 (3.00–6.00)	4.00 (3.00–5.00)
$t_{1/2}$ (h)	99.74 (18.0)	88.89 (17.1)
CL/F (l/h)	4.866 (25.5)	7.019 (29.4)
Vz/F (l)	700.1 (26.6)	900.1 (31.4)
C_{24} (ng/ml)	56.4 (22.8)	92.01 (27.9)
C_{48} (ng/ml)	41.38 (22.9)	60.33 (33.2) ^c
C_{72} (ng/ml)	29.27 (25.0)	41.78 (31.6)
MRC_{\max}	ND ^d	415.2 (57.3) ^e

Abbreviations: $\text{AUC}_{0-\infty}$, area under the concentration-time curve from time 0 to infinity; $\text{AUC}_{0-\text{last}}$, area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{24} , observed plasma concentration at scheduled 24 h post-dose sample; C_{48} , observed plasma concentration at scheduled 48 h post-dose sample; C_{72} , observed plasma concentration at scheduled 72 h post-dose sample; CL/F, apparent total oral clearance; C_{\max} , maximum plasma concentration; GCV, geometric coefficient of variation; MRC_{\max} , molar ratio of metabolite C_{\max} to parent (baloxavir marboxil) C_{\max} ; ND, not determined; PK, pharmacokinetic; $t_{1/2}$, terminal elimination half-life; T_{\max} , time to maximum plasma concentration; Vz/F, apparent volume of distribution based on the terminal phase.

^aValues are mean (SD) values unless otherwise stated.

^bPresented as median (range).

^c $n = 14$.

^dBaloxavir marboxil plasma concentrations were not quantifiable in any of the participants in the 40 mg dose group; therefore, the MRC_{\max} was not determined.

^e $n = 2$.

or concomitant medications or treatments reported for any patients.

Pharmacokinetics

Only two of the 32 patients, both in the 80 mg cohort, exhibited plasma concentrations of baloxavir marboxil above the lower limit of quantification (LLOQ; 0.5 ng/ml). Following a single oral dose of baloxavir marboxil, mean baloxavir acid plasma concentrations increased rapidly and peaked (T_{max}) at 4 h post-dosing in both cohorts (Table 2). Mean concentrations decreased gradually and remained above the LLOQ up to 336 h post-dose (Figure 2). Following the 80 mg dose, baloxavir acid peak and total exposures, based on geometric mean C_{max} , C_{24} , and AUC values, were 1.9-, 1.6-, and 1.4-fold higher than with the 40 mg dose. The mean $t_{1/2}$ was lower in the 80 mg cohort than in the 40 mg cohort (88.9 vs. 99.7 h); the inverse was observed in respect to CL/F (7.0 vs. 4.9 l/h).

Safety

No new safety signals were identified in the study (Table 3). The incidence of AEs was higher in the 80 mg cohort ($n = 11$ [68.8%]) than in the 40 mg cohort ($n = 3$ [18.8%]). A total of three and 16 AEs were reported in the 40 mg and 80 mg cohorts, respectively. AEs reported in more than one individual across both dosing cohorts included dizziness ($n = 3$), upper respiratory tract infection ($n = 3$), blood uric acid increased ($n = 3$), blood bilirubin increased ($n = 3$), and diarrhea ($n = 2$). All AEs were classified as mild in severity and were transient; no SAEs were reported. Drug-related AEs were reported in five patients ($n = 1$ and $n = 4$ in the 40 and 80 mg cohort, respectively) and included dizziness ($n = 1$ and $n = 2$ in the 40 and 80 mg cohorts, respectively), abnormal electrocardiogram (ECG) T wave, ventricular extrasystoles (ECG), hematuria, fatigue ($n = 1$, each; all in the 80 mg cohort). All drug-related AEs resolved before the end of the study. In the two patients who experienced ECG-related events, events started on day 6 and were mild in severity; subsequent review of individual participant data

