



A pharmacokinetics–time to alleviation of symptoms model to support extrapolation of baloxavir marboxil efficacy in pediatric patients with influenza

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Introduction

- Baloxavir marboxil (Bxm), prodrug of baloxavir acid (referred as baloxavir), suppresses influenza virus replication by inhibition of the cap-dependent endonuclease.¹
- Bxm is approved for the treatment and post-exposure prophylaxis of uncomplicated influenza in patients aged ≥ 3 weeks in the EU (²) and in patients who are otherwise healthy (OwH) or at high risk of developing influenza-related complications (HR) aged ≥ 5 years in the USA, with a single oral dose of 2 mg/kg for < 20 kg, 40 mg for 20 to < 80 kg, or 80 mg for ≥ 80 kg.
- The pharmacokinetic (PK) profile of baloxavir in pediatric, adolescent and adult patients was previously characterized using a population pharmacokinetic (popPK) analysis.³
- The time to alleviation of symptoms (TTAS) is an efficacy endpoint used in clinical trials that investigate the efficacy of an antiviral.
- PopPK and PK-efficacy (PK-TTAS) models can inform dose selection and efficacy extrapolation, therefore supporting the pediatric development of Baloxavir marboxil.

Objectives

- Develop a popPK-TTAS model for baloxavir using pooled data from OwH and HR adult, adolescent, and pediatric patients and a common TTAS endpoint (TTAS2), to characterize the quantitative relationship between baloxavir PK and the alleviation of influenza symptoms.
- Identify covariates influencing the natural distribution of symptom alleviation in patients who received placebo and influencing baloxavir drug effect.
- Simulate TTAS2 to support efficacy extrapolation and dosing justification in pediatric patients, including the HR pediatrics.

Methods

Data Sources:

- Dataset of pooled Phase 2/3 clinical trials, including adult, adolescent, and pediatric patients, with baloxavir plasma concentrations and TTAS were collected from 7 Bxm studies;
- A historical oseltamivir versus placebo Phase 3 trial was included in this analysis to gain information on the natural distribution of TTAS in placebo-treated pediatric patients .

Endpoints:

- The definition of TTAS was not consistent across all studies; a second TTAS endpoint (TTAS2) was derived using a set of criteria common to all studies
- TTAS2 is defined as time from treatment initiation to alleviation of cough/nasal symptoms and return to afebrile state (≤37.2°C) (**Table 2**)

Modeling Approach:

- Stepwise development of a time-to-event analysis to model the baloxavir PK-TTAS2 relationship using a parametric hazard functions (log-logistic distribution):
 - Placebo model (from the placebo arms) describing the natural TTAS2 distribution; potential factors that impact the natural TTAS2 distribution were identified
 - Investigation of the effect of baloxavir PK on the TTAS2 distribution (data from placebo and Bxm arms) and identification covariates with significant influence on baloxavir drug effect
- Model predictive performance assessed via Kaplan-Meier (KM) visual predictive checks (VPCs).

Simulations

- TTAS2 was simulated for Bxm at recommended dose or placebo, by, age group (<5, 5–<12, ≥12 years), disease status (OwH, HR), race (Asian, non-Asian), and baloxavir exposure level.

Software:

- Software: NONMEM 7.4.3 (modeling), SAS 9.4 (data management), R 4.0.3 (visualization).

Results

Population PK/TTAS2 analysis and Covariates

- The population PK/TTAS2 analysis comprised data from eight pooled studies, with a total of 2216 adult, adolescent, and pediatric patients (**Table 1**).
- Items comprised in the study definition of TTAS are compared between studies and with TTAS2 (**Table 2**): adequacy of excluding the ‘return to normal activity’ was confirmed in a post hoc sensitivity analysis.

