10 November 2022
EMA/906737/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xofluza

International non-proprietary name: baloxavir marboxil

Procedure No. EMEA/H/C/004974/X/0008/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADRs	adverse drug reactions
AE	adverse event
$AUC_{0\text{-}inf}$	area under the plasma concentration curve from time 0 to infinity
baloxavir	the active metabolite of baloxavir marboxil
BID	twice daily
$C_{24/72/240}$	plasma concentration at 24, 72 or 240 hours post-dose
CARIFS	Canadian Acute Respiratory Illness and Flu Scale
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CL/F	apparent total clearance, calculated as Dose/$AUC_{0\text{-}inf}$ (baloxavir only)
C_{max}	maximum plasma concentration
CSR	Clinical Study Report
EC_{50}	50% effective concentration
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GfOS	granules for oral suspension
HR	high risk
IC_{50}	50% inhibitory concentration
ITTI	Intention-to-Treat Infected
MAA	Marketing Authorisation Application
mITT	modified Intention-to-Treat
NAI	neuraminidase inhibitor
OwH	otherwise healthy
PA	polymerase acidic
PAM	Post Authorisation Measure
PD	pharmacodynamic
PEP	post-exposure prophylaxis
PIP	Paediatric Investigation Plan
PK	pharmacokinetic
PK-TTAS	pharmacokinetic to the time to symptom alleviation

PK-VK	pharmacokinetic to viral kinetic
RNA	ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
T0821	Study No. 1518T0821 / Roche Study No. CV40814
T0822	Study No. 1618T0822 / Roche Study No. CV40816
T0831	Study No. 1601T0831 / Roche Study No. CV40815
T0832	Study No. 1602T0832 / Roche Study No. CV40818
T0833	Study No. 1705T0833 / Roche Study No. CV40964
T0834	Study No. 1719T0834 / Roche Study No. XV41428
T0835	Study No. 1813T0835 / Roche Study No. XV41429
TTAS	time to alleviation of influenza signs and symptoms
TTIS	time to improvement of influenza symptoms
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

Roche Registration GmbH submitted on 25 November 2021 a group of variation(s) consisting of extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to introduce a new pharmaceutical form associated with new strength (2 mg/ml granules for oral suspension) grouped with a type II variation (C.I.6.a) to include paediatric use (from 1 year and above). The paediatric indication is applicable to the new presentation (2 mg/ml granules for oral suspension) as well as all approved presentations.
The RMP (version 2.0) is updated in accordance.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) (c) (d) - Extensions of marketing authorisations

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Pursuant to Article 22 of Regulation (EC) No 1901/2006 the application included an EMA Decision P/0029/2021 on a modification of the agreed paediatric investigation plan (PIP) that supersedes the previous EMA Decision(s) P/0300/2019 pursuant to Article 7 of Regulation (EC) No 1901/2006. A further modification was adopted during the procedure: P/0383/2022.

At the time of submission of the application, the PIP P/0029/2021 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4.2. Derogation(s) from market exclusivity

Not applicable

1.5. Additional Data exclusivity/Marketing protection

Not applicable.

1.6. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Thalia Marie Estrup Blicher Co-Rapporteur: Jayne Crowe

CHMP Peer reviewer(s): Not applicable

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Sonja Hrabcik

The application was received by the EMA on	25 November 2021
The procedure started on	24 December 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 March 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 March 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	07 April 2022
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	22 April 2022
The MAH submitted the responses to the CHMP consolidated List of Questions on	15 July 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	16 August 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	21 March 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	15 September 2022
The MAH submitted the responses to the CHMP List of Outstanding Issues on	11 October 2022
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC	26 October 2022

members on	
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Xofluza on	10 November 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Influenza is an acute respiratory infection caused by infection with influenza virus types A and B that occurs in outbreaks of varying severity almost every winter in temperate climates and year-round in tropical climates. Influenza viruses are highly contagious with efficient person-person spread within communities and with the potential for pandemics with severe morbidity and mortality presenting significant public health challenges.

2.1.2. Epidemiology

Epidemiology data indicates a higher frequency of influenza B infection, which may cause more severe disease than A viruses, in children relative to adults, with B viruses considered responsible for 16%-52% of influenza paediatric deaths in the US from 2016 to 2019.

Children play a central role in the dissemination of influenza in the community as children infected with influenza virus can have a longer shedding time compared to adults and by virtue of their relative serosusceptibility and consequently higher illness attack rates. They are also frequently exposed to each other in collective settings such as school and day-care, which plays a role in the prevalence and transmission of influenza.

2.1.3. Biologic features

Major antigenic variations, called antigenic shifts, may be associated with pandemics and are restricted to influenza A virus. Minor variations are called antigenic drifts. Since 1977, H1N1 and H3N2 viruses have circulated simultaneously, resulting in outbreaks of varying severity.

Influenza B viruses can co-circulate with influenza A viruses but are generally the minority type in any given season. Studies have suggested increased potency of influenza B virus in causing severe disease and mortality. Influenza B has been described to have significantly higher mortality rates compared to influenza A strains.

The quadrivalent vaccine includes lineages of both influenza A and B. These vaccines significantly decrease rates of infection; however, in susceptible populations such as children within the age group of 9–17 years of age it appears to have an effectiveness of approx. 28%. In contrast to influenza A and B viruses, influenza C virus appears to be a relatively minor cause of disease in humans.

2.1.4. Clinical presentation, diagnosis

The clinical manifestations of influenza in healthy paediatric patients are similar to those seen in adults; however, the rate of severe influenza infection and complications is higher than in their adult counterparts. Anatomical and immunological differences between children and adults may increase the severity of disease observed in this population. Young children have smaller airways more prone to obstruction by secretion produced during active infection. Additionally, young children are known to have naïve adaptive immune systems which can make them more susceptible to developing severe infection. Common complications of influenza in children include otitis media, conjunctivitis, gastrointestinal upset, pneumonia (primary influenza virus and secondary bacterial pneumonia), respiratory failure, and seizures while other serious complications can also develop, including cardiac and neurological complications. Hospitalizations and mortality rates for influenza in children are significantly higher than in adults and particularly in children aged < 5 years. Mortality in children vary across seasons and is dependent on viral subtype, pre-existing immunity and presence of underlying disease (Ruf and Knuf 2014). Recent mortality estimates for children from 92 countries, the majority of whom were < 5 years old, report between 9,000-106,000 (median: 44,888) influenza-associated deaths annually (Iuliano et al. 2018).

Influenza may be clinically diagnosed, particularly during seasonal influenza. Otherwise, molecular assays (including rapid molecular assays, reverse transcription polymerase chain reaction (RT-PCR) and other nucleic acid amplification tests); and antigen detection tests (including rapid influenza diagnostic tests and immunofluorescence assays) may be used.

2.1.5. Management

Influenza vaccination is the first line of defence against influenza. It can be administered to any person aged > 6 months (who does not have contraindications to vaccination) to reduce the likelihood of becoming ill with influenza. Trivalent and quadrivalent inactivated influenza vaccine can be used for any person aged > 6 months, including those with HR conditions. Live, attenuated influenza vaccine may be used for healthy, non-pregnant persons aged 2-49 years. Antiviral agents are required to treat established infection.

Four antiviral drugs are currently approved in the EU for the prevention and treatment of influenza: the M2 ion-channel inhibitor amantadine and the neuraminidase inhibitors (NAIs) oseltamivir, zanamivir and peramivir, plus additionally baloxavir marboxil (see below). A second M2 inhibitor, rimantadine, holds marketing authorisations in the Czech Republic, France and Poland but is not marketed in these countries. While there is widespread resistance to amantadine and rimantadine in circulating seasonal influenza, NAIs are the mainstay of treatment for influenza infections. Oseltamivir is indicated in children from birth for treatment and zanamivir is indicated from 5 years of age for treatment. Both oseltamivir and zanamivir need to be administered twice daily for 5 days. An inhalation formulation of zanamivir can be used in patients who are able to inhale the drug (excluding children aged < 5 years).

Post-exposure prophylaxis (PEP) treatments are available but are not a substitute for influenza vaccination. Oseltamivir is indicated for individuals ≥1 year of age following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community. Oseltamivir is administered once daily for 10 days following close contact with an infected individual. Oseltamivir is indicated for PEP of influenza in infants less than 1 year of age during a pandemic influenza outbreak. In addition, zanamivir is indicated for PEP from 5 years of age and is administered once daily for 10 days.

2.2. About the product

Baloxavir marboxil is a novel prodrug which is converted pre-systemically to the active form baloxavir through metabolism (hydrolysis). The active form selectively inhibits the cap-dependent endonuclease, an influenza virus-specific enzyme in the polymerase acidic (PA) subunit of the viral RNA polymerase complex, which thereby inhibits influenza virus replication.

For both indications (treatment and prophylaxis of influenza), the use of Xofluza is a single oral dose administration, and for the current indication in children from 1-12 years, granules have been developed.

2.3. Type of Application and aspects on development

The clinical development programme for the treatment indication for children from 1 to less than 12 years consists of 1 pivotal study and 3 supportive studies. Furthermore, a pivotal study for the indication of post exposure prophylaxis in children from 1 to less than 12 years were provided with the initial application in 2019. Overall, the clinical development programme supports the population for the proposed indication.

The following CMC guidance has been given in CHMP Scientific advice EMEA/H/SA/3497/1/2017/I, CHMP follow-up Scientific advice EMEA/H/SA/3497/1/FU/2018/1 and CHMP Scientific advice Clarification letter EMEA/H/SA/3497/FU/1/2018/I. Further, the Applicant had interactions with European national authorities (MHRA, BfArM and MPA) and FDA regarding the clinical development. This was also stated in the EPAR of the initial MA. The population below 12 years was not addressed in any of these advices.

The MAH is in compliance with the paediatric investigation plan, where a deferral was granted for studies in children from 1 to less than 12 years and for 0 to less than 1 year. With the current application, the study report for the pivotal study in children from 1 to less than 12 years has been submitted, whereas the study in children from 0 to less than 1 year is completed separately. Furthermore, a modelling and simulation studies in otherwise healthy and high-risk adult and paediatric subjects, evaluating relevant demographic covariates that may influence systemic drug exposure, and evaluating exposure-response should be completed at later date (by February 2024 and August 2024). Additionally, two extrapolation studies evaluating PK, PD and efficacy in otherwise healthy paediatric patients and high-risk paediatric patients from birth to less than 12 years of age is envisaged for completion by December 2024.

2.4. Quality aspects

2.4.1. Introduction

This extension application introduces a new pharmaceutical form associated with new strength (2 mg/ml granules for oral suspension) grouped with a type II variation (C.I.6.a) to include paediatric use (from 1 year and above). The paediatric indication is applicable to the new presentation (2 mg/ml granules for oral suspension) as well as all approved presentations of 20 mg and 40 mg film-coated tablet.

The finished product is presented as granules for oral suspension containing 2 mg/ml of baloxavir marboxil as active substance.

Other ingredients are: colloidal silicon dioxide (E551), hypromellose (E464), maltitol (E965), mannitol (E421), povidone K25 (E1201), sodium chloride, strawberry flavour (including propylene glycol), sucralose (E955) and talc (E553b).

The product is available in amber type III glass bottle with a tamper evident child-resistant screw cap. Co-packaged with the granules there is 1 press-in bottle adapter, 1 measuring cup, a 3 ml oral syringe with orange plunger and a 10 ml oral syringe with transparent plunger.

2.4.2. Active Substance

2.4.2.1. General information

No additional information on the active substance has been provided in relation to the application for the new dosage form 2 mg/ml granules for oral suspension to what has already been presented and approved in relation to the approved 20 mg and 40 mg film-coated tablet.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Baloxavir marboxil, granules for oral suspension, 2 mg/ml, is made up of white to light yellow granules for oral suspension. Each bottle contains 40 mg of baloxavir marboxil. The granules must be constituted with 20 ml water to yield a 2 mg/ml oral suspension.

Co-packaged with the granules there is 1 press-in bottle adapter, 1 measuring cup, a 3 ml oral syringe with orange plunger and a 10 ml oral syringe with transparent plunger.

The quantitative and qualitative composition of Baloxavir marboxil, granules for oral suspension has been stated; the list of ingredients is presented in section 2.4.1 of this report.

The pharmaceutical form is age-appropriate formulation of granules for oral suspension (GfOS) developed to support administration of baloxavir marboxil at the recommended doses to younger paediatric as well as to older patients with swallowing difficulties. Conventional sweetener, taste-masking agent, and flavour are added to the formulation to ensure palatability of the product in the paediatric population. The Quality Target Profile was defined.

The commercial formulation is manufactured with standard excipients using conventional equipment and manufacturing processes. The excipients are well-known and commonly used in solid dosage forms. The amount of each excipient has been justified regarding paediatric use. The excipients are compendial, except the strawberry flavour for which the qualitative composition has been presented. However an analytical method for identification of strawberry flavour has not yet been implemented. Thus the CHMP requested and the applicant committed to provide the revised acceptance criteria and the validation summary or provide a new method and corresponding acceptance criteria and validation summary through a post-approval (REC).

Pilot studies have been performed to evaluated the excipient concentration, compatibility with the active substance, and stability. No novel excipients have been used. Several excipients were chosen in order to improve the palatability; which has only been evaluated retrospectively using a questionnaire for investigators. Overall, the provided data indicates an adequate acceptability and palatability of GfOS in the paediatric population. Furthermore the applicant has confirmed that the palatability of the proposed formulation will be evaluated in ongoing clinical studies. Reference is made to the clinical

assessment. In addition, studies results has shown that the relatively large volume of suspension to be administered does not constitute an issue in terms of administration of the full dose. Also, it is noted that the SmPC has been updated to include a recommendation specifying that granules for oral suspension should not be mixed with food.

The polymorphic form of baloxavir marboxil used for the finished product can be distinguished from other polymorphic forms by X-ray diffraction and IR spectroscopy. The applicant has demonstrated that the polymorphic form does not change during manufacture or during storage.

Development of the manufacturing process was based on a FMEA, whereby the potential critical material attributes (CMA) and critical process parameters (CPP) identified as potential risks to the quality attributes of the finished product have been evaluated. The Proven Acceptable Ranges for CPP and non-CPPs to be applied in routine manufacturing are consistent with the ranges evaluated during manufacturing development. No design space is claimed.

Bioequivalence of baloxavir marboxil, granules in sachet 2% w/w with the finished product used in pivotal Phase III studies in adults, the baloxavir marboxil film-coated tablets 20 mg, has been demonstrated.

The dissolution method is based on the dissolution method used for Xofluza tablets and has been sufficiently justified. Discriminatory power has been shown.

A comparison of dissolution profiles in three pH conditions (1.1, 4.5, and 6.8) has been provided for baloxavir marboxil granules for oral suspension, 2 mg/mL, versus film-coated tablets, 40 mg. Both formulations, granules and film-coated tablets, were compared. From the presented results it is agreed that the profiles for both formulations, granules and film-coated tablets can be considered comparable.

A study to evaluate the uniformity of mass delivered and extractable volume based on Ph. Eur. 2.9.27 has been performed, however, it is noted that the mean dose (mg) and delivered volume (ml) are rather low for the 10 ml syringe. It is also noted that the syringes are CE-marked. A discussion on the suitability of the chosen syringes for the intended use has been provided. It is demonstrated that all results comply with the acceptance criteria defined in Ph. Eur. 2.9.27 Uniformity of mass of delivered doses from multidose containers and confirms the acceptable performance and suitability of the syringes.

Compatibility has been demonstrated for oral dispensers (syringes) and for enteral dispensers as well as enteral tubes. Due to the short contact time, it is acceptable not to perform leachable studies.

The finished product is packaged in amber glass bottles (type III according to Ph. Eur.) with a tamper-evident child-resistant screw cap. Compliance with relevant EU legislation and Ph. Eur. standards are confirmed for each primary packaging component. The child-resistant performance is verified w.r.t. ISO 8317 (2015).

The co-packaged medical devices, i.e. a measuring cup, a press-in-bottle adapter, a 3 ml oral syringe with orange plunger and a 10 ml oral syringe with transparent plunger are all CE-marked. Also, a declaration of conformity or an EC certificate referring Directive 93/42/EEC is provided for each. The manufacturer of each device is informed.

2.4.3.1. Manufacture of the product and process controls

The finished product manufacturers have been stated.

The manufacturing process comprises 7 main steps: 1-mixing, 2-wet granulation, 3-drying, 4-sizing, 5-final blending 6-bottle filling and closure, 7-assembly, labelling, and packaging. The manufacturing

process is considered a complex manufacturing process due to the finished product being a low content product (≤2% of composition).

The description of the manufacturing process reflects the enhanced development approach, i.e. criticality classification on material attributes and process parameters, target values and proven acceptable ranges are included. The manufacturing process is described in an acceptable level of detail.

A holding time study for the bulk product was carried out, and the proposed holding time and storage remark are acceptable. The bulk product specification is acceptable.

The bulk product is similarly protected in the bulk packaging as in the commercial packaging. Transport conditions has been justified and specification for the bulk container has been provided. An acceptable specification has been provided for the desiccant and conformance with CPMP/QWP/072/96 has been confirmed.

The manufacturing process has been validated using 3 full scale batches in the proposed commercial scale. The process validation data showed that the manufacturing process is consistent and under control, i.e. it is producing a product meeting the pre-determined specification limits. Also, the manufacturing process validation demonstrated that the established process results in an acceptable blend uniformity.

2.4.3.2. Product specification

The finished product release and shelf life specifications include appropriate tests and limits for container type (visual), description of bottle content (visual), description of constituted suspension (visual), constitution time (visual), fineness of dispersion (Ph. Eur.), identification (UHPLC, UV), content per bottle (UHPLC), related substances (HPLC), water content (Ph. Eur.), dissolution (Ph. Eur., UV), uniformity of dosage units (Ph. Eur., UHPLC), and microbial limit tests (Ph. Eur.).

The parameters included in the finished product specification are acceptable. An acceptable justification for parameters omitted from the specification have been provided.

Baloxavir marboxil is a prodrug. The limits for impurities are justified and acceptable based on the levels seen in the batch analysis and stability studies. The proposed limit for assay is considered acceptable.

A risk assessment for elemental impurities has been conducted in accordance with ICH Q3D, to evaluate the potential for elemental impurities to be present in the finished product and the relevant discussion has been provided. In three batches tested, no elemental impurities were identified to be present at a level of greater than 30% of the PDE limit for oral administration. Based on this, tests for elemental impurities are not included in the finished product specification.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The batch analysis data (n=8) provided confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification, when manufactured using the proposed manufacturing process at the proposed manufacturing site.