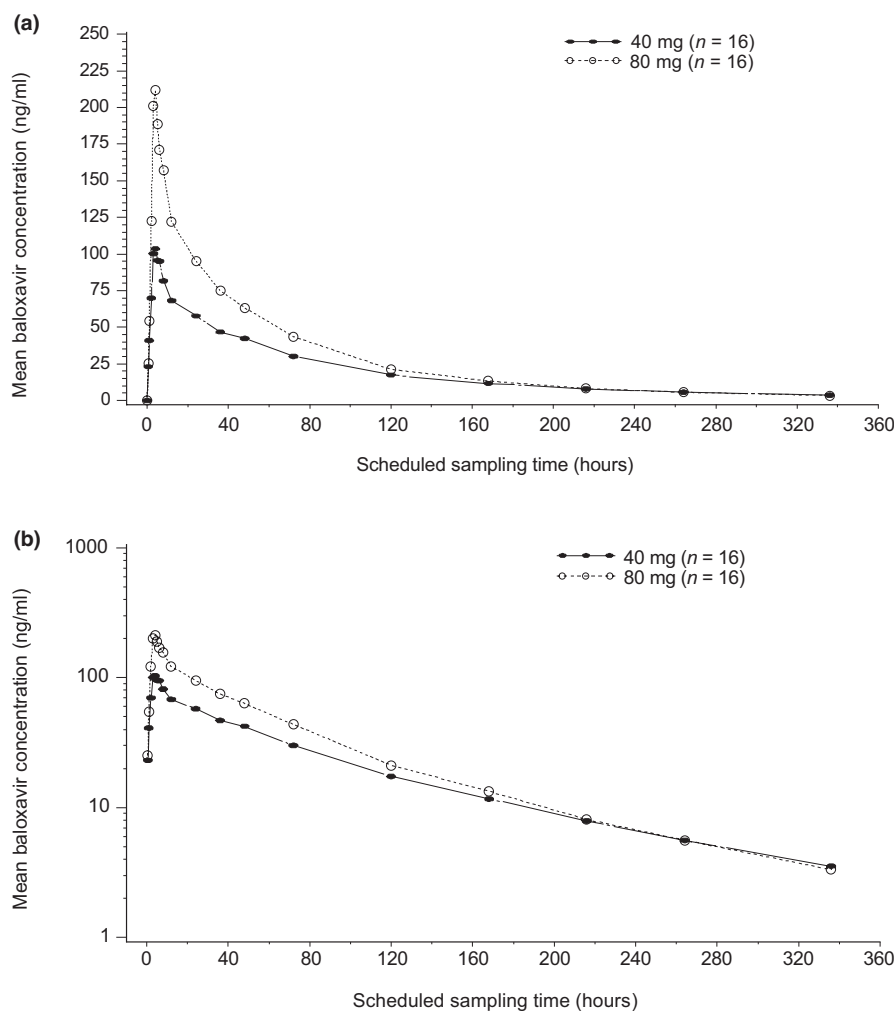


FIGURE 2 Mean baloxavir marboxil plasma concentration–time profiles for 40 and 80 mg dose cohorts. (a) Linear scale; (b) semilogarithmic scale

TABLE 3 Summary of AEs

<i>n</i> (%)	Baloxavir marboxil	
	40 mg (<i>n</i> = 16)	80 mg (<i>n</i> = 16)
Any AE	3 (18.8)	11 (68.8)
Number of events	3	16
Any drug-related AE	1 (6.3)	4 (25.0)
Number of events	1	6
Any SAE	0	0
AEs		
Blood bilirubin increased	1 (6.3)	2 (12.5)
Blood uric acid increased	1 (6.3)	2 (12.5)
Dizziness	1 (6.3)	2 (12.5)
Upper respiratory tract infection	0	3 (18.8) ^a
Diarrhea	0	2 (12.5)
ECG T wave abnormal	0	1 (6.3) ^b
Defect conduction intraventricular	0	1 (6.3) ^c
Fatigue	0	1 (6.3)
Hematuria	0	1 (6.3)
Ventricular extrasystoles	0	1 (6.3) ^c

Abbreviations: AE, adverse event; ECG, electrocardiogram; SAE, serious adverse event.

