A Pharmacokinetics–Time to Alleviation of Symptoms Model to Support Extrapolation of Baloxavir Marboxil Clinical Efficacy in Different Ethnic Groups with Influenza A or B

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Baloxavir marboxil, the prodrug of baloxavir acid, is an anti-influenza antiviral. Here, a pharmacokinetics–time to alleviation of symptoms (PK–TTAS) model was developed and used to (I) characterize the PK–TTAS relationship, (II) quantify the impact of covariates, and (III) predict TTAS in different ethnic groups. Data from 1781 otherwise-healthy (OwH) or high-risk (HR) patients included in phase II (JapicCTI-153090) and III studies (NCT02954354 and NCT02949011) were used; patients received either placebo or oral baloxavir marboxil. The natural distribution of TTAS in placebo-treated patients was modeled, then TTAS data from the baloxavir marboxil arms were added to model the impact of baloxavir acid concentration on TTAS. PK parameters estimated by a population PK model and informed by phase I data (NCT03959332 and KCT0003535) were included to simulate TTAS in Chinese and South Korean patients. Composite symptom score at baseline (TSS0), ethnicity, sex, and patient type (OwH or HR) significantly impacted the natural TTAS distribution. TTAS reduced with increasing baloxavir acid concentrations. Compared with placebo, high and low baloxavir acid exposures (AUC0-inf 5.13–16.65 and 0.72–5.13 μg.hr/mL, respectively) significantly reduced TTAS; no covariates affected the drug effect on TTAS. Simulated TTAS was similar between OwH or HR Chinese, South Korean, and other Asian patients, with median reductions from placebo between 18.3–18.8 hours and 21.2–22.0 hours in OwH and HR patients, respectively, assuming TSS0 > 10. Ethnicity (Asian vs. non-Asian) did not significantly impact the drug effect on TTAS; predicted TTAS was similar across different Asian populations. This suggests Chinese and South Korean patients may benefit from similar efficacy as other Asian patients.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Baloxavir marboxil, the prodrug of baloxavir acid, is indicated to treat influenza. A population pharmacokinetics (popPK) study identified body weight and ethnicity (Asian vs. non-Asian) as relevant covariates affecting baloxavir acid exposure; however, the effect of covariates on efficacy (time to alleviation of symptoms (TTAS)) was unknown.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ This study aimed to develop a model to characterize the baloxavir acid PK–TTAS relationship, quantify the influence of covariates on this relationship, and predict TTAS in different ethnic subgroups.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ Composite symptom score at baseline, ethnicity, sex, and patient type significantly impacted the probability of symptom alleviation in patients without any influenza treatment (placebo). No covariates significantly impacted the drug effect on TTAS. Predicted TTAS was similar across different Asian populations.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ This model-based ethnic sensitivity strategy successfully supported new drug applications in South Korea and China without the need for local phase III studies. This strategy could be used to inform future studies for other agents.
Baloxavir marboxil is the prodrug of baloxavir acid, a cap-dependent endonuclease inhibitor which prevents transcription of influenza virus genomes.\(^1\) Baloxavir marboxil is indicated for the treatment of influenza A and B infections in patients aged ≥12 years (and <12 years in Japan) who are otherwise healthy (OwH) or at high risk (HR) of developing influenza-related complications, and is administered as a single oral dose within 48 hours of symptom onset.\(^2\)–\(^4\)

A population pharmacokinetics (popPK) model was developed using data from phase I–III studies to characterize the PK parameters of baloxavir acid in patients with influenza treated with baloxavir marboxil.\(^1\) Baloxavir acid PK were well-described by a three-compartment model with first-order absorption and elimination; PK parameters were similar across studies and among patients who were OwH or HR. However, body weight and ethnicity (Asian vs. non-Asian) were identified as relevant covariates affecting baloxavir acid exposure. The Asian population was predominantly Japanese, but also included patients from Taiwan, the Philippines, and South Korea.\(^3\)–\(^4\),\(^6\)

Baloxavir marboxil has been shown to be safe and efficacious in both Asian and non-Asian patients in a phase II study conducted in Japan and in global phase III studies.\(^3\)–\(^4\),\(^6\) Subsequently, new drug applications were pursued in China and South Korea. However, no Chinese and few South Korean patients (<1%) were included in global phase III studies. Therefore, an ethnic sensitivity bridging strategy was developed to mitigate the need for local phase III studies, in order to preserve local clinical resources and accelerate access to treatment. This strategy involved comparing (I) baloxavir acid PK parameters derived from local phase I studies in healthy Chinese and South Korean subjects with those observed in Asian patients in phase II and III studies, and (II) the predicted efficacy of baloxavir marboxil in South Korean and Chinese patients with that observed in Asian patients in phase II and III studies.