2.4.3.3. Stability of the product

Stability studies has been carried out on six commercial scale batches according to ICH stability conditions. The batches were stored under long term conditions at 25°C/60% RH and 30 °C/ 75% RH for up to 36 months and under accelerated conditions at 40 °C / 75% RH for 6 months in the proposed commercial packaging.

Stability samples were tested for assay, constitution time, description of constituted suspension, related substances, description of bottle content, fineness of dispersion, water content, microbial limits, and dissolution. Content uniformity is solely tested for the primary stability batches. The methods were the same as for release.

A known degradation product increased slightly at both long term and accelerated conditions. No other significant changes were seen during storage. All results were well within the proposed specifications.

A photostability study has been carried out in accordance with the ICH Q1B guideline on one commercial batch. It was concluded that the baloxavir marboxil granules for oral suspension are not sensitive to light.

An in-use stability study (stability after constitution) has been carried out. A study has been conducted on microbial examination after constitution, based on which the Applicant proposed a storage period of 10 hours following reconstitution. After preparation the oral suspension should be used as soon as possible and a storage period of 10 hours after reconstitution is considered reasonable considering practical arrangements for reconstitution of the finished product, as proposed in the SmPC section 6.6.

Based on the submitted stability data the proposed shelf-life of 4 years with the storage condition "Keep the bottle tightly closed in order to protect from moisture" as stated in SmPC section 6.3 and 6.4 is acceptable.

2.4.3.4. Adventitious agents

No excipients derived from animal or human origin are used in the manufacture of Xofluza granules for oral suspension.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the new finished product strength has been presented in a satisfactory manner. No major objections have been raised during the line extension procedure. The overall control strategy is adequately justified and is acceptable. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there was an unresolved quality issue having no impact on the

Benefit/Risk ratio of the product, which pertain to implementing an identification test for the strawberry flavour. This point is put forward and agreed as recommendations for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- to provide the revised acceptance criteria and the validation summary of the presented strawberry flavour identification method or to provide a new method description, corresponding acceptance criteria and validation summary through a post-approval variation application.

2.5. Non-clinical aspects

2.5.1. Introduction

Xofluza has already been authorised based on a full nonclinical package on pharmacology, pharmacokinetics and toxicology in connection with the initial MAA. Hence, only the new nonclinical documentation submitted by the MAH in connection with the X-08G variation is summarised and assessed in this report.

Three primary pharmacodynamics studies investigating the inhibitory effects of baloxavir (the active metabolite of baloxavir marboxil) on transmission of influenza virus in ferrets (1102424 and 1100893) and the transmission of the influenza virus variant with reduced susceptibility to baloxavir in ferrets (1106161) were submitted as part of the variation. No new specific nonclinical supplementary data was submitted for the paediatric indication as part of the variation application. An updated environmental risk assessment (ERA) was submitted for the new granules for oral suspension formulation.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In the original MAA, a relevant clinical effect was documented in ferrets, establishing it as an alternative pharmacological animal model to mice. In the current variation X-08G, three additional pharmacology studies in ferrets showed that baloxavir is able to reduce viral shedding of H1N1 influenza virus both following treatment after 24 h and 48 h post infection in treated animals. One study (study 1102424) showed that baloxavir was able to reduce the likelihood of transmission of virus between co-housed animals (1/4 animals infected compared to 4/4 in control group) whereas decreased indirect transmission of virus between ferrets exposed in adjacent cages was observed in another study (study 1100893, 1/4 infected compared to 3/4 infected in control group). A reduction in

direct transmission frequency of virus in animals in the same cage was however not observed in this study, contradicting the results of the first study.

It was further shown that pH1N1 virus carrying the baloxavir resistant genotype PA/I38T are able to replicate and transmit between ferrets both directly (co-housing) and indirectly (adjacent cages) but that the mutation imposes a cost to viral fitness relative to wild-type in recipient animals.

2.5.3. Pharmacokinetics

No new studies investigating the pharmacokinetics were submitted as part of the X-08G variation.

2.5.4. Toxicology

No new studies investigating the toxicology were submitted as part of the X-08G variation.

2.5.5. Ecotoxicity/environmental risk assessment

In the original MAA for Xofluza, no environmental risk was identified for baloxavir marboxil formulated as tablets. The expected slightly increased use of baloxavir marboxil, due to the extended indication to include children below 12 years of age and the new formulation as granules for oral suspension, will not change the conclusion on the full environmental risk assessment already performed prior to the initial MAA.

2.5.6. Discussion on non-clinical aspects

Three new primary pharmacological studies in ferrets were submitted with the variation, which was unrelated to the extension application for the paediatric population and the new formulation as granules for oral suspension. The studies supported the establishment of clinical relevance of the ferret as a pharmacological model as the intended pharmacological effect was demonstrated in this species.

A justification was presented for the environmental risk assessment (ERA) for the variation, as the original ERA for the MAA of Xofluza is still considered valid for the extension application for the paediatric population and the new granules for oral suspension formulation.

2.5.7. Conclusion on the non-clinical aspects

The variation X-08G can be approved from a nonclinical point of view and no other concerns are raised. There is no impact on the benefit-risk assessment following the submission of the additional nonclinical data and no changes to the RMP or SmPC are proposed.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community

were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 1: Clinical Studies Used to Assess the PK and PK/PD of Baloxavir in Paediatric Patients

Study No.	Study Design	Dose and Regimen	Study Objectives	No. Patients
Pivotal Pediatric Study:				
CP40563 (Phase 3)	Multicenter, randomized, double-blind, active-controlled study in OwH pediatric patients (1 to < 12 years) with influenza-like symptoms	Baloxavir marboxil (granules for oral suspension) single dose according to body weight: • < 20 kg: 2 mg/kg • ≥ 20 kg: 40 mg Oseltamivir (powder for oral suspension) BID for 5 days according to body weight: • ≤ 15 kg: 30 mg • >15 kg to 23 kg:45 mg • >23 kg to 40 kg:60 mg • > 40 kg:75 mg	• To compare the safety of a single dose of baloxavir marboxil with 5 days of oseltamivir administered twice daily • To evaluate the PK of baloxavir marboxil after single-dose administration • To evaluate the clinical efficacy of baloxavir marboxil compared with oseltamivir • To evaluate the virological activity of baloxavir marboxil compared with oseltamivir	**Randomized:** N = 176 bxm: 117; oselt.: 59 **PKEP Population:** bxm: 107 **PK Parameter Population:** bxm: 105
Supportive Japanese Pediatric Studies:				
1618T0822 (Phase 3)	Multicenter (Japan only), open-label, non-controlled study in OwH pediatric patients (6 months to <12 years) with influenza	Single dose of baloxavir marboxil by body weight: (10 and 20 mg tablets): • 5 to <10 kg: 5 mg • 10 to <20 kg: 10 mg • 20 to <40 kg: 20 mg • ≥40 kg: 40 mg	• To assess the safety and tolerability of a single dose of baloxavir marboxil • To assess the PK of baloxavir marboxil and its active form baloxavir after single dose administration and to confirm appropriateness of the dose in pediatric patients • To assess the efficacy of baloxavir marboxil after single dose administration	**Enrolled:** N = 108 **PK Concentration Population:** bxm = 107 **PK Parameter Population:** bxm = 107
1705T0833 (Phase 3)	Multicenter (Japan only), open-label, non-controlled study in OwH pediatric patients (weighing <20 kg and aged <12 years) with influenza	Single dose of baloxavir marboxil by body weight: (granules 2%): • <10 kg: 1 mg/kg 10 to < 20 kg: 10 mg	• To assess the safety and tolerability of a single dose of baloxavir marboxil 2% granules • To assess the PK of baloxavir marboxil and its active form baloxavir after single dose administration of baloxavir marboxil 2% granules • To assess the efficacy of a single dose of baloxavir marboxil 2% granules	**Enrolled:** N = 33 **PK Concentration Population:** bxm = 32 [a] **PK Parameter Population:** bxm = 33

Table 4: Clinical Studies Used to Assess the PK and PK/PD of Baloxavir in Paediatric Patients (cont'd)

Study No.	Study Design	Dose and Regimen	Study Objectives	No. Patients
1813T0835 (Phase 3)	Multicenter (Japan only), open-label, non-controlled study in OwH pediatric patients (weighing <20 kg and aged <12 years) with influenza	Single dose of baloxavir marboxil by body weight: (granules 2%): • <10 kg: < 3 month 1 mg/kg, ≥ 3 month 2 mg/kg • 10 to < 20 kg: 20 mg	• To assess the safety and tolerability of a single dose of baloxavir marboxil 2% granules • To assess the PK of baloxavi after single dose administration of baloxavir marboxil 2% granules • To assess the efficacy of a single dose of baloxavir marboxil 2% granules	**Enrolled:** N = 45 **PK Concentration Population:** 43 **PK Parameter Population:** 43
Supportive OwH Adult and Adolescent Studies:				
1601T0831 (Phase 3)	Multicenter (U.S. and Japan) [b], randomized, placebo / active control, double-blind study in adult and adolescent patients (≥ 12 to ≤ 64 years and ≥ 40 kg) with acute uncomplicated influenza	• Single dose of Baloxavir marboxil by body weight: ○ < 80 kg: 40 mg ○ ≥ 80 kg: 80 mg • Placebo • Oseltamivir: 75 mg BID for 5 days	• To evaluate the efficacy of a single, oral dose of baloxavir marboxil compared with placebo (primary) or oseltamivir (secondary) by measuring the time to alleviation of symptoms • To compare the safety and tolerability and frequency of AEs of a single dose of baloxavir marboxil with placebo or oseltamivir • To determine the PK of baloxavir (the active form of baloxavir marboxil)	**Randomized:** N = 1436 bxm: 612; pbo: 310; oselt.: 514 **PK Concentration Population:** bxm: 589 **PK Parameter Population [b]:** bxm: 396
1518T0821 (Phase 2)	Multicenter (Japan), randomized, placebo-controlled double-blind study adult patients (≥ 20 to ≤ 64 years) with acute uncomplicated influenza	• Single dose of Baloxavir marboxil: 10, 20, 40 mg or • Placebo	• To evaluate the efficacy of baloxavir marboxil vs. placebo as measured by the time to alleviation of symptoms • To assess the safety of baloxavir marboxil (10, 20 and 40 mg) as measured by the frequency of AEs and treatment-related AEs • To determine the PK of baloxavir (the active form of baloxavir marboxil)	**Randomized:** N = 400 bxm: 300 (100 per dose group); pbo: 100 **PK Concentration Population:** bxm: 300 (100 from each dose) **PK Parameter Population [c]:** bxm: 5 (1 in the 10 mg group, 2 in the 20 mg group, and 2 in the 40 mg group)

Table 4: Clinical Studies Used to Assess the PK and PK/PD of Baloxavir in Paediatric Patients (cont'd)

Study No.	Study Design	Dose and Regimen	Study Objectives	No. Patients
Supportive HR Adult and Adolescent Study:				
1602T0832 (Phase 3)	Multicenter (global), randomized, placebo / active control, double-blind study in adults and adolescents (≥ 12 years and ≥ 40 kg) with acute uncomplicated influenza who are at high risk of developing influenza-related complications.	• Single dose of Baloxavir marboxil by body weight: ○ < 80 kg: 40 mg ○ ≥ 80 kg: 80 mg • Placebo • Oseltamivir: 75 mg BID for 5 days	• To evaluate the efficacy of a single, oral dose of baloxavir marboxil compared with placebo (primary) or oseltamivir (secondary) by measuring the time to improvement of influenza symptoms • To compare the safety and tolerability and frequency of AEs of a single dose of baloxavir marboxil with placebo or oseltamivir • To determine the PK of baloxavir (the active form of baloxavir marboxil)	**Randomized:** N = 2184 [d] bxm: 730; pbo: 729; oselt.: 725 **PK Concentration Population:** bxm: 664 **PK Parameter Population (Bayesian approach):** bxm: 664

BID = twice daily; bxm = baloxavir marboxil; HR = high risk; oselt. = oseltamivir; OwH = otherwise healthy; pbo = placebo; PK = pharmacokinetic; PKEP = pharmacokinetic-evaluable patient.

[a] The PK concentration population in Study T0833 included 32 patients because one subject 3PY002 in the 10 mg dose group did not swallow the whole drug so the actual dose was unknown. As this patient had concentrations at or above other patients in the 10 mg dose group, this patient was included in the PK Parameter Population used in the population PK model.

[b] Study T0831 was conducted at sites in Japan, the U.S., and Canada. However, no patients were enrolled at Canadian sites.

[c] PK parameters derived by model-independent method. In T0821, PK parameters were derived only in 5 patients with intensive PK sampling.

[d] The actual number of patients randomized was 2184, including 2 patients who were randomized twice in error; both patients were re-assigned to the oseltamivir group before dosing (see HR T0832 CSR Section 10.1). Thus, a total of 2182 unique patients were randomized to treatment.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

PK in adults and adolescents were assessed at the primary submission.

To support the clinical pharmacology of the present extension of indication in children, the MAH has submitted 4 studies in children below 12 years of age and 3 studies in adults and adolescents. Of those, only study CP40563, the pivotal study, provides additional data to the clinical programme.

Furthermore, relative bioavailability between tablets and suspension was assessed in study T0813 and bioequivalence between tablets and granules in study T081G.

Bioanalytical methods

Population PK analysis

The population PK, PK-VK and TTAS2 models were performed using NONMEM. The population PK of Baloxavir was previously described by a three-compartment model whereas the updated PopPK model (based on a pooled dataset from Studies CP40563, T0822, T0833, T0831, T0832 and T0821) was adequately described by a two-compartment model with first-order absorption, first-order elimination and absorption lag-time. The following covariates were identified as statistically significant: Race (Asian vs. Non-Asian) on CL/F, V/F and Q/F; age on Ka; gender (female vs. male) on Ka; and body weight on CL/F, Q/F, Vc/F and Vp/F. Effect of body weight was allometrically scaled with estimated exponents of 0.467 and 0.887 for CL/F and Vc/F, which are generally lower exponents than the typical values of 1 for V and 0.75 for CL. IIV was estimated on Ka, TLAG, CL/F, Vd/F and Q/F whilst IIV was fixed to 15% on Vp/F. The residual error model was a combined proportional and additive error model. All fixed-effects parameters were estimated with good precision (RSE<15%) expect TLAG (39.6% RSE). IIV on CL/F and Vd/F was moderate, (45.6% and 45.7%, respectively), whilst shrinkage in these parameters were low (3.22%

and 6.04%, respectively). The low shrinkage in CL/F and Vd/F indicates that the model is suitable for deriving individual exposure metrics for exposure-response analysis. The final model was evaluated by means of RSEs, shrinkage, various GOF-plots and age stratified pcVPCs. Absorption

The to-be-marketed formulation is baloxavir marboxil granules for oral suspension (GfOS), 2 mg/mL. The same baloxavir marboxil granules 2% formulation is already approved in Japan, but the granules are packaged in a sachet instead of a bottle and the mode of administration differs slightly. In Japan, the granules (for clinical and commercial use) are intended for administration directly into the mouth of the subject together with an appropriate amount of water and swallowed or can be mixed with food or drink so patients can easily swallow the product. In the Roche/Genentech-sponsored studies, baloxavir marboxil granules 2% were constituted with water first to form an oral suspension and administered with an oral dispenser (syringe).In the PK studies, the plasma concentration of the prodrug baloxavir marboxil could not be quantified as the concentration was below the lower limit of quantification. Hence the concentration of the active substance was assessed.

The bioavailability for the oral suspension used in the phase 1 study was similar to the 20 mg tablet, Furthermore, bioequivalence between the granules 2% (sachet) and 20 mg marketed tablets was shown.

In study CP40563 intensive PK sampling in 19 children was conducted, and sparse PK sampling was conducted in 107 children. Furthermore, individual Bayesian post-hoc estimates from the population PK model were used to estimate PK parameters.

Overall, AUC0-inf, Cmax, C24, and C72 were comparable between children below 20 kg and above 20 kg and among the three Japanese studies, the pharmacokinetic parameters were also comparable between weight groups. However, between non-Asian and Asian subjects, the pharmacokinetic parameters were only comparable due to a lower weight-based dose in the Japanese subjects. The dose was ½ to 1/4 of the dose used in non-Asian population. This is further discussed under Special populations in section 2.1.9. Only, in study T0835, the proposed dose to be marketed in children was applied and this was in children < 10 kg.

When compared to adolescents and adults, AUC were overall similar, whereas the mean Cmax in non-Asian subjects < 12 years was 109 ng/ml and 83 ng/ml (< 20 kg and > 20 kg, respectively), and the mean Cmax was around 75 ng/ml in the highest dose group in adults and adolescents. The C24 and C72 were lower in children < 12 years compared with adults and adolescents.

Compared with non-Asian population, the C24 was higher in Asian population for the same weight-based doses (2 mg/kg, dose to be marketed).

Table 2: Mean (range) Bayesian-Estimated PK Parameters in Paediatric Studies (CP40563, T0822, T0833 and T085)

Study	Race	Dose	Dosing BW Range	Mean BW	N	$AUC_{0\text{-}Inf}$ (ng • hr/mL)	C_{max} (ng/mL)	C_{24} (ng/mL)	C_{72} (ng/mL)
CP40563	Non-Asian	2 mg/kg	≤20 kg	15.2	36	4050 [2080] (747-9280)	109 [55.3] (14.8-277)	55.7 [28.1] (9.25-134)	13.2 [7.15] (2.02-32.1)
CP40563 [a]	Non-Asian	40 mg	>20 kg	33.0	58	4390 [2080] (1290-12600)	83.2 [36.5] (16-167)	53.2 [22.4] (12.5-126)	17.9 [8.91] (6.25-52.9)
T0822	Asian	10 mg	≥10 to <20 kg	16.3	31	3630 [1420] (1420-8030)	58.8 [18.0] (27.6-109)	41.5 [13.9] (17.3-72.2)	14.8 [5.80] (6.11-30.1)
T0822	Asian	20 mg	≥20 to <40 kg	27.3	66	5120 [1710] (1260-10600)	77.3 [25.1] (26.8-141)	56.4 [18.1] (16.1-95.5)	21.9 [7.33] (5.2-43.6)
T0822	Asian	40 mg	>40 kg	45.8	8	7190 [2290] (5290-10500)	98.3 [35.6] (59.2-163)	76 [27.5] (51.4-113)	32.4 [10.2] (24.1-48.4)
T0833	Asian	1 mg/kg	<10 kg	8.03	12	5330 [1790] (2540-8470)	109 [34.2] (27-167)	68.6 [23.3] (22.6-101)	18.6 [7.70] (7.81-32.1)
T0833	Asian	10 mg	10 to <20 kg	14.5	21	4260 [1360] (1200-6460)	73.4 [24.8] (18.9-129)	49.7 [15.6] (12.7-76.6)	16.9 [5.33] (5.61-25.7)
T0835	Asian	2 mg/kg	<10 kg (≥ 3 months)	8.5	9	8750 [4000] (4520 -15900)	191 [72.7] (103-296)	110 [45.9] (60-193)	30.4 [15.3] (16.9-62.5)
T0835	Asian	20 mg	10 to <20 kg	15.1	34	7470 [2880] (3280-15200)	145 [57.3] (62.3-368)	93.6 [35.7] (37.7-176)	28.2 [10.9] (12.1-57.8)

BW = body weight; Mean PK parameters are presented with SD in square brackets and minimum and maximum values in parentheses reported to 3 significant figures.