Table 1 - Summary of Baseline Characteristics

	Placebo (N=901)	Bxm (N=1315)
1- < 12 years of age, N (%)	194 (21.5%)	231 (17.6%)
Mean (SD) age, years	35.8 (22.0)	34.6 (20.0)
Mean (SD) bodyweight, kg	62.8 (28.0)	60.5 (24.6)
Asian, N (%)	430 (47.7%)	955 (72.6%)
Female, N (%)	445 (49.4%)	624 (47.5%)
OwH, N (%)	513 (56.9%)	946 (71.9%)

Table 2 - Definition of TTAS and TTAS2

Items / Studies	TTAS Study definition			TTAS2
	Global pediatric	Japan Pediatric	Adult / Ado	
Cough	x	x	x	x
Nasal Congestion	x	x	x	x
Body temperature	x	x	x	x
'return to normal activity'	x		Collected	
4 additional influenza symptoms			x	

- Median TTAS2 was found to be similar in non-Asian, OwH patients who received placebo across age groups: 5.68 days (95% CI 3.78–8.82), 4.65 days (95% CI 3.37–6.36) and 5.24 days (95% CI 3.11–9.32) in patients aged <5 years, 5–<12 years and ≥12 years, respectively.
- In the final popPK/TTAS2 model, the impact of the baloxavir concentrations on the TTAS2 natural distribution (placebo model) was best described by a sigmoid Emax model, which impacts the hazard additively:

Table 3 - Estimated Model Parameters

Placebo TTAS2 model			Final Model**: Baloxavir drug effect		
Parameter	Estimated value	RSE, %	Parameter	Estimated value	RSE, %
β*	1.15	3.37	E _{max}	0.267	12.2
γ*	0.44	4.23	EC ₅₀	23.7	19.5
β _{RACE}	−0.62	11.2	γ*	2.72	23.8
β _{HR}	−0.292	24.5	θ _{CSSB012} ·E _{max}	0.534	25.7
β _{CSSB}	0.348	20.9	θ _{CSSB06} ·E _{max}	−1.16	26.8
			θ _{VTYPE} ·E _{max}	−0.505	35.8
			θ _{smoke} ·EC ₅₀	−0.891	29.9
			θ _{Sex} ·EC ₅₀	0.558	42.5

*β and γ: parameter estimates of log-logistic model; ** Joint sequential modelling approach: estimated parameters of placebo model fixed while investigating baloxavir effect on the TTAS2 model; CSSB, composite symptom score at baseline (integrating cough and nasal congestion, this score increases with severity of symptoms; if CSSB <3, then θ_{CSSB} = θ_{CSSB012}; if CSSB =3 or 4, then θ_{CSSB} = 0, if CSSB ≥5, then θ_{CSSB} = θ_{CSSB06}); EC₅₀, half-maximal effective concentration; E_{max}, maximum effect; Gender: sex (gender =0: male, 1: female); HR: high risk disease status (HR = 0: OwH, 1: HR); RACE: Asian vs non-Asian patients (RACE =0: Asian, 1: non-Asian), RSE, relative standard error; Smoke: smoking status (if Smoke =1: smoker, else 0); Vtype: Influenza virus type (Vtype =1: Influenza type B, 0: Influenza type A).

- Covariates analysis:
 - Placebo model:** Race, disease status (OwH/HR), and symptom score (i.e. severity of symptoms) at baseline significantly influenced natural TTAS2; Asian and HR patients had longer TTAS2; milder symptoms at baseline associated with shorter TTAS2;
 - Baloxavir model:** Influenza type (Influenza Type A or Type B) and symptom score at baseline impacted E_{max}; sex and smoking status impacted EC₅₀.
- ⇒ **Age, race, and disease status did not significantly influence baloxavir drug effect**

Model Performance

- There was good overlay between the predicted and observed TTAS in the KM VPCs for all patients who received placebo or baloxavir, showing good predictive performances of the model (**Figure 1, Figure 2**).
- The age-independent faster symptom alleviation on Bxm treatment vs. placebo is well-captured by the model.