^aThe etiology of the upper respiratory tract infection was thought to be the common cold in all three patients. Bronchitis, nasopharyngitis, headache, and nausea did not occur in this study.

^bECG T wave abnormal was observed on days 6–8. This AE was mild in severity and resolved before the end of the study.

^cDefect conduction intraventricular (days 6–8) and ventricular extrasystoles (days 8–15) were observed in a patient who had an abnormal ECG at baseline and were considered unrelated to baloxavir marboxil.

suggested these events were unrelated to baloxavir marboxil. No trends in changes from baseline or increase in abnormalities were identified for clinical laboratory tests, vital signs, or ECG assessments.

Simulations of efficacy in Chinese and Asian patients

Population PK model-derived parameters used to inform the PK-TTAS model are presented in Table 4. Compared with placebo, the simulated median TTAS was shorter with baloxavir marboxil for OwH (57.1 vs. 75.4 h) and HR (65.2 vs. 86.4 h) Chinese patients (Table 4). With baloxavir marboxil, the simulated median TTAS for OwH and HR Chinese patients (57.1 and 65.2 h, respectively) closely aligned with simulated values for OwH and HR Asian patients (56.6 and 64.4 h, respectively).

DISCUSSION

This is the first clinical study evaluating PK and safety of baloxavir marboxil in Chinese individuals. A single dose of 40 or 80 mg baloxavir marboxil was well-tolerated in healthy Chinese individuals; all AEs were mild and transient, and no new safety signals were identified. The type and incidence of AEs observed in healthy Chinese volunteers are consistent with the established safety profile of baloxavir marboxil.

Baloxavir exposures in healthy Chinese individuals were similar to other phase I studies conducted in healthy Japanese (study 1510T0811) and Korean patients (study ML40799), as well as in OwH and HR Asian patients in phase II and III studies.^{12,16,18} In the present study, the mean C_{max} and AUC_{0-inf} was 1.9 and 1.4 times higher in patients who received 80 mg than in those who received 40 mg of baloxavir marboxil. Similar dose-responses were observed in Japanese and Korean individuals who received 80 mg baloxavir marboxil compared with 40 mg, whereby mean C_{max} values were 2.1 and 1.9 times higher, respectively.^{12,18} Mean AUC_{0-inf} was 1.8 times higher for both Japanese and Korean individuals who received 80 mg compared with those who received 40 mg of baloxavir marboxil.^{12,18} The slightly lower than proportional ratio in AUC_{0-inf} is in line with the slightly higher oral clearance (CL/F) observed in the 80 mg dose group (7.02 L/h, geometric CV = 9.4) compared with the 40 mg dose group (4.87 L/h, geometric CV = 25.5). Variability of the parameter estimates was moderate and comparable between the two dose levels, ranging from ~ 25 to 30 CV% for most PK parameters. Given the small sample size ($n = 16$ per dose group), the CL/F at the 80 mg dose relative to the 40 mg dose falls within the known moderate between-subject variability. The linear PK of baloxavir was demonstrated using a large database of 1827 individuals, which included data from phase I to phase III baloxavir marboxil studies with doses ranging from 6 to 80 mg.¹⁹

Previous population PK analyses identified body-weight and ethnicity as major covariates affecting baloxavir exposure.¹⁶ As PK parameters among Japanese and Chinese individuals were similar, it was anticipated that efficacy would also be similar. Subsequently, in place of a phase III study, TTAS was estimated for Chinese individuals using an established PK-TTAS model, which is robust in its predictive capabilities.¹⁵ Model-based PK parameters for Chinese and Asian patients were derived from a population-PK model and used to inform the baloxavir exposure part of the PK-TTAS model. As patient status (OwH or HR), sex, and composite symptom score at baseline affect TTAS outcomes, both simulations