[a] One Asian subject included in the Study CP40563 was removed from the summary statistics.

Note: The 5 mg dose group from T0822 is not shown due to low numbers in this dosing group (n = 2).

Source: Projects/Baloxavir_Influenza_30202/PopPK_peds_OwH/_FDA_RtQs/PK parameters by age and wt groups/Step 21/t_2ndPK_AsianNonAsian_Pediatrics.sas executed on 20210712T113032 (Patient PopPK Report, Appendix 35; CSR T0835 Appendix 16.1.9).

No new data on the influence of food was provided with the current application. In the initial application, it was indicated that food decreased the Cmax, AUC0-last, and AUC0-inf of baloxavir by 47%, 37%, and 37%, respectively. However, in the large phase II/III studies, the effect of food was minimal, and the efficacy was not affected by concomitant food intake. There is no reason to believe that food intake should affect the efficacy in children differently than in adults.

Distribution

In the adult studies, apparent volume of distribution differed markedly between non-Asian and Asian subjects. No additional data on the paediatric population was provided.

Elimination

Excretion: In adult studies clearance differed markedly between Asian and non-Asian subjects. In the paediatric studies, AUC was markedly higher in the Asian subjects than non-Asian subjects indicating a lower clearance in Asian paediatric subjects. The MAH has updated the SmPC with the relevant information in 5.2.

Metabolism: Baloxavir is the main metabolite of baloxavir marboxil and was assessed in the initial application. No additional data on metabolism were provided in the current application.

Dose proportionality and time dependencies

No additional information on dose proportionality was provided with the current application.

In the initial application data was indicative of linear pharmacokinetics. There are no reasons to believe that this should be different in the paediatric population.

Intra- and inter-individual variability

The estimated between patient variability (%CV) ranges from 45.6% to 113%.

Pharmacokinetics in the post exposure prophylaxis population

No PK studies in paediatric non-Asian subjects for post exposure prophylaxis were conducted. Hence, an extrapolation approach was used.

In the Asian adult population, similar PK between PEP and otherwise healthy and high risk subjects were seen for the same doses.

In the Asian paediatric population below 12 years, a numerically lower exposure was seen in the POP population compared with otherwise healthy, especially for the lower doses, which is considered caused by the sampling procedure. Hence, the PK is considered similar in the non-Asian PEP paediatric population and otherwise healthy non-Asian paediatric population.

Special populations

Impaired renal function: In the popPK model, creatinine clearance was not a significant covariate, hence, impaired renal function is not considered to impact the PK in paediatric subjects. In the initial application, it was shown that only 3.3% of baloxavir is recovered in the urine. No dose adjustment in patients (adults and paediatric patients) with impaired renal function is necessary, which is reflected in the SmPC.

Impaired hepatic function: In the popPK model, alanine aminotransferase, aspartate aminotransferase and bilirubin were not significant covariates. In the initial application, the MAH showed that in 8 subjects with moderate hepatic impairment, the mean Cmax was lower (20% decrease) and the AUC0-inf was higher (12% increase) than in 8 subjects with normal hepatic function. However, the differences were small and not considered clinically relevant, and no dose adjustment is considered necessary in adolescents and adults with mild or moderate hepatic impairment. The same can be expected for the paediatric population, in light of the metabolism and clearance of baloxavir.

Gender: In the initial application an 15% higher Cmax and a 7% higher AUC0-inf in women than in men were observed. This was not considered clinically relevant and no dose adjustment is required based on gender. In the popPK model, gender was a significant covariate for estimating ka. No dose adjustment by gender is considered necessary in children < 12 years either.

Race: When comparing data between Asian and non-Asian paediatric studies, a doubling in exposure is observed in Asian subjects compared with non-Asian subjects, or a similar exposure with half the dose has been observed in Japanese subjects as shown in Table 2 above. Predicted values of AUC, Cmax and C24 also showed a marked difference between Asian and non-Asian subjects – especially for AUCinf, where the predicted exposure in Asian subjects were doubled the expose in non-Asian subjects (Table 3). The difference was not as marked in adult subjects. This issue was explored in detail in the initial MAA and a correlation between plasma exposures and safety has not been established. Hence, this issue will not be pursued further.

Table 3: Impact of Age, Body Weight, Race, and Gender on the Predicted Mean Baloxavir AUC_{inf}, C_{max}, and C_{24} following Administration of a Single Oral Dose of Baloxavir Marboxil (2 mg/kg for Patients <20 kg and 40 mg for Patients ≥20 kg)

Age (y)	Body Weight (kg)	Dose	Race	Predicted mean AUC_{inf} (ng•hr/mL)	Gender	C_{max} (ng/mL)	C_{24} (ng/mL)
0.5	7	2 mg/kg	Non-Asian	3723	Male	96.8	47.0
					Female	92.9	48.2
0.5	7	2 mg/kg	Asian	7507	Male	152	87.1
					Female	147	88.8
3	15	2 mg/kg	Non-Asian	5589	Male	117	64.5
					Female	114	65.2
3	15	2 mg/kg	Asian	11269	Male	180	114
					Female	176	115
10	30	40 mg	Non-Asian	5392	Male	88.8	55.3
					Female	87.1	55.7
10	30	40 mg	Asian	10870	Male	136	94.3
					Female	134	94.8
37	70	40 mg	Non-Asian	3630	Male	43.4	30.7
					Female	43.0	30.8
37	70	40 mg	Asian	7318	Male	66.0	50.5
					Female	65.5	50.6

AUC_{inf}: area under the plasma concentration-time curve (ng•hr/mL) from time 0 to infinity; C_{max} = maximal baloxavir concentration (ng/mL) ; C_{24} = baloxavir concentration at 24 hours (ng/mL).

Weight: Bodyweight was a significant covariate in the popPK model, and the dose is based on body weight in children weighing less than 20 kg.

Elderly: Not relevant for the current indication that includes children from 1-12 years of age.

Pharmacokinetic interaction studies

No new interaction studies were provided with the current application. The drug-drug interaction in children from 1-12 years is considered similar to the drug-drug interaction in adolescents and adults.

Pharmacokinetics using human biomaterials

No additional interaction studies were conducted using human biomaterials.

2.6.2.2. Pharmacodynamics

Mechanism of action

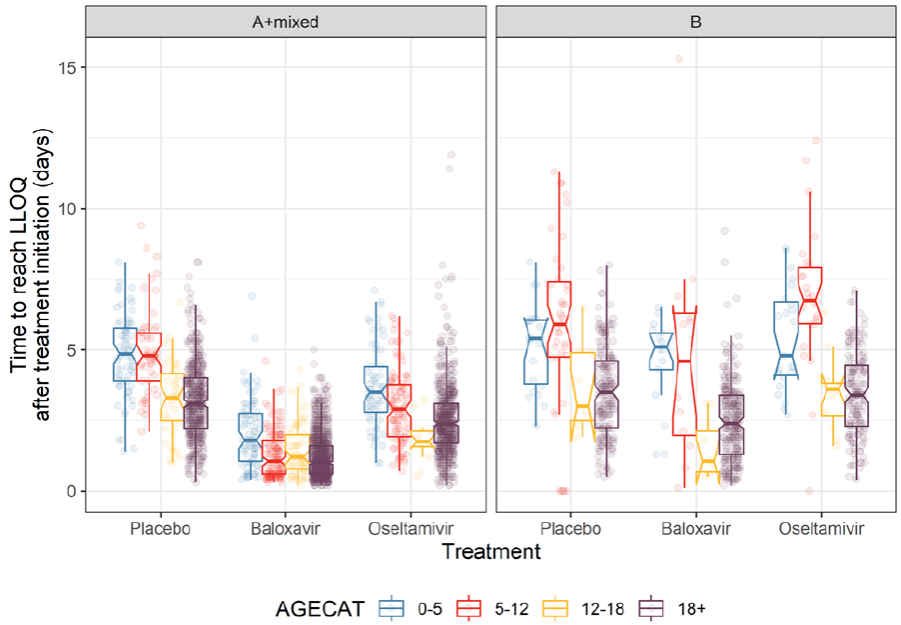
Baloxavir marboxil is a prodrug and is converted pre-systemically to the active form (baloxavir) through metabolism (hydrolysis). The active form selectively inhibits the cap-dependent endonuclease, an influenza virus-specific enzyme in the polymerase acidic subunit of the viral RNA polymerase complex, which thereby inhibits influenza virus replication.

Primary and Secondary pharmacology

No new clinical PD studies were performed, but the MAH developed two models: PK-VK (viral kinetics) model to estimate the effect of baloxavir and oseltamivir on viral load and PK-TTAS2 (symptom alleviation) in order to analyse exposure-response.

Primary pharmacology

Based on the results from the PK-VK model, the effect of baloxavir is similar across age groups for virus type A+ mixed and B, although a high variation is present for virus B and the results should be interpreted with caution (Figure 1 and Figure 2).

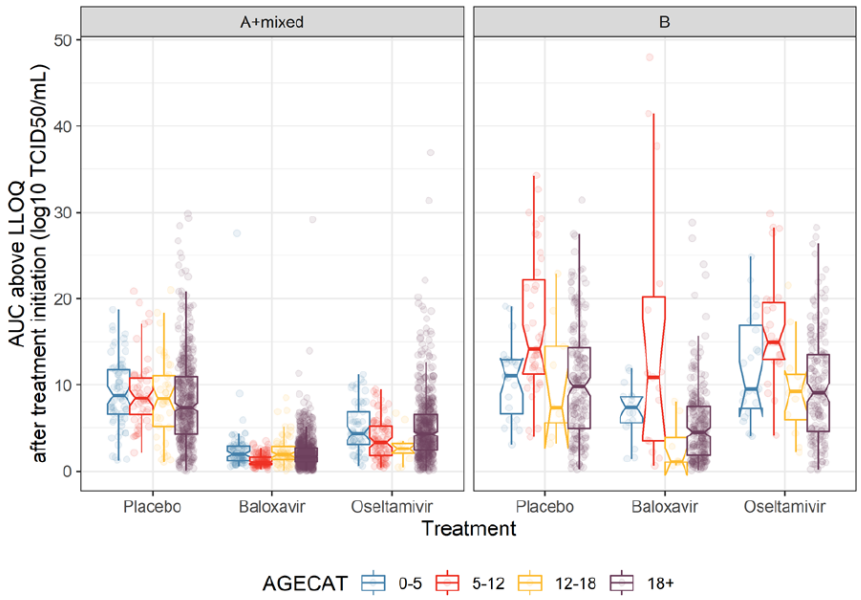


AGECAT=age category; LLOQ=lower limit of quantification

Source: 1112254

Note: The dots are the derived individual values, the upper and lower side of the box represent the Inter-quartile range (IQR); ie, 1st and third quartiles. The whiskers represent the 1.5.IQR interval and the notches represent the CI of the median.

Figure 1: Time to Reach the Viral Titer LLOQ by Age Group and Virus Type



AGECAT=age category; AUC=area under curve (Viral Titer AUC); LLOQ=lower limit of quanification; TCID=tissue culture infective dose

Source: 1112254

Note: The dots are the derived individual values, the upper and lower side of the box represent the Inter-quartile range (IQR); ie, 1st and third quartiles. The whiskers represent the 1.5.IQR interval and the notches represent the CI of the median.

Figure 2: Viral Titer AUC per Treatment and Virus Type

Secondary pharmacology:

No new information was provided with the current application. In the initial application, a dedicated QTc study was conducted that did not show prolongation of the QTc. No difference between adults and children is expected with regards to QTc.

Exposure-response and exposure-safety

Based on the PK-TTAS model, no differences between high and low exposure groups were seen in relation to Time to alleviation of signs and symptoms (Figure 3).

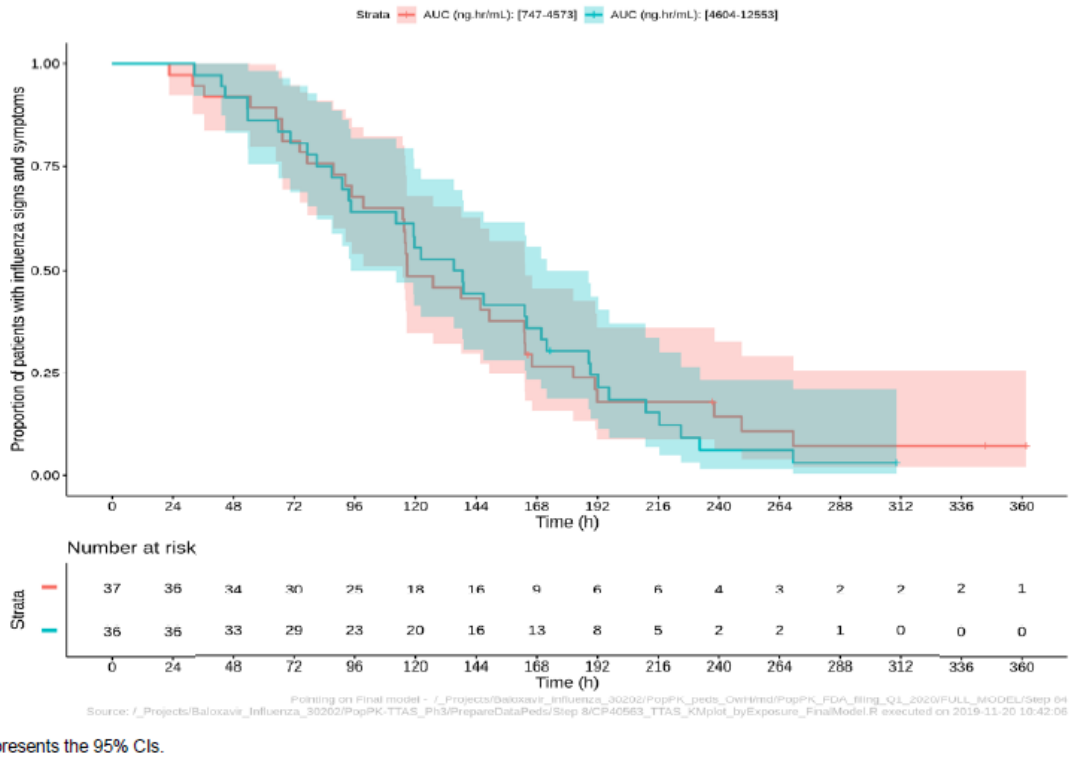


Figure 3: Kaplan-Meier Plot of TTAS by Low or High Baloxavir Exposure Category and Associated Number of Patients at Risk over Time (PK/PD Population)

Numerically higher adverse event rate was observed in the low exposure arm for both Cmax and AUC (see section 3.4.1). It is not likely that the marginally higher Cmax seen in the paediatric population will turn into a higher risk of adverse events in this population compared with the adult population.

2.6.3. Discussion on clinical pharmacology

Baloxavir marboxil is a prodrug and is converted pre-systemically to the active form (baloxavir) through metabolism (hydrolysis). The active form selectively inhibits the cap-dependent endonuclease, an influenza virus-specific enzyme in the polymerase acidic subunit of the viral RNA polymerase complex, which thereby inhibits influenza virus replication.

PK and PD in adults and adolescents were assessed at the primary submission.

To support the clinical pharmacology of the present extension of indication in children from 1-12 years of age, the MAH has submitted 4 studies in children below 12 years of age and 3 studies in adults and adolescents. Furthermore, population PK models were updated and for the assessment of pharmacodynamics, two models were developed: PK-VK (viral kinetics) model to estimate the effect of baloxavir and oseltamivir on viral load and PK-TTAS2 (symptom alleviation) in order to analyse exposure-response.

Overall, the pharmacology programme to support the paediatric indication is considered acceptable.

The population PK of Baloxavir was previously described by a three-compartment model whereas the updated PopPK model was adequately described by a two-compartment model with first-order absorption, first-order elimination and absorption lag-time. The following covariates were identified as statistically significant: Race (Asian vs. Non-Asian) on CL/F, V/F and Q/F; age on Ka; gender (female

vs. male) on Ka; and body weight on CL/F, Q/F, Vc/F and Vp/F. TLAG was estimated with high imprecision (39.6 RSE). IIV on Ka and TLAG was high (113% and 62.6%, respectively). Ka and TLAG were estimated with good precision but shrinkage was high (41.8% and 92.3%, respectively), hence the information for these effects should be interpreted with caution, although oral absorption parameters often have high IIV and shrinkage.

A new formulation, baloxavir marboxil granules 2%, was developed for the extension of the indication to be used in children, and bioequivalence between the to-be-marketed formulation of baloxavir marboxil granules 2% and 20 mg tablets was demonstrated.

PK in children was estimated from intensive PK sampling in 19 children and sparse PK sampling in 107 children in the pivotal study in which non-Asian subjects were included. Furthermore, PK was assessed in Japanese children. PK was overall similar to PK in adults and adolescents, however, the distribution volume was lower in Japanese children than non-Asian children, and in adults the clearance was lower in Japanese subjects. The difference was not as marked in adult subjects. This issue was explored in detail in the initial MAA and a correlation between plasma exposures and safety has not been established. Hence, this issue will not be pursued further.

The clearance was lower in subjects with lower bodyweight. In the SmPC clearance is stated to be 79.1 hours in Caucasian subjects. In paediatric non-Asian subjects, the mean T½ are 29.4 in children <12 years and 50.3 in adolescents. This is reflected in the SmPC.

PK in the PEP population was not assessed in non-Asian subjects. In the Asian population, a numerically lower exposure was seen in the PEP population than in otherwise healthy especially for the lower doses, which is considered to be due to the sampling procedure.