PK bridging studies were performed in healthy Chinese (study YP40902; NCT03959332) and South Korean (study ML40799; KCT0003535) volunteers.\(^5\)–\(^7\) Baloxavir acid PK parameters were similar between Chinese and South Korean participants and other Asian patients in phase II and III studies, suggesting that efficacy could also be similar.

Modeling activities to further assess efficacy were performed. Time to alleviation of symptoms (TTAS) is commonly used as a measure of the efficacy of antiviral drugs against influenza virus and enables cross-trial comparisons of available anti-influenza therapeutics.\(^3\)–\(^4\) Herein, we describe a baloxavir acid PK–TTAS model and leverage global phase II and III data to (I) characterize the baloxavir acid PK–TTAS relationship in OwH and HR patients with influenza treated with baloxavir marboxil, (II) quantify the potential influence of covariates, including ethnicity, on the baloxavir acid PK–TTAS relationship, and (III) predict TTAS in different ethnic groups. Together with the phase I bridging studies, these data were used to inform new drug applications in China and South Korea.

**METHODS**

**Trial design and patients**

Data from the placebo and/or baloxavir marboxil arms of the following studies were used in the development of the PK–TTAS model (Table S1): T0821 (JapicCTI-153,090), a phase II study in Japanese patients with acute uncomplicated influenza who were OwH; CAPSTONE-1 (NCT02954354), a global phase III study in OwH patients with influenza; and CAPSTONE-2 (NCT02949011), a global phase III study in HR patients.\(^3\)–\(^4\),\(^6\) Patients at high risk of influenza complications were defined in CAPSTONE-2, using criteria adapted from the Centers for Disease Control and Prevention (CDC), which included patients aged ≥65 years, and those with asthma or chronic lung disease.\(^4\)–\(^9\)

Once the baloxavir PK–TTAS model had been developed, PK data from two phase I studies in healthy adult volunteers, YP40902 (NCT03959332) and ML40799 (KCT0003535), were used to predict efficacy in Chinese and South Korean populations.\(^7\)–\(^8\)

**Efficacy end point**

TTAS is defined as the time between the initiation of the study treatment and the alleviation of seven influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue). Patients in T0821, CAPSTONE-1, and CAPSTONE-2 self-assessed symptom severity using a 4-point scale: 0, no symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms.\(^3\)–\(^4\),\(^6\) The composite symptom score at baseline (TSS0) was the total score attributed to the seven influenza symptoms as assessed by the patient (range: 0–21). Symptom alleviation was achieved when the patient scored all 7 symptoms as 0 or 1 for a duration of at least 21.5 hours. Self-assessments were performed twice daily (morning and evening) on days 1 to 9, then once daily (evening) on days 10 to 14.

**Modeling strategy**

A time-to-event analysis was performed for TTAS using data from intention-to-treat infected patients included in phase II (T0821) and III studies (CAPSTONE-1 and CAPSTONE-2) who were infected with either type A or B influenza only; data from patients with mixed infection were excluded.

A parametric proportional hazard model \(b(t)\) was developed to describe the instantaneous rate of symptom alleviation at time \(t\) (assuming symptoms had not yet alleviated):

\[
b(t) = \lim_{\Delta t \to 0} \frac{Pr(t \leq TTAS < t + \Delta t) | TTAS \geq t)}{\Delta t}
\]

The proportion of patients that had not yet experienced symptom alleviation at time \(t\) was defined by the survival function \(S(t)\), such that:

\[
S(t) = e^{-\int_0^t b(u)du}
\]

An interval-censoring approach was undertaken to reflect uncertainty in capturing the time of symptom alleviation. It was assumed that the actual time of symptom alleviation occurred between the time of the last record when symptoms were not alleviated and the time of the record when symptoms were reported as alleviated. A maximum likelihood approach was undertaken for parameter estimation.