Figure 1 - Kaplan Meier VPC (Placebo model)

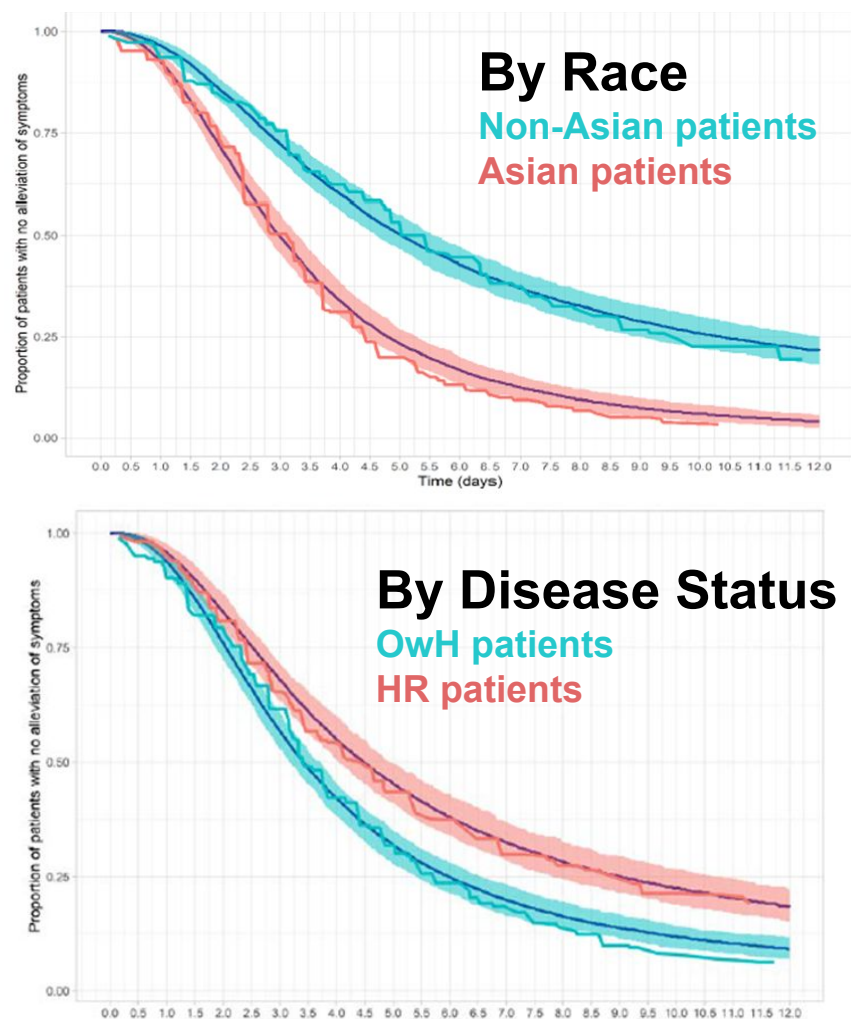
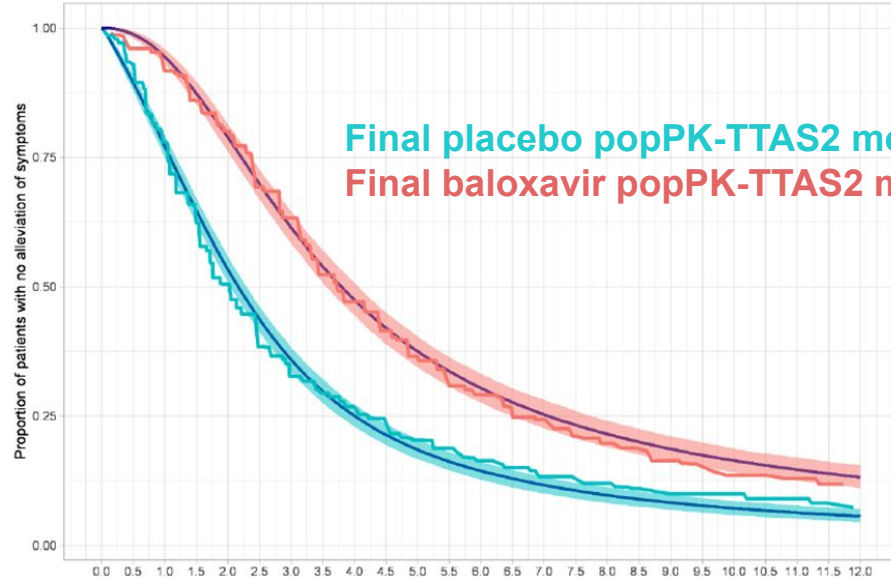