No studies in children with impaired renal or hepatic function was conducted. As only 3.3% of baloxavir is excreted by the kidney, the lack of data in children is acceptable. However, in adults with moderate hepatic impairment, a 20% lower Cmax but an 12% higher increase in AUC 0-inf were seen. This was considered clinically irrelevant in adolescents and adults. The same can be expected for the paediatric population, in light of the metabolism and clearance of baloxavir.

Bodyweight was a significant covariate in the popPK models, and a few OCs has been raised. The dose is depended on body weight in children below 20 kg, which is acceptable. No dose-adjustment is needed based on gender.

No new interaction studies have been conducted. This is acceptable as no differences in drug-drug interaction are expected between adults and children.

Regarding pharmacodynamics, the PK-VK study showed that the effect of baloxavir is similar across age groups (0-5 years, 5-12 years, 12-18 years and 18+ years) for virus type A+ mixed and B, although a high variation is present for virus B and the results should be interpreted with caution. In the exposure response analysis of TTAS2, no differences in TTAS2 were seen between the low and high exposure group. In the exposure-safety analyses, no indications of a higher incidence of adverse events with a higher exposure were seen. In contrast that rate was numerically lower among the highest exposure group.

In the adult population, a dedicated QTc study was conducted that did not show prolongation of the QTc. No difference between adults and children is expected.

No new information regarding pharmacodynamic interaction was provided with the current application. In the initial application, a preclinical study showed a synergistically effect of baloxavir and neuraminidase inhibitor. In a clinical study, the pharmacokinetic interaction between baloxavir and oseltamivir was examined in healthy subjects, and a small but clinically irrelevant increase in

oseltamivir exposure was observed. The pharmacodynamic interaction between baloxavir and oseltamivir was not evaluated.

2.6.4. Conclusions on clinical pharmacology

Overall, the pharmacology of baloxavir marboxil in children is adequately described.

2.6.5. Clinical efficacy

Baloxavir marboxil has been approved in the European Union for the treatment and post-exposure prophylaxis (PEP) of influenza in individuals 12 years of age and older.

The Applicant has submitted a type II variation for an extension of the indication for baloxavir marboxil for the treatment of uncomplicated influenza and PEP of influenza to paediatric patients aged 1 to <12 years.

The application also includes an extension of the marketing authorisation to introduce Xofluza granules for oral suspension, 2 mg/ml as a new pharmaceutical form.

The proposed indications are as follows:

- Xofluza is indicated for the treatment of uncomplicated influenza in patients aged 1 year and above.
- Xofluza is indicated for post-exposure prophylaxis of influenza in individuals aged 1 year and above.

The efficacy evaluation is divided in two parts; first, the efficacy of baloxavir marboxil as a treatment of influenza infection is evaluated, second, the efficacy of baloxavir marboxil as post-exposure prophylaxis is evaluated in a separate section.

Clinical efficacy in the treatment indication

The efficacy evaluation of baloxavir marboxil used for treatment in paediatric patients with influenza is primarily based on data from one pivotal randomized double-blind Phase 3 study. Study CP40563 was a global Phase 3, multicenter, randomized, double-blind, active-controlled study to assess the safety, pharmacokinetics, and efficacy of baloxavir marboxil granules compared with oseltamivir in otherwise healthy (OwH) paediatric patients 1 to <12 years of age with influenza-like symptoms.

Supporting data are provided from three non-controlled, single-arm Phase 3 studies conducted exclusively in the Japanese population. As the study designs, dosing regimens, and endpoints of the three supportive studies were different to those of the pivotal study, the efficacy data from the four studies have not been pooled. The assessment of the indication for treatment in paediatrics with influenza will focus on study CP40563.

Table 4: Summary of Clinical Studies Contributing to the Efficacy Evaluation of Baloxavir Marboxil in Paediatric Patients

Study No.	Study Design	Dose and Regimen	Efficacy Endpoints	No. Patients
Pivotal Pediatric Study:				
CP40563 (Phase 3)	Multicenter, randomized, double-blind, active-controlled study in OwH pediatric patients (1 to < 12 years) with influenza-like symptoms	Baloxavir marboxil (granules for oral suspension) single dose according to body weight: • < 20 kg: 2 mg/kg • ≥ 20 kg: 40 mg Oseltamivir (powder for oral suspension) BID for 5 days according to body weight: • ≤ 15 kg: 30 mg BID • >15 kg to 23 kg:45 mg BID • >23 kg to 40 kg:60 mg BID • > 40 kg:75 mg BID	**Key Clinical Efficacy Endpoints** • Time to alleviation of influenza signs and symptoms • Time to alleviation of individual symptoms • Duration of fever • Duration of symptoms • Time to return to normal health and activity • Frequency of influenza-related complications • Proportion of patients requiring antibiotics **Key Virology Efficacy Endpoints** • Time to cessation of viral shedding by virus titer • Time to cessation of viral shedding by RT-PCR • Change from baseline in influenza virus titer at each time point • Proportion of patients with positive influenza virus titer at each timepoint **Other Endpoints** • Polymorphic and treatment-emergent amino acid substitutions in the PA, PB1, PB2, and NA genes	**Randomized:** 176 (baloxavir marboxil 117; oseltamivir 59) **ITTI**: 124 (baloxavir marboxil 81, oseltamivir 43)

Table 5: Summary of Supportive Clinical Studies

Study No.	Study Design	Dose and Regimen	Study Objectives	No. Patients
Supportive Pediatric Studies:				
1618T0822 (Phase 3)	Multicenter (Japan only), open-label, non-controlled study in OwH pediatric patients (6 months to <12 years) with acute uncomplicated influenza	Baloxavir marboxil (10 and 20 mg tablets): single dose according to body weight: • 5 to < 10 kg: 5 mg • 10 to < 20 kg: 10 mg • 20 to < 40 kg: 20 mg • ≥ 40 kg: 40 mg	• To assess the safety and tolerability of a single dose of baloxavir marboxil • To assess the PK of baloxavir marboxil and its active form baloxavir after single-dose administration and to confirm appropriateness of the dose in pediatric patients • To assess the efficacy of baloxavir marboxil after single-dose administration	**Treated patients**: 107 **Safety Population:** 107 **ITTI**: 104
1705T0833 (Phase 3)	Multicenter (Japan only), open-label, non-controlled study in OwH pediatric patients (weighing < 20 kg and aged < 12 years) with acute uncomplicated influenza	Baloxavir marboxil (2% granules): single dose according to body weight: • < 10 kg: 1 mg/kg • 10 to < 20 kg: 10 mg	• To assess the safety and tolerability of a single dose of baloxavir marboxil 2% granules • To assess the PK of baloxavir marboxil and its active form baloxavir after single-dose administration of baloxavir marboxil 2% granules • To assess the efficacy of a single dose of baloxavir marboxil 2% granules	**Enrolled, Safety Population and ITTI**: 33
1813T0835 (Phase 3)	Multicenter (Japan only), open-label, non-controlled study in OwH pediatric patients aged less than 12 years and weighing less than 20 kg with acute uncomplicated influenza	Baloxavir marboxil (2% granules): single dose according to age and body weight: • < 10 kg (< 3 months): 1 mg/kg • < 10 kg (≥ 3 months): 2 mg/kg 10 to < 20 kg: 20 mg	• To assess the safety and tolerability of a single dose of baloxavir marboxil 2% granules • To assess the PK of baloxavir marboxil and its active form baloxavir after single dose administration of baloxavir marboxil 2% granules • To assess the efficacy of a single dose of baloxavir marboxil 2% granules	**Enrolled and ITTI:** 43 **Safety Population (all baloxavir marboxil):** 45

The studies have been conducted in compliance with the PIP.

2.6.5.1. Dose response studies

The safety and efficacy of baloxavir marboxil in adult and paediatric patients with influenza virus infection have been demonstrated in previous studies using baloxavir marboxil 10-mg and 20-mg tablets.

In this study, baloxavir marboxil was administered as granules for suspension. Bioequivalence of the suspension and the 20-mg tablet was confirmed in a previous study (Study 1703T081G).

The doses of baloxavir marboxil in this study were determined using PK simulations in a Caucasian paediatric population.

The optimal dose and body weight cut-off for flat dosing were based on a comparison of the simulated drug exposures with those obtained in the following 3 studies:

- Phase III Study 1601T0831 for adolescent and adult otherwise healthy patients,
- Paediatric Phase III Study 1618T0822, and
- Phase I thorough corrected QT interval (QTc) Study 1527T0816.

Model-based simulations (accounting for ethnic effect as well as bodyweight) indicated a regimen of 2 mg/kg up to 20 kg and 40 mg above 20 kg could be expected to mimic adult drug exposure adequately in terms of AUC_{inf}, C_{24} and C_{72}, while containing C_{max} below the upper limit of exposure achieved and confirmed to be safe in humans in previous studies.

Based on these results, in this study, baloxavir marboxil was administered based on patient body weight at screening (i.e., 2 mg/kg for patients weighing < 20 kg or 40 mg for patients weighing ≥ 20 kg).

2.6.5.2. Main study for treatment indication

Study CP40563: (miniSTONE-2) A Multicenter, Randomized, Double-Blind, Active (Oseltamivir)-Controlled Study to assess the Safety, Pharmacokinetics, and Efficacy of Baloxavir Marboxil in Otherwise Healthy Paediatric Patients 1 to < 12 Years of Age with Influenza-Like symptoms

Methods

Study Participants

Inclusion Criteria

Patients had to meet the following criteria for study entry:

- Written informed consent/assent for study participation obtained from patient's parents or legal guardian, with assent as appropriate by the patient, depending on the patient's level of understanding
- Aged 1 to < 12 years at randomization (Day 1)
- Parent/guardian willing and able to comply with study requirements, in the investigator's judgment
- Patient able to comply with study requirements, depending on the patient's level of understanding

- Patient with a diagnosis of influenza virus infection confirmed by the presence of all of the following:
    - Fever ≥ 38°C (tympanic temperature) at screening
    - At least one respiratory symptom (either cough or nasal congestion)
- The time interval between the onset of symptoms and screening was ≤48 hours (the onset of symptoms was defined as the time when body temperature first exceeded 37.5°C if known, or the time when the first symptom was noticed by patient, parent, or caregiver)

Exclusion Criteria

Patients who met any of the following criteria were excluded from study entry:

- Severe symptoms of influenza virus infection requiring inpatient treatment
- Concurrent infections requiring systemic antiviral therapy at screening
- Required, in the opinion of the investigator, any of the prohibited medication during the study
- Previous treatment with peramivir, laninamivir, oseltamivir, zanamivir, or amantadine within 2 weeks prior to screening
- Immunization with a live/attenuated influenza vaccine in the 2 weeks prior to randomization
- Concomitant treatment with steroids or other immuno-suppressant therapy
- Known HIV infection or other immunosuppressive disorder
- Uncontrolled renal, vascular, neurologic, or metabolic disease (e.g., diabetes, thyroid disorders, adrenal disease), hepatitis, cirrhosis, or pulmonary disease or patients with known chronic renal failure
- Active cancer at any site
- History of organ transplantation
- Known allergy to either study drug (i.e., baloxavir marboxil and oseltamivir) or to acetaminophen
- Females who had commenced menarche (i.e., child-bearing potential)
- Participation in a clinical trial within 4 weeks or five half-lives of exposure to an investigational drug prior to screening, whichever was longer

The inclusion- and exclusion criteria in the study selected a healthy population without either acute or chronic illnesses. The inclusion- and exclusion criteria are appropriate for the sought indication of treatment of uncomplicated influenza.

Treatments

Baloxavir Marboxil and Placebo

Baloxavir marboxil was provided as granules for oral suspension; administered orally as a single dose on Day 1 only. The granules for oral suspension were reconstituted with water by site staff to provide a

2 mg/mL suspension. A dose was administered based on the body weight of the child (2 mg/kg for patients weighing < 20 kg, or 40 mg for patients weighing ≥ 20 kg).

The baloxavir marboxil matching placebo was provided as granules for oral suspension and was administered orally on Day 1 only.

Oseltamivir and Placebo

Oseltamivir was administered orally BID (morning and evening) for 5 days. The powder for suspension was reconstituted by site staff with water to provide a suspension of 6 mg/mL. A dose was administered based on the body weight of the child.

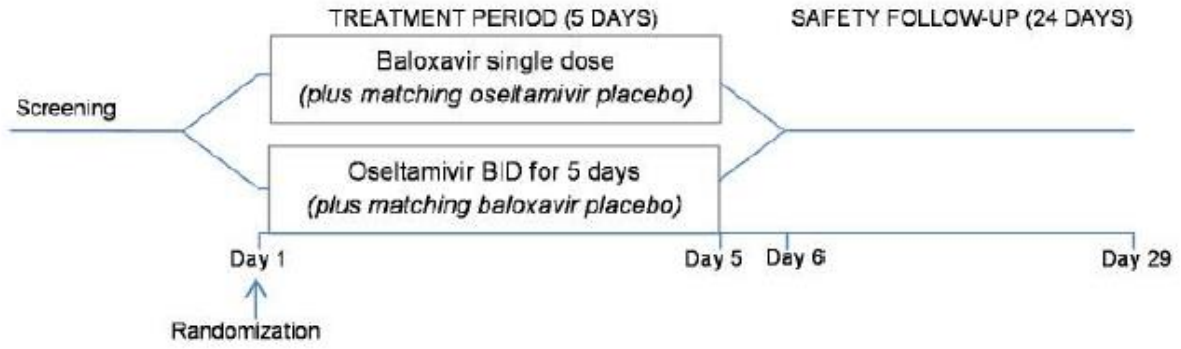
The body weight-adjusted dosing regimen for children aged 1 to 12 years was as follows:

- < 15 kg: 30 mg BID
- > 15 kg to 23 kg: 45 mg BID
- > 23 kg to 40 kg: 60 mg BID
- > 40 kg: 75 mg BID

The oseltamivir matching placebo powder was an oral suspension and was administered orally BID (morning and evening) for 5 days.

Rescue medication

Paracetamol use was permitted between Days 1 and 29 for the relief of severe influenza symptoms at a dose appropriate to the weight and age of the child. The use of the following drugs was prohibited from Day 1, after administration of study drug, until study completion or early termination: systemic antiviral drugs, antipyretics/analgesics (except acetaminophen), corticosteroids (injection, oral, or inhalation formulations), and immunosuppressants.



Baloxavir = baloxavir marboxil; BID = twice daily.
Note: The baloxavir marboxil dose was based on the body weight of the child (2 mg/kg for patients weighing < 20 kg or 40 mg for patients weighing > 20 kg). Oseltamivir was administered per the Tamiflu® local prescribing information.

Figure 4: Overview of Study Design of Pivotal Paediatric Study CP40563

The choice of Oseltamivir as comparator is acceptable as an EU-approved medicinal product indicated for "*treatment of in adults and children including full term neonates who present with symptoms*

typical of influenza, when influenza virus is circulating in the community. Efficacy has been demonstrated when treatment is initiated within two days of first onset of symptoms"

The study medication is adequately described. The choice of paracetamol as rescue medication is acceptable. However, the evaluation of acetaminophen use was not described in the dossier. Since the acetaminophen use could confound the efficacy results, the applicant has been asked to elaborate on how the antipyretic effect has been considered. Further, the MAH has been asked to provide information on paracetamol use in both study arms over time and to provide a sensitivity analysis accounting for (the differences in) the use of rescue medication in the main efficacy outcome by for example preparing a composite endpoint of alleviation of symptoms in the absence of rescue medication use. The results are provided in the paragraph "Ancillary analyses.

Objectives

The primary objective of the study was to compare the safety of a single dose of baloxavir marboxil with the safety of 5 days of oseltamivir administered BID. Evaluation of the clinical efficacy and virological activity of baloxavir marboxil compared with oseltamivir were secondary objectives.

The efficacy secondary objective was to evaluate the clinical efficacy of baloxavir marboxil compared with oseltamivir.

Outcomes/endpoints

Efficacy was a secondary objective in the study, no primary efficacy endpoint was specified.

The key clinical and virology efficacy endpoints in Study CP40563 are defined in Table *6* and Table 7, respectively. With exception of duration of fever, all time-to-event clinical efficacy endpoints are based on responses to the CARIFS questionnaire.

The clinical and virology efficacy data are summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Time-to-event endpoints and duration endpoints are summarised using Kaplan-Meier plots and summaries of the median survival time with the 95% confidence interval (CI). In all time-to-event analyses, patients who did not experience the event of interest prior to completion or withdrawal from the study were censored at the last observation time point.

Table 6: Pivotal Study CP40563: Definitions of Key Clinical Efficacy Endpoints

Endpoint	Definition
TTAS (hours) [a]	The time from the start of study treatment to the point at which all of the following criteria were met and maintained for at least 21.5 hours: a score of 0 (no problem) or 1 (minor problem) for cough and nasal symptoms (items 14 and 15, respectively) in the CARIFS questionnaire. a "yes" response to the CARIFS question, "*Since the last assessment, has the subject been able to return to day care/school or resume his or her normal daily activity in the same way as performed prior to developing the flu?*" [a] first return to afebrile state (tympanic temperature ≤ 37.2°C). Patients with symptom scores ≤ 1 for items 14 and 15, a tympanic temperature ≤ 37.2°C, and a "yes" response to the CARIFS question on return to normal health and activity at baseline had all symptoms set to missing. Baseline was defined as the first CARIFS assessment after the start of treatment on Day 1. If a score of 4 ("do not know" or "not applicable") occurred at any assessment during the study for items 14 or 15, the assessment was not included in the calculation of the alleviation of symptoms because the assessment was unobservable.
Duration of fever (hours)	The time from the start of study treatment to the time when the patient had returned to an afebrile state [tympanic temperature ≤ 37.2°C] for at least 21.5 hours.
Duration of symptoms (hours)	The time from the start of study treatment to the point at which all 18 symptoms specified in the CARIFS questionnaire had been alleviated (as defined by a score of 0 [no problem] or 1 [minor problem]) for at least 21.5 hours. If a score of 4 ("do not know" or "not applicable") occurred at any assessment during the study for any item, with the exception of items 10, 11 and 12, the assessment was not included in the calculation of the alleviation of symptoms because the assessment was unobservable. However, if a score of 4 occurred for items 10, 11 or 12, the assessment was included with a score of missing for these items.
Duration of individual symptoms (hours)	The time from the start of study treatment to alleviation of the symptom specified in the CARIFS questionnaire (as defined by a score of 0 [no problem] or 1 [minor problem]). Assessed for all 18 symptoms: poor appetite; not sleeping well; irritable, cranky, fussy; feeling unwell; low energy, tired; not playing well; crying more than usual; needing extra care; clinginess; headache; sore throat; muscle aches or pains; fever; cough; nasal congestion, runny nose; vomiting; not interested in what's going on; unable to get out of bed. Patients with an individual symptom score ≤1 at baseline had the duration of that symptom set to missing.
Time to return to normal health and activity	The time from the start of study treatment to the point at which the following was obtained: a "yes" response to the CARIFS question, "*Since the last assessment, has the subject been able to return to day care/school or resume his or her normal daily activity in the same way as performed prior to developing the flu?*"

Table 6: Pivotal Study CP40563: Definitions of Key Clinical Efficacy Endpoints (cont.)