Development of the PK–TTAS model comprised two steps. In step 1, the natural TTAS distribution in patients without influenza treatment was determined using data from the placebo arms of the clinical studies T0821, CAPSTONE-1, and CAPSTONE-2.\(^2\)–\(^6\),\(^8\) In step 2, the effect of baloxavir PK on the natural TTAS distribution was modeled using data from the placebo and baloxavir marboxil arms of T0821, CAPSTONE-1, and CAPSTONE-2.\(^2\)–\(^6\)

During step 1, a placebo TTAS hazard model was developed to describe the natural TTAS distribution. Exponential-, Weibull-, Gompertz-, log-normal-, and log-logistic distributions were investigated to best model the baseline hazard function \(b_0(t)\).\(^10\) Covariates with the potential to impact the natural TTAS distribution were then investigated in a stepwise manner and included age, body weight, ethnicity (Asian or non-Asian), sex, patient type (OwH or HR), virus type (influenza type A or B),
influenza vaccination status, smoking status, viral load at baseline, time from symptom onset to screening, and TSS0. First, univariate analyses were conducted to test the influence of each covariate on the baseline TTAS hazard \( h_0(t) \). Eq. 1 was used to describe the effect of categorical covariates, where \( \beta \) was the coefficient of the effect of covariate \( X \) on the hazard function.

\[
b_{\text{placebo}}(t) = h_0(t) \cdot e^{\beta X} \tag{1}
\]

Continuous covariates were normalized to a value of reference (e.g., population median) and their effect was described by Eq. 2, whereby \( f \) represented a power function or a maximum effect \( (E_{\text{max}}) \) function.

\[
b_{\text{placebo}}(t) = h_0(t) \cdot f(\text{Conc}_i) \tag{2}
\]

The retained covariates were further tested simultaneously in a full covariate model. Inferences regarding covariate effects and clinical relevance were based on parameter estimates and measures of estimation precision (90% confidence intervals based on nonparametric bootstrap). Covariates were considered potentially clinically relevant if they impacted the hazard function by > 20%.

During step 2, a sequential modeling approach was taken to model the impact of each individual’s concentration–time profile on the TTAS distribution. Parameters from the placebo–TTAS hazard model \( b_{\text{placebo}}(t) \) were fixed to the estimated values from step 1.

Using the popPK model developed by Koshimichi et al., empirical Bayes estimates of popPK parameters were performed. The individual baloxavir concentration–time course of each patient, \( \text{Conc}_i(t) \), was derived, as well as their individual exposure, \( \text{AUC}_{0-\text{inf}} \), defined as the total area under the concentration curve. \( \text{Conc}_i(t) \) was assumed to impact the hazard proportionally, related to a function \( f \) of \( \text{Conc}_i(t) \), whereby Eq. 3 represented the hazard function of TTAS events with baloxavir marboxil treatment.

\[
b(t)_{\text{baloxavir}} = b_{\text{placebo}}(t) \cdot 1 + f(\text{Conc}_i(t)) \tag{3}
\]

Proportional, power, \( E_{\text{max}} \), and sigmoid \( E_{\text{max}} \) functions of the concentration, \( f \), were investigated:

- **Linear:** \( f = \lambda \times \text{Conc}_i(t) \)
- **Power:** \( f = \lambda \times \text{Conc}_i(t)^g \)
- **Proportional Sigmoid:** \( f = \frac{E_{\text{max}} \times \text{Conc}_i(t) \vert_{E_{\text{max}}}}{\text{EC}_{50} + \text{Conc}_i(t) \vert_{E_{\text{max}}}} \)
- **Sigmoid:** \( f = \frac{E_{\text{max}} \times \text{Conc}_i(t) \vert_{E_{\text{max}}}}{\text{EC}_{50} + \text{Conc}_i(t) \vert_{E_{\text{max}}}} \).

A covariate analysis, similar to that described for the placebo–TTAS hazard model \( b_{\text{placebo}}(t) \), was conducted to detect covariates that may influence the baloxavir acid concentration effect on TTAS. This led to the final PK–TTAS model.

For both step 1 and step 2, objective function values (OFVs) were used to compare and select the model with the best overall fit. A \( P \) value of 0.01 was chosen to select appropriate models and corresponds to an OFV difference of 6.64 for a difference in the number of parameters of one between two competitive models. The predictive performance of the models was assessed using Kaplan–Meier visual predictive checks (VPCs), comparing the 95% confidence intervals of predicted Kaplan–Meier curves derived from model-based simulated events over 1,000 virtual trials to the Kaplan–Meier curve computed from the observed TTAS data.