	Chinese individuals (50–80 kg)	Asian patients	
		(40–80 kg)	All bodyweights
PK parameters used to inform PK–TTAS model, mean (SD)			
<i>N</i>	32	479	544
CL/F (l/h)	6.21 (1.95)	6.35 (2.93)	6.54 (2.94)
AUC _{0–inf} ng•h/ml	5954 (1725) ^b	6218 (2275) ^b	6611 (2611)
Simulated median TTAS, hours (95% CI) ^c			
Otherwise-healthy patients			
Baloxavir marboxil	57.1 (54.2–60.5)	56.6 (53.4–60.0)	56.3 (53.3–59.0)
Placebo	75.4 (70.8–79.6)	75.4 (70.7–79.6)	75.4 (70.8–79.6)
High-risk patients			
Baloxavir marboxil	65.2 (61.3–69.0)	64.4 (60.2–67.7)	63.5 (60.0–67.3)
Placebo	86.4 (81.7–90.4)	86.4 (81.7–90.4)	86.5 (81.6–90.4)

Abbreviations: AUC_{0–inf}, area under the concentration-time curve from time 0 to infinity; CI, confidence interval; CL/F, apparent total oral clearance; PK, pharmacokinetic; TTAS, time to alleviation of symptoms.

^aAUC_{0–inf} was recalculated based on the estimated CL/F assuming patients received a dose of 40 mg for a bodyweight <80 kg.

^bTTAS was simulated for 1400 individuals.

(in Chinese and Asian patients respectively) were performed for OWH or HR patients. Those with composite symptom scores at baseline greater than 10 (comprising 50% men) were included to allow for the unbiased comparison of TTAS predictions.¹⁵ The simulated median TTAS was shorter in baloxavir marboxil-treated patients than with placebo; the simulated values are comparable with the significant TTAS reductions observed with baloxavir marboxil in phase III studies.^{9,11} There was a strong alignment in predicted TTAS between OWH and HR patients for both Chinese and Asian populations. TTAS could only be predicted for Chinese patients treated with 40 mg baloxavir marboxil and with a bodyweight of 50–80 kg (bodyweight range from the inclusion criteria of study YP40902). The globally adopted dosing strategy recommends patients with a bodyweight greater than or equal to 80 kg should be treated with 80 mg. As there were no patients with a bodyweight greater than or equal to 80 kg enrolled into this phase I study in Chinese individuals, no observed PK parameters were available to inform TTAS predictions in these patients.

In conclusion, based on the similarity of observed PK and simulated efficacy, no meaningful differences in the efficacy of baloxavir marboxil are anticipated between Chinese patients and other Asian patients. The data presented here support the adoption of the global baloxavir marboxil dosing strategy (40 mg for patients weighing <80 kg) in Chinese patients. Baloxavir marboxil (40 mg for patients weighing <80 kg) was approved in China on April 27, 2021, for the treatment of influenza.

TABLE 4 Bayesian estimated PK parameters and simulated efficacy for Chinese and Asian patients treated with baloxavir marboxil 40 mg

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CONFLICTS OF INTEREST

Y.L., J.J., Y.Z., and Y.W. were study investigators and declare no conflicts of interest. S.R., V.C., S.J., and S.D.B. are employees and shareholders of F. Hoffmann-La Roche Ltd. V.D. was an employee of Certara while the study was conducted. Certara received funding from F. Hoffmann-La Roche Ltd to conduct this study but were not paid for the development of this manuscript.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. Y.L. and J.J. designed the research. Y.L., J.J., Y.Z., and Y.W. performed the research. All authors analyzed the data.

REGISTRATION

Clinicaltrials.gov identifier: National Cancer Institute at the National Institutes of Health (grant number NCT03959332).

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