Endpoint	Definition
Frequency of influenza-related complications	Influenza-related complications included death, hospitalization, radiologically-confirmed pneumonia, bronchitis, sinusitis, otitis media, encephalitis/encephalopathy, febrile seizures, and myositis as recorded in the relevant influenza-related complications section of the AE pages of the eCRF based on predefined diagnostic criteria.
Proportion of patients requiring antibiotics	The number (%) of patients requiring antibiotics for any reason.

AE = adverse event; CARIFS = Canadian Acute Respiratory Illness and Flu Scale; eCRF = electronic case report form; TTAS = time to alleviation of influenza signs and symptoms.

[a] sensitivity analysis of TTAS was carried out post hoc to evaluate the impact of the "*return to normal health and activity*" component, in which the second criterion was removed.

Table 7: Pivotal Study CP40563: Definitions of Key Virology Efficacy Endpoints

Endpoint	Definition
Time to cessation of viral shedding by virus titer [a]	The time from the start of study treatment to the time at which the virus titer fell below the limit of detection for the first time. Only patients with a positive virus titer on Day 1 were included in the analysis.
Time to cessation of viral shedding by RT-PCR [b]	The time from the start of study treatment to the time at which the virus RNA by RT-PCR fell below the lower limit of detection for the first time. For patients with multiple virus types, this endpoint was defined as the time between the initiation of the study treatment and first time when the virus RNA by RT-PCR was below the limit for all virus types. Only patients positive for virus RNA by RT-PCR on Day 1 were included in the analysis.
Change from baseline in influenza virus titer at each time point [a]	The change from baseline in influenza virus titer on Days 2, 4, 6, and 10. If influenza virus titer was less than the lower limit of quantification, the virus titer was imputed as 0.749 (log_{10} $TCID_{50}$/mL). Only patients with a positive virus titer on Day 1 were included in the analysis.
Proportion of patients with positive influenza virus titer at each time point [a]	The number (%) of patients whose influenza virus titer was not less than the lower limit of quantification or positive among those assessed for influenza virus titer on Days 2, 4, 6, and 10. Only patients with a positive influenza virus titer on Day 1 were included in the analysis.

RNA = ribonucleic acid; RT-PCR= reverse transcription polymerase chain reaction; $TCID_{50}$ = 50% tissue culture infective dose.

[a] For virus titer, the lower limit of detection and the lower limit of quantification were both 0.75 log_{10} $TCID_{50}$/mL.

[b] For RT-PCR, the lower limits of detection and quantification were 2.05 and 2.13 log_{10} virus particles/mL, respectively, for flu A, and 2.83 and 2.93 log_{10} virus particles/mL, respectively, for flu B.

Other Endpoints

Drug Susceptibility at Baseline

The 50% effective concentration (EC_{50}) of baloxavir at baseline was determined by Virospot™ assay and the ratio relative to the EC_{50} of the corresponding reference strain (EC_{50} / EC_{50} reference) was

calculated. The following influenza virus vaccines strains from the 2018-2019 season were used as references:

- **A/H1N1:** A/Michigan/45/2015 (H1N1)pdm09.
- **A/H3N2:** A/Singapore/INFIMH-16-0019/2016 for samples from the Northern hemisphere and A/Switzerland/8060/2017 for samples from the Southern hemisphere.
- **Type B:** B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage) and B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage). The mean EC_{50} value of the two B reference strain EC_{50} values was used to calculate the EC_{50} ratio.

The 50% inhibitory concentration (IC_{50}) of oseltamivir acid at baseline was determined by NA-star® assay and the ratio relative to the IC_{50} of the corresponding reference strain (IC_{50} / IC_{50} reference) was calculated. The following influenza virus strains were used as references:

- **Type A:** A/Puerto Rico/8/34.
- **Type B:** B/Lee/40.

Treatment-emergent Amino Acid Substitutions in the PA, PB1, PB2, and NA Genes

Sanger sequencing of the PA gene was performed for all patients with paired (pre- and post-dose) samples available at baseline and at the last evaluable time point (last sample with >4 log_{10} viral particles/mL).

For patients with an amino acid substitution in the PA gene, additional sequencing was performed for all earlier time point samples to evaluate the time point of emergence of the amino acid substitution.

Sanger sequencing of the PB1 and PB2 genes was performed on samples selected according to the following criteria:

- baseline viruses with reduced susceptibility to baloxavir (fold-change in EC_{50} > 10 for type A viruses and > 5 for type B viruses compared to reference virus in phenotypic assay).
- viruses (baseline and last evaluable time point) without amino acid substitution in the PA gene, but with reduced response to treatment or with virus rebound.

The NA gene was sequenced for all oseltamivir-treated patients with paired (pre- and post-dose) samples available at baseline and the last evaluable time point (last sample with > 4 log_{10} viral particles/mL).

Sample size

No formal sample size calculations have been performed in this study. 80 patients in the baloxavir marboxil treatment group and 40 patients in the oseltamivir treatment group were planned to be recruited to detect adverse events with a 3% incidence for at least 1 patient with a probability of ≥ 90%.

Randomisation and blinding (masking)

Patients were recruited in parallel to the following two cohorts:

- 5 to < 12 years of age (minimum 40 patients)

- 1 to < 5 years of age (minimum 20 patients)

Patients were subsequently randomized on a permuted block basis in a 2:1 ratio to receive either baloxavir marboxil or oseltamivir.

Study site personnel and patients was blinded to treatment assignment during the study. The Sponsor and its agents were also blinded to treatment assignment, with the exception of individuals who required access to patient treatment assignments to fulfill their job roles during a clinical trial.

Statistical methods

Analysis population

The intent-to-treat-infected (ITTi) population is a subset of ITT patients who have had a laboratory confirmation of influenza infection (polymerase chain reaction [PCR] result) from any swab sample collected at baseline or during the study. The ITTi population is the primary efficacy population, unless specified otherwise. Patients will be grouped based on randomised treatment.

Decisions on patient exclusion from the ITTi population will be made prior to database closure. Excluded patients will be documented, together with the reason for exclusion.

As in prior treatment studies that have supported NAI approvals, the primary efficacy analysis was conducted in the ITTI population, comprising all treated subjects with a positive RT-PCR on day 1 or during the study period.

Relevant post-hoc subgroup analyses on co-infection, age (1-5 years and 5-<12 years), gender, and vaccination status were provided on request during the assessment procedure.

Results

Participant flow

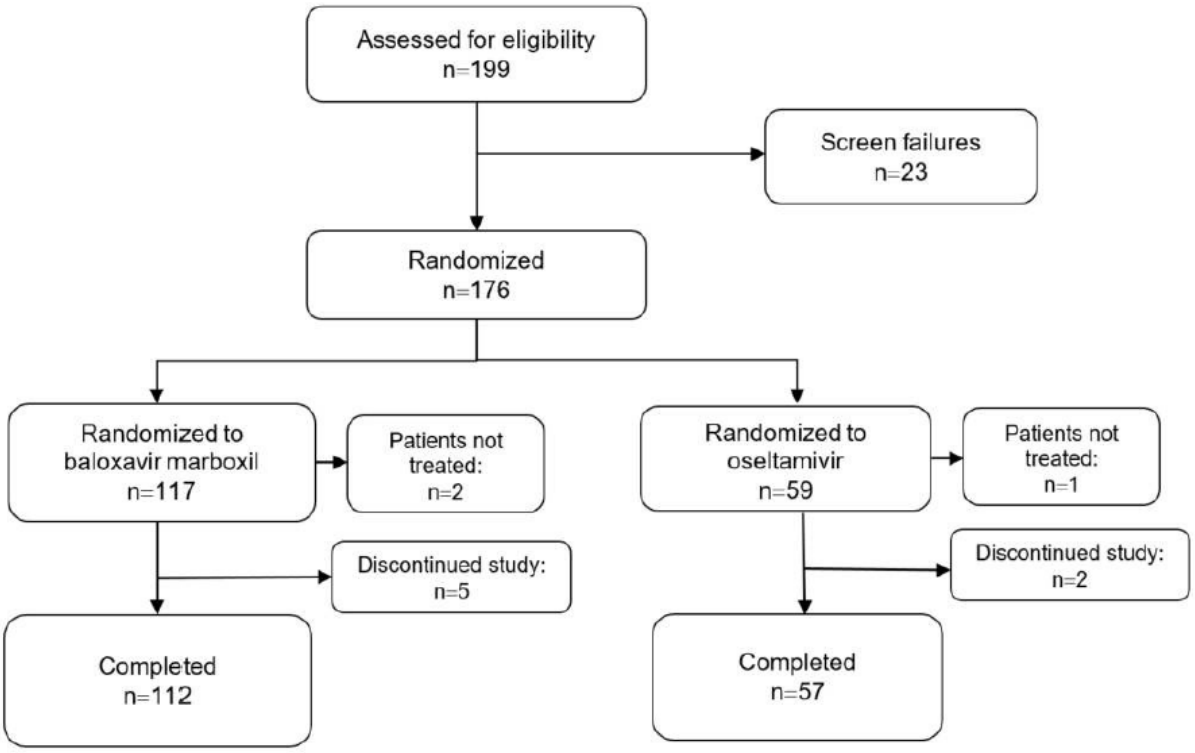


Figure 5: Summary of Patient Disposition

The efficacy analysis was based on the ITTI population. This included all patients who received any portion of a single dose and who had a laboratory confirmation of influenza infection (RT-PCR result) from any swab sample collected at baseline or during the study. It comprised 124 randomized patients (81 [69.2%] in the baloxavir marboxil group and 43 [72.9%] in the oseltamivir group).

3 patients were excluded from the safety population (not dosed) and in total 173 patients were evaluable for safety (115 baloxavir marboxil and 58 oseltamivir).

Table 8: Summary of Analysis Population (Randomised Patients)

Analysis Population	Baloxavir Marboxil (N=117)	Oseltamivir (N=59)	All Patients (N=176)
Randomized Population	117 (100%)	59 (100%)	176 (100%)
Intent-to-Treat Population	115 (98.3%)	58 (98.3%)	173 (98.3%)
Not Treated	2 (1.7%)	1 (1.7%)	3 (1.7%)
Intent-to-Treat Influenza-Infected Population	81 (69.2%)	43 (72.9%)	124 (70.5%)
Not Confirmed PCR Positive	36 (30.8%)	16 (27.1%)	52 (29.5%)
Pharmacokinetic-Evaluable Population	107 (91.5%)	0	107 (60.8%)
Not Treated	2 (1.7%)	1 (1.7%)	3 (1.7%)
No PK Assessment	8 (6.8%)	58 (98.3%)	66 (37.5%)
Safety Population	115 (98.3%)	58 (98.3%)	173 (98.3%)
Not Treated	2 (1.7%)	1 (1.7%)	3 (1.7%)

Patients are counted by treatment assigned unless stated otherwise.

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Recruitment

All of the patients were enrolled during the 2018-2019 influenza season. The first patient was enrolled on 20 November 2018 and the last patient last visit was on 3 April 2019.

With a 24-day safety follow-up period after treatment, the total study duration for each patient was 29 days.

Patients were enrolled into the study at 36 centres across 6 countries including the United States (164/176), Mexico (1/176), Costa Rica (2/176), Spain (3/176), Poland (5/176), and Russia (1/176). The highest recruiting country was the United States (93.2% of patients).

Conduct of the study

Major protocol deviations included those impacting patient safety, eligibility, study procedures, study assessments and data integrity. These were pre-defined prior to study start. A total of 30 major protocol deviations occurred in 29 patients in the study (21 [17.9%] patients in baloxavir marboxil group and 8 [13.6%] patients in oseltamivir group; Table 9). No patients were excluded from analyses due to a major protocol deviation.

Table 9: Summary of Major Protocol Deviations (Randomised Patients)

Protocol Deviation Coded Term Protocol Deviation Details	Treatment Group Baloxavir Marboxil (N=117)	 Oseltamivir (N=59)	 All Patients (N=176)
Total number of patients with at least one major protocol deviation	21 (17.9%)	8 (13.6%)	29 (16.5%)
Overall total number of events	22	8	30
Medication			
Total number of patients with at least one major protocol deviation	15 (12.8%)	7 (11.9%)	22 (12.5%)
Total number of events	16	7	23
Incorrect study drug dosing and schedule	11 (9.4%)	2 (3.4%)	13 (7.4%)
Received prohibited medication as per protocol	4 (3.4%)	5 (8.5%)	9 (5.1%)
Procedural			
Total number of patients with at least one major protocol deviation	5 (4.3%)	1 (1.7%)	6 (3.4%)
Total number of events	5	1	6
Failure to follow safety study procedures	4 (3.4%)	0	4 (2.3%)
Patient issued with incorrect YPrime device to record CARIFs data	1 (0.9%)	1 (1.7%)	2 (1.1%)
Inclusion criteria			
Total number of patients with at least one major protocol deviation	1 (0.9%)	0	1 (0.6%)
Total number of events	1	0	1
Patient without clinical diagnosis of influenza	1 (0.9%)	0	1 (0.6%)

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Major protocol deviations were in general comparable between the two treatment groups. However, four patients (3.4%) in the baloxavir marboxil group had "failure to follow safety study procedures" compared to none in the oseltamivir group. The MAH has been asked to clarify those deviations, and based on the MAH's response, there is no indication that those have had an impact on the results on safety.

Further, it is noted that the Major protocol deviation "incorrect study drug dosing and schedule" were more frequent in the baloxavir marboxil group compared to the oseltamivir group (9.4% vs. 3.4%). This is partly due to the 2:1 randomisation. The majority of the dosing mistakes took place at a single site that was subsequently retrained or were related to the placebo drugs.

Baseline data

Demographic data and baseline disease characteristics for the ITTI population were well balanced across the two treatment groups (Table 10).

Table 10: Study CP40563: Demographic and Baseline Disease Characteristics (ITTI Population)

Demographics and Baseline Characteristics, Intent-to-Treat Influenza-Infected Population
Protocol: CP40563

	Baloxavir Marboxil (N=81)	Oseltamivir (N=43)	All Patients (N=124)
Age (yr)			
n	81	43	124
Mean (SD)	6.7 (2.59)	6.7 (3.04)	6.7 (2.74)
Median	7.0	7.0	7.0
Min - Max	1 - 11	1 - 11	1 - 11
Age group (yr)			
n	81	43	124
1-<5	20 (24.7%)	10 (23.3%)	30 (24.2%)
5-<12	61 (75.3%)	33 (76.7%)	94 (75.8%)
Sex			
n	81	43	124
Female	44 (54.3%)	23 (53.5%)	67 (54.0%)
Male	37 (45.7%)	20 (46.5%)	57 (46.0%)
Ethnicity			
n	81	43	124
Hispanic or Latino	37 (45.7%)	19 (44.2%)	56 (45.2%)
Not Hispanic or Latino	44 (54.3%)	24 (55.8%)	68 (54.8%)
Race			
n	81	43	124
Asian	1 (1.2%)	0	1 (0.8%)
Black or African American	2 (2.5%)	4 (9.3%)	6 (4.8%)
Native Hawaiian or other Pacific Islander	0	1 (2.3%)	1 (0.8%)
White	72 (88.9%)	38 (88.4%)	110 (88.7%)
Multiple	3 (3.7%)	0	3 (2.4%)
Unknown	3 (3.7%)	0	3 (2.4%)
Weight (kg) at Baseline			
n	81	43	124
Mean (SD)	28.47 (12.416)	29.63 (14.023)	28.88 (12.950)
Median	26.00	27.30	26.40
Min - Max	12.3 - 64.4	10.4 - 72.0	10.4 - 72.0
Height (cm) at Baseline			
n	80	42	122
Mean (SD)	124.30 (18.616)	122.75 (21.103)	123.77 (19.435)
Median	125.35	123.00	124.75
Min - Max	81.0 - 162.5	78.0 - 157.8	78.0 - 162.5
BMI(kg/m^2) at Baseline			
n	80	42	122
Mean (SD)	17.59 (3.610)	18.72 (4.077)	17.98 (3.799)
Median	16.79	17.60	17.15
Min - Max	12.0 - 28.3	13.4 - 29.6	12.0 - 29.6
Vaccination Status			
n	81	43	124
Yes	41 (50.6%)	22 (51.2%)	63 (50.8%)
No	40 (49.4%)	21 (48.8%)	61 (49.2%)
Influenza Subtype by PCR			
n	76	40	116
B	5 (6.6%)	2 (5.0%)	7 (6.0%)
H1_2009	18 (23.7%)	10 (25.0%)	28 (24.1%)
H3	48 (63.2%)	28 (70.0%)	76 (65.5%)
UNKNOWN [a]	4 (5.3%)	0	4 (3.4%)
H1_2009/B	1 (1.3%)	0	1 (0.9%)

[a] UNKNOWN was reported when Type A PCR was positive but Subtype PCR returned a negative result. This could have been the case if (1) it was a subtype different from H1 or H3 (e.g H5), or (2) there was a "technical issue" such as a titer that was too low.
Source: t_dm_ITTI in CP40563 CSR.

Summary of Age Categories (ITTI Population)
Protocol: CP40563

Age group (yr)	Baloxavir Marboxil (N=81)	Oseltamivir (N=43)
<1 years	0	0
1 years	1 (1.2%)	3 (7.0%)
2 years	2 (2.5%)	3 (7.0%)
3 years	9 (11.1%)	2 (4.7%)
4 years	8 (9.9%)	2 (4.7%)
5 years	7 (8.6%)	5 (11.6%)
6 years	8 (9.9%)	5 (11.6%)
7 years	13 (16.0%)	2 (4.7%)
8 years	12 (14.8%)	8 (18.6%)
9 years	10 (12.3%)	5 (11.6%)
10 years	3 (3.7%)	3 (7.0%)
11 years	8 (9.9%)	5 (11.6%)
<5 years	20 (24.7%)	10 (23.3%)
>=5 years	61 (75.3%)	33 (76.7%)

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Overall, the demographic and baseline disease characteristics were well balanced between the two treatment groups in terms of demographics, subtype of influenza infection, and percentage of patients who received influenza vaccination.