### Ethnic sensitivity assessment

For the phase I studies in healthy Chinese and South Korean volunteers, a Bayesian approach was used to derive the individual PK parameters from the individual observed concentrations and the popPK model reported by Koshimichi et al.

Subsequently, the final PK–TTAS model was used to illustrate the potential influence of ethnicity on natural disease progression (TTAS in the absence of drug treatment) as well as on the drug effect. This was performed for Asian vs. non-Asian patients, and Chinese or South Korean vs. other Asian patients. In total, 1,400 virtual patients treated with placebo or baloxavir marboxil were simulated per ethnicity and patient type (OW4 or HR). For each simulated population, 50% men, 50% women, and a TSS0 > 10 were selected to focus on patients with either several mild symptoms or those with more severe symptoms. In baloxavir marboxil-treated groups, the globally adopted dosing strategy (i.e., a single dose of 40 mg or 80 mg), was used for patients with a body weight of < 80 kg or ≥80 kg, respectively.

### Software and hardware

The PK- TTAS model was developed using NONMEM software version 7.3.0. Parameters were estimated using the Laplacian method. All analyses datasets were created using SAS for Windows version 9.4 TS Level 1 M2. R version 3.5.3 was used for pre- and postprocessing data, graphical visualization, and model diagnostics.

### RESULTS

A total of 1,781 patients with available PK concentrations were included in these analyses: 689 received placebo and 1,092 received baloxavir marboxil. Prior to development of the PK–TTAS model, exploratory survival analyses with Kaplan–Meier estimation and log-rank tests were conducted to determine if there was an association between baloxavir acid exposure and TTAS. Baloxavir marboxil-treated patients were split into low and high baloxavir acid exposure groups; the low exposure group included those with an \( \text{AUC}_{0-\text{inf}} \) of 0.72–5.13 \( \mu \text{g} \cdot \text{hr} / \text{mL} \) (minimum to median range), and the high exposure group included those with an \( \text{AUC}_{0-\text{inf}} \) of 5.13–16.65 \( \mu \text{g} \cdot \text{hr} / \text{mL} \) (median to maximum range). There was a statistically significant difference in the observed TTAS Kaplan–Meier curves between the placebo group and the low and high baloxavir acid exposure groups (log-rank test, \( P < 0.0001 \); Figure 1a). A pairwise comparison demonstrated a significant reduction in TTAS for patients with low baloxavir acid exposure compared with those administered placebo (\( P < 0.0001 \)). Similarly, a statistically significant difference was observed between low and high baloxavir exposure groups across all patients (\( P = 0.03 \); Figure 1a) as well as when focusing on patients with worse influenza symptoms (TSS0 ≥ 13; \( P < 0.01 \); Figure 1b). These findings suggested that baloxavir acid exposure was associated with reduced TTAS and guided the development of the baloxavir acid PK–TTAS model. However, these results should be interpreted with caution owing to the potential immortal time bias introduced when using AUC as a classifying variable during this exploratory analysis; please refer to the Discussion section for further information.
Continuous and categorical covariates were broadly comparable between T0821 and CAPSTONE-1, both of which comprised predominantly OwH Asian patients, whereas CAPSTONE-2 involved an HR patient population comprised of <50% Asian patients (Table S2). Across the three studies (T0821, CAPSTONE-1, and CAPSTONE-2), a similar distribution of TSS0, viral load at baseline, sex, time from symptom onset to screening, and influenza vaccination status was observed.

The structural placebo–TTAS model was best described using a log-logistic distribution whereby:

$$b_0(t) = \frac{1}{\Psi} \cdot \frac{1}{\gamma} - 1 \frac{1}{\gamma \cdot \left( 1 + (\Psi \cdot t)^{\gamma} \right)}$$

with $\Psi = e^{-\delta}$

The shape and scale parameters are denoted by $\gamma$ and $\beta$, respectively. In the univariate covariate analysis, body weight, ethnicity, sex, patient type (OwH or HR), and TSS0 were found to significantly influence the hazard function (Table S3). Body weight strongly excluded with patient type and sex, and was subsequently excluded from the full model. Smoking status was excluded from the full model as it had an estimated effect close to 0, with a large uncertainty (relative standard error (RSE) = 161.6%).