Figure 2 - Kaplan-Meier VPC of the final popPK-TTAS2 model (all patients)



Smooth lines: median predicted KM curves over 1000 simulations; shaded areas: 95% CI of the model prediction; and the stair-step curves represent the observed TTAS2 KM curve.

popPK/TTAS2 Simulations

- After oral administration of Bxm at the recommended dose, same baloxavir PK is observed in OwH and HR patients, and in pediatric and adult patients (by race).³ Baloxavir reduced TTAS2 by ≥1 day vs. placebo across age, race, and disease status (**Table 4**).
- Similar efficacy is predicted in pediatric, adolescent and adult patients, in Asian and non-Asian patients, and in HR and OwH pediatric patients, supporting exposure-matching for extrapolation of efficacy between groups.

Table 4 - Predicted TTAS2 (t | P(TTAS2>t)=0.5, in hours) by Patient Group

Age Group	Exposure Group & Treatment	Asian OwH	Asian HR	Non-Asian OwH	Non-Asian HR
Pediatrics (1-<12 y)	Placebo	68.2 (65.6–70.6)	74.7 (71.1–78.2)	84.4 (81.2–87.7)	107 (102–112)
	Baloxavir	45.6 (43.2–47.6)	43.4 (40.7–45.8)	44.6 (41.7–47.5)	48.1 (44.7–51.7)
	Low Exposure	51.0 (42.4–61.8)	49.6 (41.2–59.7)	51.2 (41.7–62.9)	58.7 (46.8–73.2)
	High Exposure	45.1 (42.7–47.3)	42.8 (40.6–45.1)	43.0 (40.7–45.2)	46.5 (44.1–49.0)
Adolescents & Adults (≥ 12 y)	Placebo	68.3 (66.1–70.7)	74.6 (71.2–78.2)	84.2 (81.2–87.2)	107 (102–112)
	Baloxavir	47.6 (45.2–49.8)	43.3 (40.7–45.8)	49.6 (47.2–52.1)	57.0 (53.6–60.7)

t | P(TTAS2>t)=0.5 is the time at which 50% of the virtual patients have not yet their symptoms alleviated (i.e., 50% of patients remain symptomatic); All values are t | P(TTAS2>t)=0.5 (median), with 95% CI.
Low Exposure = AUC_{0-inf} < 4.6 µg·hr/mL; High Exposure = AUC_{0-inf} ≥ 4.6 µg·hr/mL (median AUC_{0-inf})

Conclusions

- An exposure-response relationship was established between baloxavir plasma concentrations and TTAS2 for both OwH and HR patients, irrespective of age.
- Covariate analysis confirmed that age, race, and disease status do not meaningfully impact baloxavir drug effect.
- Baloxavir marboxil at the recommended dose of 2 mg/kg for < 20 kg, 40 mg for 20 to < 80 kg, or 80 mg for ≥ 80 kg demonstrates consistent efficacy in reducing TTAS2 across age, race, irrespective of the disease status at baseline.
- The model-based simulations **supported the extrapolation of efficacy to pediatric patients** aged 1- <12 years, including those who are at high risk of developing influenza related-complications, and between populations based on exposure-matching, therefore **justifying current dosing recommendations**.
- PopPK/PD modeling is a valuable tool for bridging efficacy across populations in pediatric drug development. Recently, it was also leveraged to support Bxm dose optimization and label extension to pediatrics aged 3 weeks to < 1 year.²

References

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