The two cohorts based on age reached the minimum of 15 patients 1 to < 5 years of age and minimum 30 patients 5 to < 12 years of age as agreed in the PIP. However, the number of patients within the two age groups are somewhat skewed. There is only one 1 year old and two 2 years old patients who were included in the baloxavir marboxil group in study CP40563 compared to three 1 year old and three 2 years old patients in the oseltamivir group. However, since the application in <12 years is to a large extend based on extrapolation from older subjects, this will not be pursued.

25 (30.9%) patients in the baloxavir marboxil group and 7 (16.3%) patients in the oseltamivir group were co-infected with another respiratory virus at baseline.

Numbers analysed

The efficacy analysis was based on the ITTI population. It comprised 124 randomized patients (81 [69.2%] in the baloxavir marboxil group and 43 [72.9%] in the oseltamivir group).

Outcomes and estimation

In pivotal Study CP40563, the TTAS based on the CARIFS questionnaire was comparable in the two treatment groups. The median time was 138.1 hours (95% CI: 116.6, 163.2) in the baloxavir marboxil group compared with 150.0 hours (95% CI: 115.0, 165.7) in the oseltamivir group (Table 11), and the Kaplan-Meier curves for the two treatment groups generally overlapped (Figure 6).

Overall, the clinical efficacy results in the baloxavir marboxil group were comparable with those in the oseltamivir group for all other endpoints analyzed including, duration of fever, duration of symptoms, time to return to normal health and activity, frequency of influenza-related complications, and the proportion of patients requiring antibiotics (Table 11). In addition, the Kaplan-Meier curve for duration of fever (Figure 7) for the two treatment groups generally overlapped.

Table 11: Study CP40563: Summary of Clinical Efficacy Endpoints (ITTI Population)

	Baloxavir marboxil (N=81)	Oseltamivir (N=43)
TTAS		
Patients with event (%)	73 (91.3)[a]	36 (83.7)
Median time to event in hours [95%CI]	138.1 [116.6, 163.2]	150.0 [115.0, 165.7]
Post hoc sensitivity analysis for TTAS [b]		
Patients with event (%)	*79 (98.8)*[a]	*40 (93.0)*
Median *time to event in hours [95%CI]*	*69.8 [54.8, 86.9]*	*94.3 [56.0, 118.4]*
Duration of fever (return to afebrile state) [c]		
Patients with event (%)	80 (100.0)[a]	41 (95.3)
Median time to event in hours [95%CI]	41.2 [24.5, 45.7]	46.8 [30.0, 53.5]
Duration of symptoms [c]		
Patients with event (%)	79 (98.8)[a]	38 (88.4)
Median time to event in hours [95%CI]	66.4 [43.7, 76.4]	67.9 [45.8, 88.7]
Time to return to normal health and activity [d]		
Patients with event (%)	74 (92.5)[a]	36 (83.7)
Median time to event in hours [95%CI]	116.5 [94.9, 138.0]	111.6 [80.8, 138.3]
Frequency of influenza-related complication		
Patients with event (%)	6 (7.4)	3 (7.0)
Proportion requiring antibiotics		
Patients (%)	4 (4.9)	2 (4.7)

TTAS = time to alleviation of influenza signs and symptoms.

[a] The percentage denominator is 80 in the baloxavir marboxil group because 1 patient did not have a CARIFS assessment.

[b] A sensitivity analysis of TTAS was carried out post hoc to evaluate the impact of the "return to normal health and activity" component, in which the following criterion was removed: a "yes" response to the question "Since the last assessment has the subject been able to return to day care/school, or resume his or her normal daily activity in the same way as performed prior to developing the flu?" (Table 2).

[c] The duration of symptoms was defined as the time from the start of study treatment to the point at which all 18 symptoms specified in the CARIFS questionnaire had been alleviated for at least 21.5 hours.

[d] The time to return to normal health and activity was based on a 'yes' response to the final question in the CARIFS questionnaire.

Source: Table 12 in CP40563 CSR.

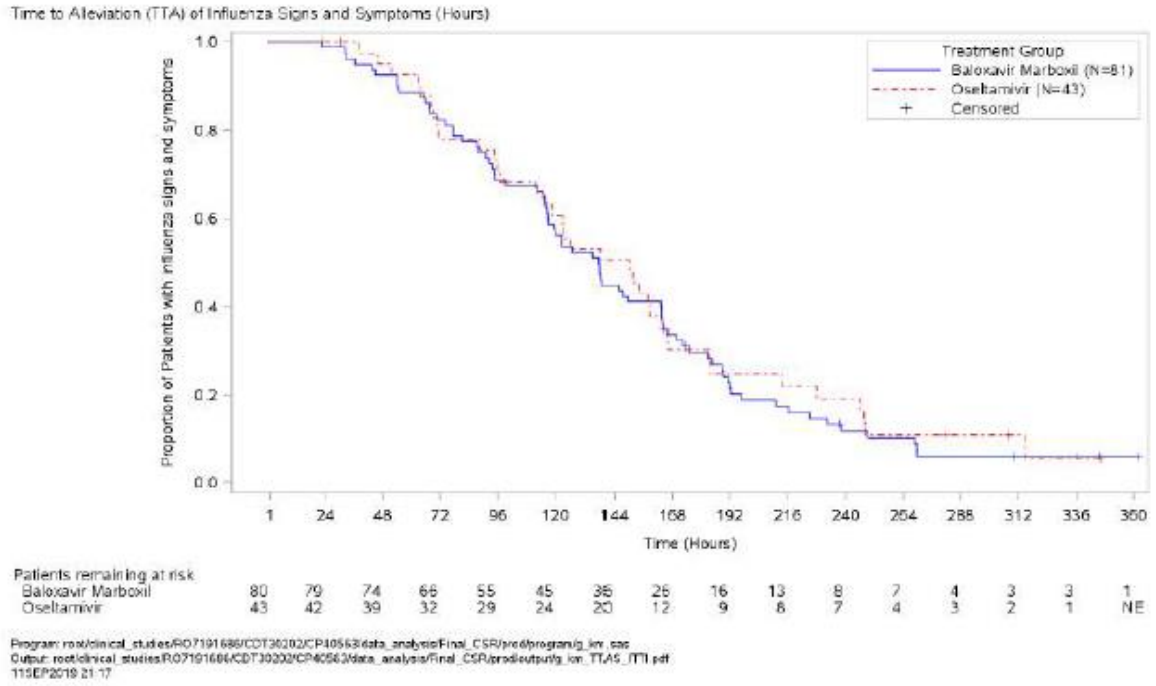

Figure 6: Study CP40563: Kaplan-Meier Plot of Time to Alleviation of Influenza Signs and Symptoms (ITTI Population)

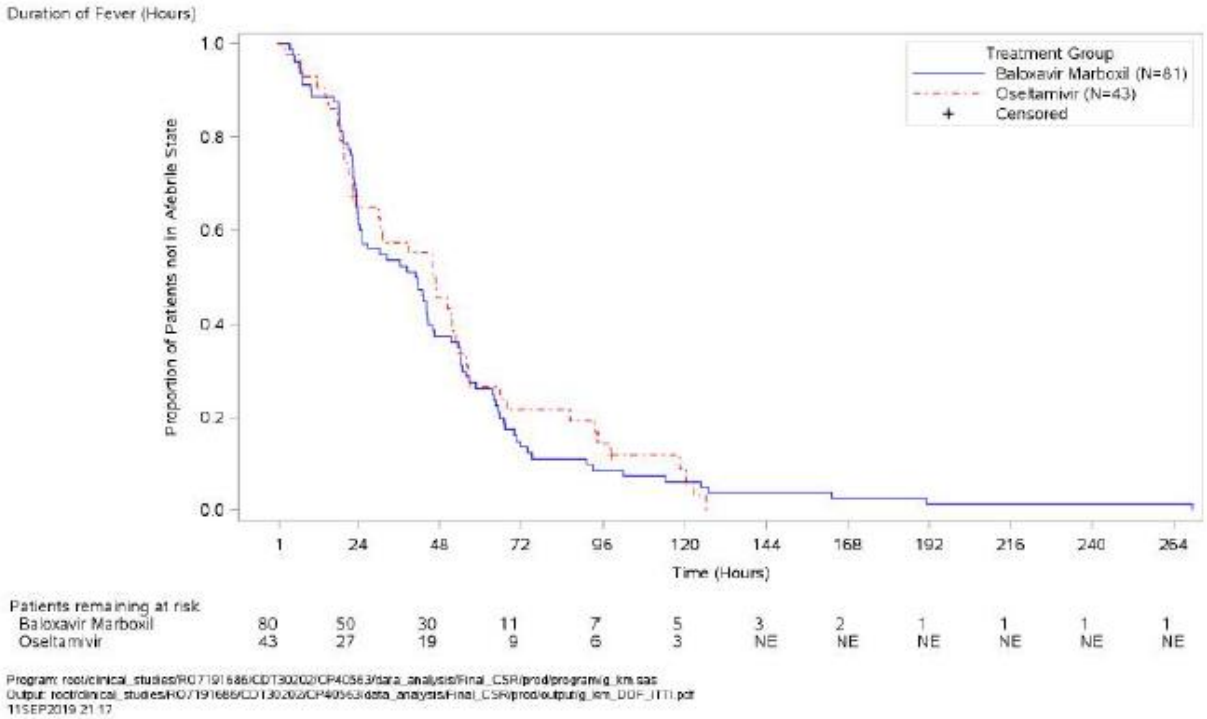

Figure 7: Study CP40563: Kaplan-Meier Plot of Time to Return to Afebrile State (ITTI Population)

Table 12: Study CP40563: Incidence of Influenza-related Complications (ITTI Population)

	Study CP40563	
	Baloxavir marboxil (N=81)	Oseltamivir (N=43)
Any influenza-related complication, n (%)	6 (7.4%)	3 (7.0%)
Death	0	0
Hospitalization	0	0
Sinusitis	1 (1.2%)	0
Otitis media	3 (3.7%)	2 (4.7%)
Pneumonia	1 (1.2%)	0
Bronchitis	1 (1.2%)	0
Encephalitis/encephalopathy	0	0
Febrile seizures	0	1 (2.3%)
Myositis	0	0

Source: Table 18 in CP40563 CSR.

Overall, the duration of the events was shorter in the baloxavir marboxil group compared to the oseltamivir group, except for "time to return to normal health and activity". The median time here was 116.5 hours (95% CI: 94.9, 138.0) in the baloxavir marboxil group compared with 111.6 hours (95% CI: 80.8, 138.3) in the oseltamivir group.

Of important clinical relevance, the incidence of influenza-related complications was low and similar in both treatment groups; 6 (7.4%) patients in the baloxavir marboxil group and 3 (7.0%) in the oseltamivir group and the proportion of patients requiring antibiotics was similar in each treatment group; 4.9% in the baloxavir marboxil group and 4.7% in the oseltamivir group. Acknowledging that overall numbers are small, nonetheless these findings contrast to the results from the pivotal studies in adults (which are given in the SmPC as comparison vs. placebo only). The MAH has included the frequencies of influenza-related complication in both SmPC's.

Virology Efficacy Endpoints

In terms of virology endpoints based on virus titre, the data were more favourable in the baloxavir marboxil group than in the oseltamivir group (Table 13).

The median time to cessation of viral shedding determined by virus titre was approximately two-thirds shorter for baloxavir marboxil compared with oseltamivir. In addition, the Kaplan-Meier curves for the time to cessation of viral shedding by virus titre show a clear separation in favour of the baloxavir marboxil group after 24 hours (Figure 8).

Using RT-PCR methodology, the median time to cessation of viral shedding was similar in the two treatment groups (Table 13, Figure 9). This observation is likely due to the highly sensitive nature of the RT-PCR methodology, which detects viable and nonviable virus or virus fragments, in contrast to virus titre, which is a culture based assay and only detects intact virus capable of growing in tissue culture.

Table 13: Study CP40563: Summary of Virology Endpoints (ITTI Population)

	Baloxavir marboxil (N=81)	Oseltamivir (N=43)
Time to cessation of viral shedding by virus titer [a, b]	(n=67)	(n=37)
Patients with event (%)	67 (100.0%)	36 (97.3%)
Median time to event in hours (95% CI)[c]	24.2 [23.5, 24.6]	75.8 [68.9, 97.8]
Time to cessation of viral shedding by RT-PCR [a, b]	(n=76)	(n=39)
Patients with event (%)	45 (59.2%)	23 (59.0%)
Median time to event in hours (95% CI)	242.5 [235.8, 262.8]	238.9 [214.0, 286.7]
Mean ± SD change from baseline in influenza virus titer ($log_{10}TCID_{50}$/mL) [a]		
Baseline	(n=67) 4.43 ± 1.36	(n=38) 4.27 ±1.48
Day 2	(n=64) -3.59 ± 1.34	(n=37) -1.79 ± 1.54
Day 4	(n=61) -3.53 ± 1.38)	(n=31) -3.27 ± 1.54)
Day 6	(n=63) -3.55 ± 1.32)	(n=35) -3.52 ± 1.50)
Day 10	(n=63) -3.66 ±1.40)	(n=32) -3.50 ± 1.42
Proportion of patients with a positive influenza virus titer, n (%) [a]		
Day 2	(n=64) 10 (15.6%)	(n=37) 28 (75.7%)
Day 4	(n=61) 16 (26.2%)	(n=31) 9 (29.0%)
Day 6	(n=63) 8 (12.7%)	(n=35) 2 (5.7%)
Day 10	(n=63) 1 (1.6%)	(n=32) 0

CI = confidence interval; RNA = ribonucleic acid; RT-PCR = reverse transcriptase-polymerase chain reaction; SD = standard deviation.

[a] Patients with a positive virus titer/RNA on Day 1 are included in the analysis.

[b] Patients whose virus titers/RNA did not reach the limit by the last observation time point are treated as censored at that time point.

[c] Median time was estimated from the Kaplan-Meier curve.

Source: Table 22, Table 23, Table 24, and Table 26 in CP40563 CSR.

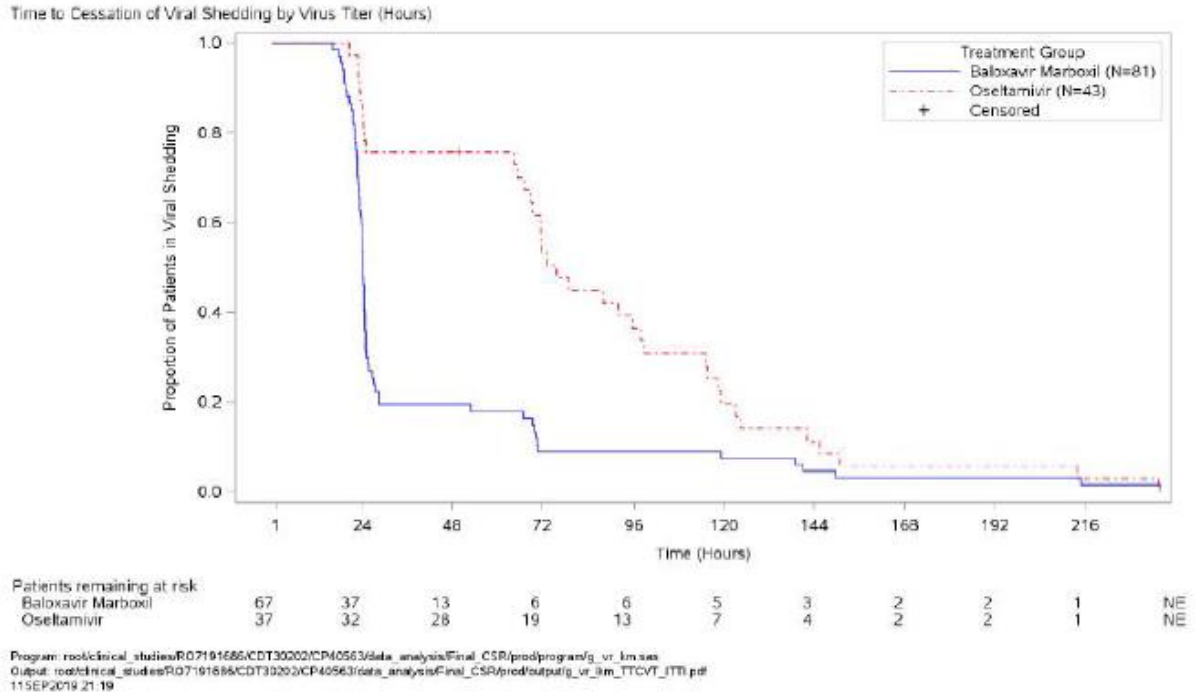

Figure 8: Study CP40563: Kaplan-Meier Plot of Time to Cessation of Viral Shedding by Virus Titer (ITTI Population)

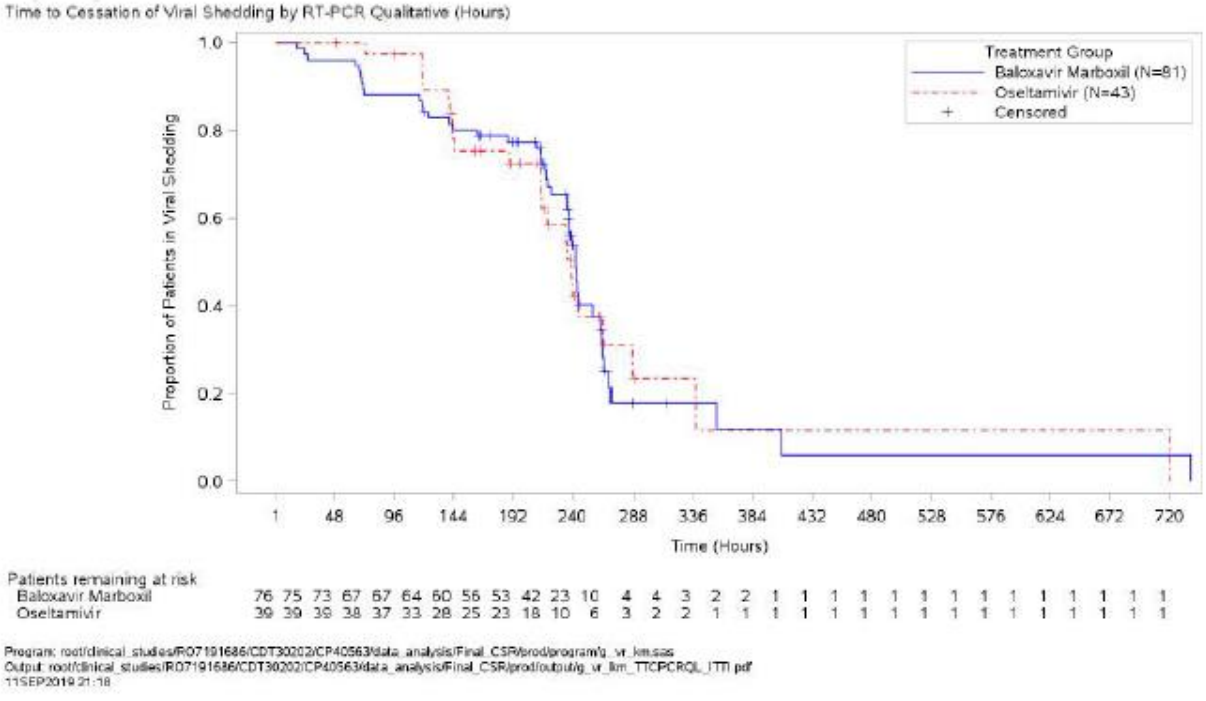

Figure 9: Study CP40563: Kaplan-Meier Plot of Time to Cessation of Viral Shedding by RT-PCR (ITTI Population)

The observation reflects the different methodology with RT-PCR, which detects viable and nonviable virus or virus fragments, in contrast to virus titre, which is a culture based assay and only detects intact virus capable of growing in tissue culture.