The final placebo model was:

$$b(t)_{\text{placebo}} = b_0(t) \cdot e^{\beta_{\text{ethnicity}}} \cdot e^{\beta_{\text{sex}}} \cdot e^{\beta_{\text{HR}}} \cdot \frac{E_{\text{max}} \cdot (TSS0 - 4)^{-1}}{(TSS0 - 4)^{-1} + TSS0_{50}^{-1}}$$

where $\beta_{\text{ethnicity}}$, $\beta_{\text{sex}}$ and $\beta_{\text{HR}}$ represent the ethnicity, sex, and patient type (OwH or HR) effects on the hazard function, respectively. Asian and non-Asian, men and women, and OwH and HR were valued at 0 and 1, respectively. The effect of TSS0 was best described by an inhibitory $E_{\text{max}}$ model, calibrated by the lowest observed TSS0 value (4) in the database. The parameter estimates for the final placebo model are reported in Table 1.

Good correlation between the predicted TTAS time-course and observed data was achieved in the Kaplan–Meier VPC (Figure 2a). Kaplan–Meier VPCs performed per category of covariate also showed good predictive performance of the placebo TTAS model (Figure 2b–e). The impact of each covariate on TTAS, relative to a reference patient (male patient, Asian, OwH, TSS0 = 13), is illustrated in Figures S1a–d (the impact on the hazard function is shown in Figure S2). Non-Asian patients had a longer TTAS compared with the reference patient (Asian), with a median TTAS of 3.8 and 2.6 days, respectively. TSS0 had the greatest impact on the hazard function; compared with the reference patient (TSS0 = 13), patients with a low (TSS0 = 7) and very high (TSS0 = 21) score had a shorter and longer TTAS, respectively. Median TTAS was 1.9 and 3.5 days for patients with a TSS0 of 7 and 21, respectively, compared with 2.6 days for the reference patient (TSS0 = 13). The difference in median TTAS was less pronounced for patient type (OwH or HR) and sex (male or female patients), with a maximum increase of 0.5 days for HR patients and women compared with the reference patient (OwH and male patient).

Baloxavir acid concentration was a significantly better predictor of TTAS than the dose of baloxavir marboxil ($P < 0.001$). The proportional impact of baloxavir acid concentration on the TTAS hazard function was best described by a linear function (Table S4) whereby:

$$b(t)_{\text{baloxavir}} = b_{\text{placebo}}(t) \cdot (1 + \lambda \cdot Conc(t))$$

It was found that TTAS decreased as baloxavir acid concentration increased; the slope of the drug effect, $\lambda$, was estimated to be...
0.0125 (RSE = 12.2%). Figure 3a–d illustrates the impact of different baloxavir acid concentration levels on TTAS. For patients with a TSS0 of 13, a difference of 0.5 days was observed when comparing the impact of baloxavir acid concentration profiles on TTAS; these patients had baloxavir acid concentrations 50% greater or 50% lower than the estimated mean values in non-Asian patients. This difference was up to 0.8 days for similar non-Asian patients with a TSS0 of 21. In addition, slightly larger TTAS reductions from placebo were predicted in non-Asian patients compared with Asian patients. This is consistent with the estimated proportional drug effect on the hazard function, and the longer natural TTAS distribution in non-Asian patients.

In the univariate covariate analysis, none of the investigated covariates, including ethnicity, were found to significantly influence the baloxavir acid concentration effect on the hazard function (Table S5). Close agreement was observed between predicted and observed TTAS in the Kaplan–Meier VPC of the final PK–TTAS model (Figure 4). The similarity between observed and predicted TTAS was further corroborated by the results for patients with high and low baloxavir acid exposures (Figure 5).

**Ethnic sensitivity assessment**

The popPK model-derived PK parameters for Chinese and South Korean volunteers were similar to those estimated for Asian patients included in the phase III studies (Table S6). Subsequently, PK parameters were used to estimate TTAS in typical OwH and HR Chinese, South Korean, and non-Asian patients (Table 2). In total, 1,400 individuals with a TSS0 > 10 (50% male and 50% female individuals) were simulated per ethnic group.