Overall, efficacy of the treatment of influenza with baloxavir maboxil and oseltamivir is comparable, based on TTAS. The other secondary endpoints did not conflict with this finding.

Ancillary analyses

Post-hoc sensitivity analysis of TTAS

The post-hoc sensitivity analysis of TTAS, which excluded the 'return to normal health and activity' in the key efficacy endpoint, revealed a lower TTAS in both treatment groups compared with the original TTAS definition, with a numerically lower median in the baloxavir marboxil group (69.8 hours [95% CI: 54.8, 86.9]) compared with the oseltamivir group (94.3 hours [95% CI: 56.0, 118.4]). The Kaplan-Meier curves show some separation of the curves in favor of the baloxavir marboxil group beginning soon after 24 hours.

Table 14: TTAS and Post-Hoc Sensitivity Analysis for TTAS in Study CP40563 (ITTI Population)

	Baloxavir marboxil (N = 81)	Oseltamivir (N = 43)
TTAS		
Patients with event (%)	73 (91.3)[a]	36 (83.7)
Median time to event in hours [95%CI]	138.1 [116.6, 163.2]	150.0 [115.0, 165.7]
Post-hoc sensitivity analysis for TTAS		
Patients with event (%)	*79 (98.8)[a]*	*40 (93.0)*
Median *time to event in hours [95%CI]*	*69.8 [54.8, 86.9]*	*94.3 [56.0, 118.4]*

[a] The percentage denominator is 80 in the baloxavir marboxil group because 1 patient did not have CARIFS assessment

Source: CSR CP40563, Table 12

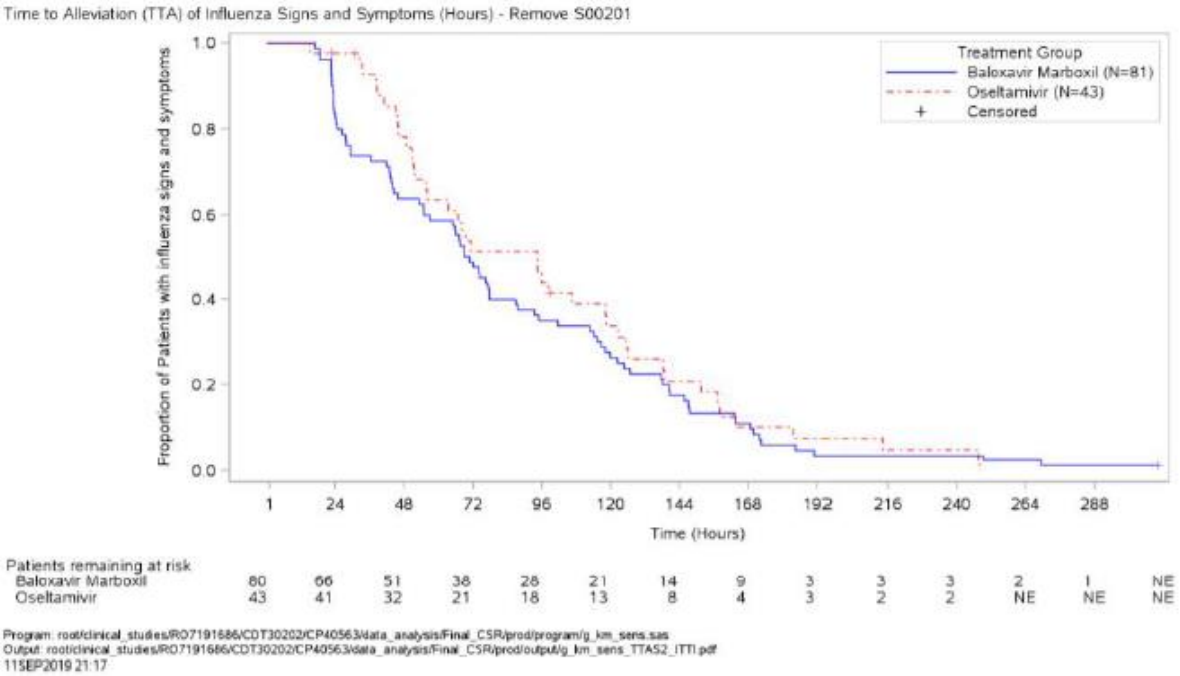

Figure 10: Kaplan-Meier Plot of Time to Alleviation of Influenza Signs and Symptoms (Sensitivity Analysis by Removing Time to Return to Normal Health and Activity Criteria) (ITTI Population)

In a post-hoc sensitivity analysis on request, the MAH has used a composite endpoint of time to alleviation of symptoms (TTAS) in the absence of rescue medication use (acetaminophen).

The results were overall similar to the primary analysis (Table 15, Figure 11).

Table 15: Summary of TTAS, including Acetaminophen use (ITTI Population)

Summary of Time to Alleviation of Influenza Signs and Symptoms, Intent-to-Treat Influenza-Infected Population
Protocol: CP40563
Reporting Event: CSR

Time to Alleviation (TTA) of Influenza Signs and Symptoms (Hours)

	Baloxavir Marboxil (N=81)	Oseltamivir (N=43)
Patients with CARIFS Assessment	80	43
Patients with event (%)	71 (88.8%)	36 (83.7%)
Patients Censored (%)	9 (11.3%)	7 (16.3%)
Time to event (hours) (a)		
Median (b)	138.4	151.5
95% CI	(119.3, 163.4)	(118.4, 165.9)
Min - Max	32 - 362*	23* - 346*

(a) Time from start of treatment to the point as which all of the following criteria are met and remain so for at least 21.5 hours:
- A score of 0 (no problem) or 1 (minor problem) for cough and nasal symptoms in CARIFS questionnaire,
- A "yes" response to the question "Since the last assessment has the subject been able to return to day care/school, or resume his or her normal daily activity in the same way as performed prior to developing the flu?" and
- A First return to afebrile state (tympanic temperature =<37.2°C).
- A Without paracetamol use for atleast 21.5 hours
(b) Median time was estimated from the Kaplan-Meier curve.
*: Censored time

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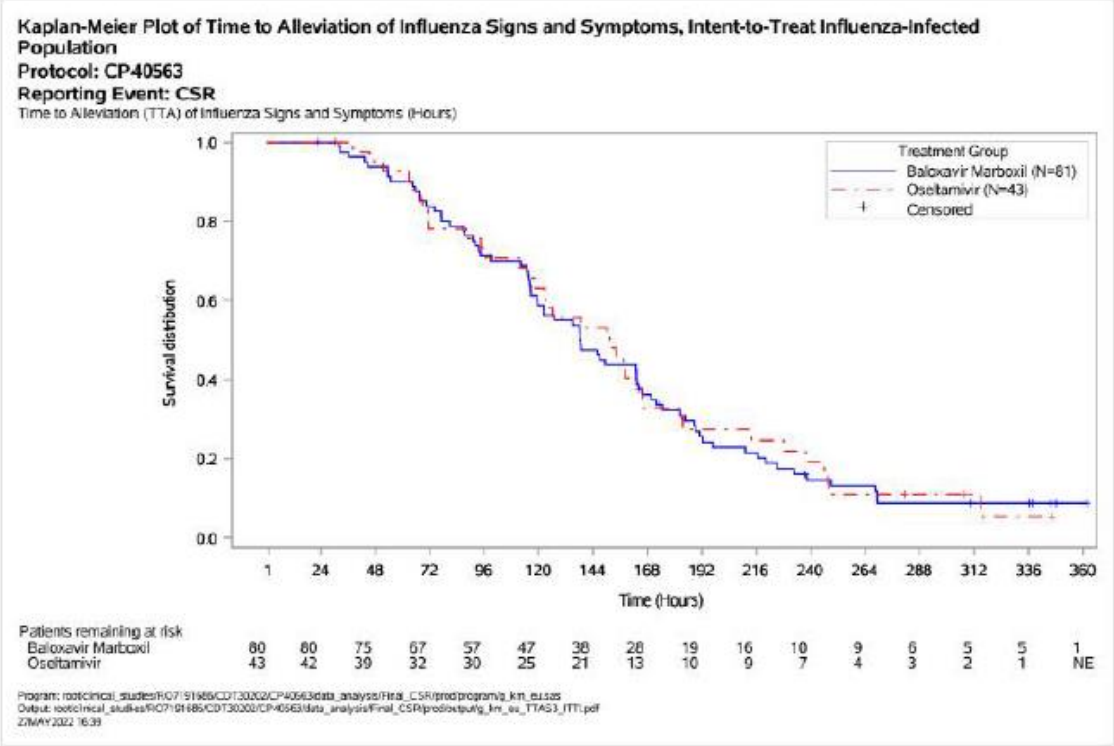

Figure 11: KM Plot of TTAS, including Acetaminophen use (ITTI Population)

Subgroup analyses

In the subgroup analyses for virus subtype, the median TTAS was comparable in the baloxavir marboxil and oseltamivir treatment groups for virus A/H3. For subtype A/H1N1, the median TTAS was

longer in the oseltamivir group. However, no conclusions can be made, due to the low number of patients in this subgroup. The subgroup analyses for time to cessation of viral shedding by virus titre and RT-PCR were consistent with the results of the overall ITTI population.

Table 16: Study CP40563: Subgroup Analysis of Time to Alleviation of Influenza Signs and Symptoms by Virus Subtype (ITTI Population)

	Baloxavir marboxil (N=81)	Oseltamivir (N=43)
Time to alleviation of influenza signs and symptoms		
Subtype A/H3	(n=47)	(n=28)
Patients with event (%)	44 (93.6%)	26 (92.9%)
Median time to event in hours [95%CI]	126.9 [112.3, 163.0]	118.4 [95.9, 158.1]
Subtype A/H1N1	(n=18)	(n=10)
Patients with event (%)	17 (94.4%)	6 (60.0%)
Median time to event in hours [95%CI]	115.8 [86.9, 166.1]	206.9 [122.5, 314.7]

Source: Table 20 in CP40563 CSR.

Table 17: Study CP40563: Subgroup Analysis of Time to Cessation of Viral Shedding (by Virus Titer and RT-PCR) by Virus Subtype (ITTI Population)

	Baloxavir marboxil (N=81)	Oseltamivir (N=43)
Time to cessation of viral shedding by virus titer		
Subtype A/H3	(n=46)	(n=26)
Patients with event (%)	46 (100.0%)	26 (100.0%)
Median time to event in hours [95%CI]	24.6 [24.2, 25.5]	83.3 [68.9, 98.6]
Subtype A/H1N1	(n=17)	(n=9)
Patients with event (%)	17 (100.0%)	9 (100.0%)
Median time to event in hours [95%CI]	22.7 [21.4, 23.3]	69.3 [23.5, 71.8]
Time to cessation of viral shedding by RT-PCR		
Subtype A/H3	(n=48)	(n=28)
Patients with event (%)	27 (56.3%)	17 (60.7%)
Median time to event in hours [95%CI]	242.5 [223.0, 264.3)	238.9 [189.4, 338.4]
Subtype A/H1N1	(n=18)	(n=9)
Patients with event (%)	13 (72.2%)	6 (66.7%)
Median time to event in hours [95%CI]	243.5 [235.8, 263.4]	234.5 [214.0, 286.7]

RT-PCR = reverse transcription polymerase chain reaction.

Source: Table 30 and Table 31 in CP40563 CSR.

30.9% of patients in the baloxavir marboxil group and 16.3% of patients in the oseltamivir group were co-infected with another respiratory virus at baseline. In a post-hoc subgroup analysis with TTAS as endpoint, the results in patients with or without co-infection were similar to those of the primary analysis (Table 18).

Table 18: Summary of Time to Alleviation of Influenza Signs and Symptoms of Patients with or without Co-Infections (ITTI population)

Time to Alleviation (TTA) of Influenza Signs and Symptoms (Hours)

	Baloxavir Marboxil (N=81)	Oseltamivir (N=43)
Patients With Co-infections		
Patients with CARIFS Assessment	25	7
Patients with event (%)	25 (100.0%)	5 (71.4%)
Patients Censored (%)	0	2 (28.6%)
Time to event (hours) (a)		
Median (b)	135.2	150.0
95% CI	(112.3, 182.4)	(71.3, NE)
Min - Max	45 - 269	38 - 346*
Patients Without Co-infections		
Patients with CARIFS Assessment	55	36
Patients with event (%)	48 (87.3%)	31 (86.1%)
Patients Censored (%)	7 (12.7%)	5 (13.9%)
Time to event (hours) (a)		
Median (b)	138.1	138.8
95% CI	(116.2, 164.0)	(115.0, 165.7)
Min - Max	23 - 362*	23* - 315

(a) Time from start of treatment to the point as which all of the following criteria are met and remain so for at least 21.5 hours:
- A score of 0 (no problem) or 1 (minor problem) for cough and nasal symptoms in CARIFS questionnaire,
- A "yes" response to the question "Since the last assessment has the subject been able to return to day care/school, or resume his or her normal daily activity in the same way as performed prior to developing the flu?" and
- First return to afebrile state (tympanic temperature =<37.2°C).
(b) Median time was estimated from the Kaplan-Meier curve.
*: Censored time

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Post-hoc subgroup analyses by age, showed no clear differences between age groups in TTAS (Table 19).

Table 19: Summary of Time to Alleviation of Influenza Signs by Age Subgroup (ITTI Population)

Summary of Time to Alleviation of Influenza Signs and Symptoms of Age Sub-group, Intent-to-Treat Influenza-Infected Population
Protocol: CP40563
Reporting Event: CSR

Time to Alleviation (TTA) of Influenza Signs and Symptoms (Hours)

	Baloxavir Marboxil (N=81)	Oseltamivir (N=43)
Age (years)		
<5		
Patients with CARIFS Assessment	20	10
Patients with event (%)	17 (85.0%)	9 (90.0%)
Patients Censored (%)	3 (15.0%)	1 (10.0%)
Time to event (hours) (a)		
Median (b)	121.4	158.8
95% CI	(93.7, 188.5)	(123.2, 247.9)
Min - Max	36 - 346*	46 - 346*
5-<12		
Patients with CARIFS Assessment	60	33
Patients with event (%)	56 (93.3%)	27 (81.8%)
Patients Censored (%)	4 (6.7%)	6 (18.2%)
Time to event (hours) (a)		
Median (b)	138.4	126.1
95% CI	(116.7, 163.4)	(95.9, 165.7)
Min - Max	23 - 362*	23* - 308*

(a) Time from start of treatment to the point as which all of the following criteria are met and remain so for at least 21.5 hours:
- A score of 0 (no problem) or 1 (minor problem) for cough and nasal symptoms in CARIFS questionnaire,
- A "yes" response to the question "Since the last assessment has the subject been able to return to day care/school, or resume his or her normal daily activity in the same way as performed prior to developing the flu?" and
- First return to afebrile state (tympanic temperature =<37.2°C).
(b) Median time was estimated from the Kaplan-Meier curve.
*: Censored time

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Drug Susceptibility at Baseline

Drug susceptibility of virus at baseline was determined by measuring the EC_{50} for baloxavir and the IC_{50} for oseltamivir acid as described in the method section. Since all viruses showed similar or even better susceptibility to oseltamivir acid compared with the respective reference virus, no reduced susceptibility of baseline viruses was detected in Study CP40563.

Treatment-emergent Amino Acid Substitutions in the PA, PB1, PB2, and NA Genes

11 (19.3%) baloxavir marboxil-treated patients with paired samples had treatment-emergent I38X substitutions in the PA genes. TTAS for these patients was comparable to the oseltamivir group. A subgroup analysis by age found prevalence rates of I38X to be higher in children 1 to < 5 years (5/16

patients [31.3%] with paired sequences) compared to children aged 5 to < 12 years (6/41 patients [14.6%] with paired sequences). None of the selected patients had treatment-emergent amino acid substitutions in PB1 or PB2. The possible clinical impact of these gene changes, i.e. time to alleviation / improvement, cannot be properly evaluated due to a relatively low number of patients, who were infected with a virus that expressed the gene changes. Thus, it is noted that a change in virus genome may occur on treatment with baloxavir marboxil, this is in line with the results from the clinical trials in adults and adolescents.