Across all patient groups, placebo-treated HR patients had a longer estimated TTAS compared with placebo-treated OwH patients. Estimated TTAS was also longer in placebo-treated OwH and HR non-Asian patients compared with corresponding Asian patients. Estimated median TTAS was 119 and 75.4 hours in OwH non-Asian and Asian patients, respectively; for HR non-Asian and Asian patients, estimated median TTAS was 139 and 86.5 hours, respectively. Estimated TTAS was similar for placebo-treated Chinese, South Korean, and other Asian patients; negligible variations occurred due to the randomness of the simulations, with 1,400 new virtual patients created for each ethnicity simulation. In placebo-treated OwH Chinese, South Korean, and other Asian patients, estimated median TTAS was 75.4, 76.9, and 75.4 hours, respectively; in corresponding HR patients, median TTAS was 86.4, 87.1, and 86.5 hours, respectively. TTAS was shorter with baloxavir marboxil treatment compared with placebo but remained similar across different Asian subgroups. Median TTAS was 57.1, 58.4, and 56.3 hours for OwH Chinese, South Korean, and other Asian patients, respectively; for corresponding HR patients, median TTAS was 65.2, 66.5, and 63.5 hours, respectively. Therefore, there was no anticipated difference in baloxavir efficacy between Chinese or South Korean and other Asian patients.

**DISCUSSION**

A baloxavir acid PK–TTAS model was developed using time-to-event analyses and PK data to characterize the baloxavir acid PK–TTAS relationship, quantify the influence of covariates on this relationship, and predict TTAS in different ethnic groups.

In the absence of antiviral treatment, TSS0 had the greatest impact on the probability distribution (hazard function) of symptom alleviation, with a trend toward a longer TTAS in patients with a higher TSS0. Although this was expected, the placebo model offers a quantitative characterization of such a trend, demonstrating a 37% decrease in the instantaneous rate of TTAS between a patient with a TSS0 of 21 and a patient with a TSS0 of 13. This translated into a 0.9-day increase and 0.7-day decrease in median TTAS for patients with a TSS0 of 21 or 7, respectively, compared with the reference patient (TSS0 of 13). Other factors found to impact the natural distribution of TTAS in patients treated with placebo included ethnicity (Asian vs. non-Asian), patient type (OwH or HR), and sex. Non-Asian patients exhibited a 42% decrease in the instantaneous rate of TTAS compared with Asian patients, which corresponded to a 1.2-day increase in median TTAS. This is consistent with findings from CAPSTONE-1 and CAPSTONE-2, whereby non-Asian patients exhibited a longer TTAS than Asian patients regardless of patient type (OwH or HR). The time between study entry and symptom onset was not shown to impact TTAS; however, a potential difference between Asian and non-Asian patients in terms of care-seeking behavior cannot be excluded. Additionally, compared with OwH patients,
Figure 2: Predictive performance of the final placebo–TTAS model using Kaplan–Meier visual predictive check (a) overall, (b–e) per covariate categories: (b) ethnicity, (c) patient type (OwH or HR), (d) TSS0, (e) sex. Smooth curve: median of the predicted Kaplan–Meier curves over 1,000 simulations; shaded areas: 95% confidence interval of the model prediction; staggered curve: Kaplan–Meier curve of the observed TTAS. HR, high risk; OwH, otherwise healthy; TSS0, composite symptom score at baseline; TTAS, time to alleviation of symptoms. [Colour figure can be viewed at wileyonlinelibrary.com]
HR patients exhibited a longer TTAS. Last, the instantaneous rate of symptom alleviation decreased by 21% in female patients compared with male patients. This is in agreement with research indicating that elevated levels of testosterone and amphiregulin, an epidermal growth factor, have been shown to contribute to better influenza outcomes and faster recovery in male patients compared with female patients.14

Airway function can be influenced by circadian rhythms, whereby respiratory conditions can be exacerbated late at night or in the early hours of the morning.15 However, in this study,

**Figure 3** The impact of baloxavir acid concentration levels on TTAS survival curves. The percentage of patients with no symptom alleviation at a given time was computed for patients treated with placebo (blue line) or baloxavir marboxil (red lines). The solid red line indicates patients with baloxavir acid concentrations equal to the estimated population value; the dotted red line represents patients with baloxavir acid concentrations 50% greater than the estimated population value; the dashed red line indicates patients with baloxavir acid concentrations 50% lower than the estimated population value. TTAS was predicted for (a) a non-Asian male patient with TSS0 = 13, (b) an Asian male patient with TSS0 = 13, (c) a non-Asian male patient with TSS0 = 21, and (d) an Asian male patient with TSS0 = 21. TSS0, composite symptom score at baseline; TTAS, time to alleviation of symptoms. [Colour figure can be viewed at wileyonlinelibrary.com]
influenza symptom alleviation was considered achieved when the patient scored all 7 symptoms as 0 or 1 for a duration of at least 21.5 hours. Therefore, it was assumed that TTAS would not be influenced by daily circadian rhythm, and no related covariate was assessed in the PK–TTAS model.

A non-steepest exposure–response relationship was established between systemic baloxavir acid exposure and TTAS, with a proportional impact of the baloxavir acid concentration–time course on the parametric TTAS hazard function. Summary statistics of concentration–time course, such as AUC, were not considered in the PK–TTAS model development. This type of approach would consider AUC as information available at baseline rather than calculated post-baseline, and thus it may introduce immortal time bias in the time-to-event analysis.16

Although the developed model implies that a larger dose amount of baloxavir marboxil would lead to greater efficacy, the globally adopted dosing strategy for baloxavir marboxil (40 or 80 mg for < 80 kg and ≥ 80 kg body weight, respectively) was determined as the dosing with the highest benefit–risk profile based on available data, balancing efficacy and safety. This was guided by a thorough QT/QTc study in Japanese subjects including an 80 mg dose administered regardless of body weight and showing no effect on the QT interval.2 The exposure data of this study was therefore considered as the best estimate of a safe upper limit of exposure in humans so far.

TTAS was shorter in Asians compared with non-Asians; however, simulated TTAS was shown to be comparable between Chinese or South Korean and other Asian patients. Assuming a TSS0 > 10, for Chinese or South Korean and other Asian patients the reduction in predicted median TTAS from placebo was 18.3, 18.5, and 18.8 hours, respectively, in OwH patients and was 21.2, 20.6 and 22 hours, respectively, in HR patients. PK were similar between healthy Chinese or South Korean volunteers and other Asian patients in phase III studies, indicating influenza infection did not affect the PK of baloxavir.3,6,17,18 The exposure observed in healthy South Korean volunteers in study ML40799 was slightly lower than that observed in Japanese subjects in phase I studies; however, exposures were similar when compared with Asian patients from phase III studies.3,4,7,17 Based on the known PK and metabolism characteristics (i.e., bioavailability, protein binding, metabolism, sex, patient type, and drug–drug interaction profile) and the absence of external factors, it was not anticipated that the PK of baloxavir acid in Chinese and South Korean patients would differ from that in other Asian patients.

Medical practices in China and South Korea for the diagnosis and treatment of influenza are in alignment with those in Japan and are broadly comparable with those in other regions such as the United States. Therefore, there are no regional differences...
in the diagnosis of influenza or approach to the use of antivirals that would be expected to result in a different treatment effect in Chinese or South Korean patients compared with patients in other countries.

Pharmacometric techniques allowed global analysis of pooled patient data across phase II and III studies, resulting in more accurate quantification of the PK–TTAS relationship and an increased power to detect any potential covariate effects. The global need for improved allocation of local resources and accelerated drug access, without compromising the scientific integrity, efficacy, or safety of the administered drug in the targeted patients, has led to alternative regulatory registration pathways. Prior to 2018, China required clinical data to be collected locally to support marketing authorizations, but now permits reliable foreign clinical data to be assessed for ethnic sensitivity in support of new drug applications.19,20 The analyses presented in this paper are in line with such an approach and integrate all available patient data from global studies, supporting ethnic sensitivity bridging approaches that led to the approval of baloxavir marboxil in both China and South Korea, without the need for local phase III studies.

### Supporting Information

Supplementary information accompanies this paper on the Clinical Pharmacology & Therapeutics website (www.cpt-journal.com).

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### Author Contributions

All authors wrote the manuscript. S.R. and V.C. designed the research. S.R. and S.J. performed the research. All authors analyzed the data.

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### Conflict of Interest

S.R., S.D.B., S.J., and V.C. 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 paper.
DATA AVAILABILITY STATEMENT
Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche’s criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche’s Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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