From the initial assessment in adults and adolescents the Applicant presented all available evidence including literature data (human and animal) related to resistance development. The presented data suggested that baloxavir-resistant viruses rarely emerge and I38X mutant viruses become a minority due to reduced fitness compared to the wildtype virus.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 20: Summary of efficacy for trial CP40563

Title: Study CP40563, (miniSTONE-2) A Multicenter, Randomized, Double-Blind, Active (Oseltamivir)-Controlled Study to assess the Safety, Pharmacokinetics, and Efficacy of Baloxavir Marboxil in Otherwise Healthy Paediatric Patients 1 to < 12 Years of Age with Influenza-Like Symptoms		
Study identifier	CP40563, (miniSTONE-2)	
Design	This was a global, multicenter, randomized, double-blind, active-controlled study to compare baloxavir marboxil with oseltamivir in paediatric patients with influenza-like symptoms. Patients received either a single dose of baloxavir marboxil or oseltamivir for 5 days. During the 5-day treatment period, each randomized patient also received the corresponding placebo of its comparator. With a 24-day safety follow-up period after treatment, the total study duration for each patient was 29 days.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	29 days not applicable not applicable
Hypothesis	The statistical analyses of efficacy endpoints were descriptive.	
Treatments groups	Trial drug	• Baloxavir marboxil • Dose based on body weight of child (2 mg/kg for patients < 20 kg, or 40 mg for patients > 20 kg) / granules for oral suspension • Single dose on Day 1 only • N=117
	Reference drug	• Oseltamivir • Body weight-adjusted dosing ranging from 30 mg to 75 mg / powder for oral suspension • Twice-a-day for 5 days • N=59

Title: Study CP40563, (miniSTONE-2) A Multicenter, Randomized, Double-Blind, Active (Oseltamivir)-Controlled Study to assess the Safety, Pharmacokinetics, and Efficacy of Baloxavir Marboxil in Otherwise Healthy Paediatric Patients 1 to < 12 Years of Age with Influenza-Like Symptoms			
Study identifier	CP40563, (miniSTONE-2)		
Endpoints and definitions	Key secondary efficacy endpoint	TTAS	Time to alleviation of influenza signs and symptoms, defined as the length of time taken from the start of treatment to the point at which all of the following criteria are met and remain so for at least 21.5 hours: - A score of 0 (no problem) or 1 (minor problem) for cough and nasal symptoms (items 14 and 15 of the CARIFS) - A "yes" response to the following question on the CARIFS: "Since the last assessment has the subject been able to return to day care/school, or resume his or her normal daily activity in the same way as performed prior to developing the flu?" - First return to afebrile state (tympanic temperature ≤ 37.2°C)
	Secondary efficacy endpoint		• Duration of fever (time to return to afebrile state [tympanic temperature ≤ 37.2°C] and remaining so for at least 21.5 hours) • Duration of symptoms (alleviation of all symptoms as defined by a score of 0 [no problem] or 1 [minor problem] and remaining so for at least 21.5 hours, for all 18 symptoms specified in the CARIFS questionnaire) • Time to return to normal health and activity • Frequency of influenza-related complications (death, hospitalization, radiologically confirmed pneumonia, bronchitis, sinusitis, otitis media, encephalitis/encephalopathy, febrile seizures, myositis) • Proportion of patients requiring antibiotics
	Secondary virology endpoint		• Time to cessation of viral shedding by virus titer • Time to cessation of viral shedding by RT-PCR • Change from baseline in influenza virus titer at each time point • Proportion of patients with positive influenza virus titer at each time point
Database lock	27-Aug-2019		
Results and Analysis			
Analysis description	**Secondary Efficacy Analysis**		

Title: Study CP40563, (miniSTONE-2) A Multicenter, Randomized, Double-Blind, Active (Oseltamivir)-Controlled Study to assess the Safety, Pharmacokinetics, and Efficacy of Baloxavir Marboxil in Otherwise Healthy Paediatric Patients 1 to < 12 Years of Age with Influenza-Like Symptoms			
Study identifier	CP40563, (miniSTONE-2)		
Analysis population and time point description	Intention-to-treat infected population (ITTI) The total study duration for each patient was 29 days. The ITTI population had a laboratory confirmation of influenza infection (PCR result) from any swab sample collected at baseline or during the study. The ITTI population was the primary efficacy population. Patients were grouped based on randomized treatment.		
	Treatment group	Baloxavir marboxil	Oseltamivir
Descriptive statistics and estimate variability	Number of subjects	81	43
	TTAS (Median hours)	138.1	150.0
	95% confidence interval (hours)	116.6, 163.2	115.0, 165.7
	Duration of fever (Median hours)	41.2	46.8
	95% confidence interval (hours)	24.5, 45.7	30.0, 53.5
	Duration of symptoms (Median hours)	66.4	67.9
	95% confidence interval (hours)	43.7, 76.4	45.8, 88.7
	Time to return to normal health and activity (median hours)	116.5	111.6
	95% confidence interval (hours)	94.9, 138.0	80.8, 138.3
	Frequency of influenza-related complication (%)	7.4	7.0
	Proportion requiring antibiotics (%)	4.9	4.7
Analysis description	**Secondary Virology Analysis**		
Analysis population and time point description	Intention-to-treat infected population (ITTI) The total study duration for each patient was 29 days. The ITTI population had a laboratory confirmation of influenza infection (PCR result) from any swab sample collected at baseline or during the study. The ITTI population was the primary efficacy population. Patients were grouped based on randomized treatment.		
	Treatment group	Baloxavir marboxil	Oseltamivir
Descriptive statistics and estimate variability	Number of subjects	81	43
	Time to cessation of viral shedding by virus titer (median hours)	24.2	75.8
	95% confidence interval (hours)	23.5, 24.6	68.9, 97.8
	Time to cessation of viral shedding by RT-PCR (median hours)	242.5	238.9

Title: Study CP40563, (miniSTONE-2) A Multicenter, Randomized, Double-Blind, Active (Oseltamivir)-Controlled Study to assess the Safety, Pharmacokinetics, and Efficacy of Baloxavir Marboxil in Otherwise Healthy Paediatric Patients 1 to < 12 Years of Age with Influenza-Like Symptoms				
Study identifier	CP40563, (miniSTONE-2)			
	95% confidence interval (hours)	235.8, 262.8		214.0, 286.7
	Change from baseline in influenza virus titer (Mean ± SD)	Baseline Day 2 Day 4 Day 6 Day 10	4.43 ± 1.36 -3.59 ± 1.34 -3.53 ± 1.38 -3.55 ± 1.32 -3.66 ±1.40	4.27 ±1.48 -1.79 ± 1.54 -3.27 ± 1.54 -3.52 ± 1.50 -3.50 ± 1.42
	Proportion of patients with a positive influenza virus titer (n (%))	Day 2 Day 4 Day 6 Day 10	10 (15.6%) 16 (26.2%) 8 (12.7%) 1 (1.6%)	28 (75.7%) 9 (29.0%) 2 (5.7%) 0
Notes				

2.6.5.3. Clinical studies in special populations

Gender

The median time to alleviation of influenza signs and symptoms (TTAS) by gender in is shown in Table 21.

Table 21: Summary of Time to Alleviation of Influenza Signs and Symptoms by Gender (ITTI population)

Time to Alleviation (TTA) of Influenza Signs and Symptoms (Hours)

	Baloxavir Marboxil (N=81)	Oseltamivir (N=43)
Gender		
Female		
Patients with CARIFS Assessment	43	23
Patients with event (%)	41 (95.3%)	19 (82.6%)
Patients Censored (%)	2 (4.7%)	4 (17.4%)
Time to event (hours) (a)		
Median (b)	135.2	154.5
95% CI	(93.7, 163.2)	(94.5, 213.9)
Min - Max	32 - 336*	31* - 308*
Male		
Patients with CARIFS Assessment	37	20
Patients with event (%)	32 (86.5%)	17 (85.0%)
Patients Censored (%)	5 (13.5%)	3 (15.0%)
Time to event (hours) (a)		
Median (b)	138.9	126.1
95% CI	(116.6, 174.7)	(96.8, 163.5)
Min - Max	23 - 362*	23* - 346*

(a) Time from start of treatment to the point as which all of the following criteria are met and remain so for at least 21.5 hours:
- A score of 0 (no problem) or 1 (minor problem) for cough and nasal symptoms in CARIFS questionnaire,
- A "yes" response to the question "Since the last assessment has the subject been able to return to day care/school, or resume his or her normal daily activity in the same way as performed prior to developing the flu?" and
- First return to afebrile state (tympanic temperature =<37.2°C).
(b) Median time was estimated from the Kaplan-Meier curve.
*: Censored time

Median TTAS were similar for female and males in the baloxavir marboxil treatment group (135.2 vs. 138.9). This is in consistence with the result for the adult population. Median TTAS are different

between females and males for the oseltamivir group (154.5 vs. 126.1). However, the subgroup analysis should be interpreted with caution due to the low number of patients in the subgroups as well as overlapping confidence intervals in both the baloxavir marboxil and the oseltamivir groups. Further, in the initial application an 15% higher Cmax and a 7% higher AUC0-inf in women than in men were observed. This was not considered clinically relevant and no dose adjustment is required based on gender. In the popPK model, gender was a significant covariate for estimating ka. No dose adjustment by gender is considered necessary in children < 12 years either.

Race/region

When comparing data between Asian and non-Asian paediatric studies, a doubling in exposure is observed in Asian subjects compared with non-Asian subjects, or a similar exposure with half the dose has been observed in Japanese subjects. Predicted values of AUC, Cmax and C24 also showed a marked difference between Asian and non-Asian subjects – especially for AUCinf, where the predicted exposure in Asian subjects were doubled the expose in non-Asian subjects. The difference was not as marked in adult subjects. This issue was explored in detail in the initial MAA and a correlation between plasma exposures and safety has not been established. Since baloxavir directly targets the influenza virus, not the host, the same treatment benefit is to be expected regardless of race or region in adults, adolescents and paediatrics.

Vaccination Status

The TTAS in vaccinated and unvaccinated patients in Study CP40563 are shown in Table 22.

Table 22: Summary of Time to Alleviation of Influenza Signs and Symptoms by Vaccination Status (ITTI population)

Time to Alleviation (TTA) of Influenza Signs and Symptoms (Hours)

	Baloxavir Marboxil (N=81)	Oseltamivir (N=43)
Vaccination Status		
No		
Patients with CARIFS Assessment	40	21
Patients with event (%)	40 (100.0%)	19 (90.5%)
Patients Censored (%)	0	2 (9.5%)
Time to event (hours) (a)		
Median (b)	118.0	157.4
95% CI	(94.7, 138.1)	(111.6, 213.9)
Min - Max	23 - 225	46 - 315
Yes		
Patients with CARIFS Assessment	40	22
Patients with event (%)	33 (82.5%)	17 (77.3%)
Patients Censored (%)	7 (17.5%)	5 (22.7%)
Time to event (hours) (a)		
Median (b)	163.6	131.0
95% CI	(126.9, 192.3)	(95.9, 165.7)
Min - Max	32 - 362*	23* - 346*

(a) Time from start of treatment to the point as which all of the following criteria are met and remain so for at least 21.5 hours:
- A score of 0 (no problem) or 1 (minor problem) for cough and nasal symptoms in CARIFS questionnaire,
- A "yes" response to the question "Since the last assessment has the subject been able to return to day care/school, or resume his or her normal daily activity in the same way as performed prior to developing the flu?" and
- First return to afebrile state (tympanic temperature =<37.2°C).
(b) Median time was estimated from the Kaplan-Meier curve.
*: Censored time

Adapted from t_tte_sbrg_eu_TTAS_ITTI

In vaccinated patients, the median TTAS was numerically higher in the baloxavir marboxil group compared to the oseltamivir group (163.6 h vs 131 h). The opposite was seen in the unvaccinated group; a numerically longer median TTAS was seen among unvaccinated oseltamivir patients compared to unvaccinated baloxavir marboxil patients (157.4 h vs 118 h). The data should be interpreted with caution due to the low number of patients in these subgroups as well as wide, overlapping confidence intervals in both the baloxavir marboxil and the oseltamivir group.

In 1601T0831 in adult about 25% of subjects had received influenza vaccine. In the vaccinated subgroup median TTAS for baloxavir vs. placebo was numerically shorter (52.1 vs, 71.9 h). A numerically longer TTAS was seen among placebo treated patients that did not receive an influenza vaccination (54.1 vs. 81.2 h). In 1602T0832 a similar proportion had received influenza vaccine. In the vaccinated subgroup the median TTIS was numerically shorter for baloxavir vs. placebo (65.4 vs. 92.7 h) whereas median TTIS was significantly shorter for those who had not received an influenza vaccine (76.9 h vs. 103.1 h). The findings suggest that patients with breakthrough influenza (i.e. disease despite vaccination) may have been less ill but could still derive a benefit from intervention. The same is expected in the paediatric population.

Renal or Hepatic Impairment

In the popPK model, creatinine clearance, alanine aminotransferase, aspartate aminotransferase and bilirubin were not significant covariates. In the initial application, the MAH showed that in 8 subjects with moderate hepatic impairment, the mean Cmax was lower (20% decrease) and the AUC0-inf was higher (12% increase) than in 8 subjects with normal hepatic function. However, the differences were small and not considered clinically relevant, and no dose adjustment is considered necessary in adolescents and adults with mild or moderate hepatic impairment. The same can be expected for the paediatric population, in light of the metabolism and clearance of baloxavir. Hence, impaired renal function, mild or moderate hepatic impairment is not considered to impact the PK, safety or efficacy in paediatric subjects.

The PK of baloxavir in patients with severe hepatic impairment has not been evaluated.

Overall, the subgroup analyses and discussion on subgroups suggested similar efficacy in subjects 1 to < 12 year old, regardless of gender, race/region, vaccination status and renal or hepatic impairment.

2.6.5.4. Supportive studies

The three non-controlled, single arm, Japanese paediatric studies: T0822, T0833 and T0835, are considered supportive for the treatment indication. A summary of methods are presented in Table 23.

Table 23: Summary of Supportive Clinical Studies

Study No.	Study Design	Dose and Regimen	Study Objectives	No. Patients
Supportive Pediatric Studies:				
1618T0822 (Phase 3)	Multicenter (Japan only), open-label, non-controlled study in OwH pediatric patients (6 months to <12 years) with acute uncomplicated influenza	Baloxavir marboxil (10 and 20 mg tablets): single dose according to body weight: • 5 to < 10 kg: 5 mg • 10 to < 20 kg: 10 mg • 20 to < 40 kg: 20 mg • ≥ 40 kg: 40 mg	• To assess the safety and tolerability of a single dose of baloxavir marboxil • To assess the PK of baloxavir marboxil and its active form baloxavir after single-dose administration and to confirm appropriateness of the dose in pediatric patients • To assess the efficacy of baloxavir marboxil after single-dose administration	**Treated patients**: 107 **Safety Population:** 107 **ITTI**: 104
1705T0833 (Phase 3)	Multicenter (Japan only), open-label, non-controlled study in OwH pediatric patients (weighing < 20 kg and aged < 12 years) with acute uncomplicated influenza	Baloxavir marboxil (2% granules): single dose according to body weight: • < 10 kg: 1 mg/kg • 10 to < 20 kg: 10 mg	• To assess the safety and tolerability of a single dose of baloxavir marboxil 2% granules • To assess the PK of baloxavir marboxil and its active form baloxavir after single-dose administration of baloxavir marboxil 2% granules • To assess the efficacy of a single dose of baloxavir marboxil 2% granules	**Enrolled, Safety Population and ITTI**: 33
1813T0835 (Phase 3)	Multicenter (Japan only), open-label, non-controlled study in OwH pediatric patients aged less than 12 years and weighing less than 20 kg with acute uncomplicated influenza	Baloxavir marboxil (2% granules): single dose according to age and body weight: • < 10 kg (< 3 months): 1 mg/kg • < 10 kg (≥ 3 months): 2 mg/kg 10 to < 20 kg: 20 mg	• To assess the safety and tolerability of a single dose of baloxavir marboxil 2% granules • To assess the PK of baloxavir marboxil and its active form baloxavir after single dose administration of baloxavir marboxil 2% granules • To assess the efficacy of a single dose of baloxavir marboxil 2% granules	**Enrolled and ITTI:** 43 **Safety Population (all baloxavir marboxil):** 45

The results for the endpoints are presented in Table 24.

Table 24: Studies T0822, T0833, and T0835: Summary of Clinical and Virology Efficacy Endpoint Results (ITTI Population)

	Study T0822 (N = 104)	Study T0833 (N = 33)	Study T0835 (N = 43)
Summary of Clinical Efficacy Endpoint Results			
Median time (hours) to alleviation of			
Influenza illness [95%CI]	n=103 44.6 [38.9, 62.5]	n=33 45.3 [28.5, 64.1]	n=43 37.8 [27.5, 46.7]
Cough [95%CI]	n=77 28.6 [19.8, 43.8]	n=10 20.6 [1.0, 130.8]	n=11 4.6 [1.3, 30.8]
Nasal discharge/congestion [95%CI]	n=58 38.7 [18.3, 61.0]	n=15 52.7 [16.3, 92.4]	n=19 30.8 [3.7, 68.0]
Median time (hours) to			
Resolution of fever (axillary temperature < 37.5°C) [95%CI]	n=103 21.4 [19.8, 25.8]	n=33 34.0 [25.0, 43.1]	n=43 22.0 [95% CI: 20.2, 28.6]
Resumption of normal activity [95%CI]	n=100 126.3 [99.4, 130.7]	n=31 80.3 [51.5, 131.4]	n=43 80.3 [95% CI: 55.8, 103.6]
Incidence of influenza-related complication (n, %)[a]	n=104 2 (1.9%)	n=33 3 (9.1%)	n=43 3 (7.0%)
Summary of Virology Efficacy Endpoint Results			
Median time (hours) to			
Cessation of viral shedding by virus titer [95%CI] [b, c]	n=101 24 [-,-] [d]	n=32 48 [24.0, 144.0]	n=42 24 [-,-] [d]
Cessation of viral shedding by RT-PCR [95%CI] [c, e]	n=104 216 [192.0, 216.0]	n=33 240 [240.0, -] [d]	n=43 240.0 [216.0, 384.0]

Table 31: Studies T0822, T0833, and T0835: Summary of Clinical and Virology Efficacy Endpoint Results (ITTI Population) (cont'd)

	Study T0822 (N = 104)	Study T0833 (N = 33)	Study T0835 (N = 43)
Mean ± SD change from baseline in influenza virus titer at each time point (log_{10} $TCID_{50}$/mL) [b]			
Baseline	n=104 5.11 ± (2.04)	n=33 5.76 ± (1.84)	n=43 5.26 ± 1.78
Day 2	n=101 –4.20 ± 1.94	n=32 –4.62 ± 1.61	n=42 –4.40 ± 1.62
Day 3 [f]	n=61 –4.60 ± 2.16	n=17 –5.19 ± 1.58	n=24 –3.95 ± 1.73
Day 4 [f]	n=52 –4.00 ± 1.92	n=20 –3.05 ± 2.39	n=26 –4.13 ± 2.17
Day 6	n=101 –4.18 ± 1.94	n=32 –3.94 ± 2.11	n=42 –3.36 ± 2.27
Day 9	n=101 –4.44 ± 1.97	n=32 –5.04 ± 1.64	n=42 –4.23 ± 1.68
Proportion of patients with positive influenza virus titer at each time point (n, %) [b]			
Day 2	n=101 30 (29.7%)	n=32 19 (59.4%)	n=42 10 (23.8%)
Day 3 [f]	n=61 13 (21.3%)	n=17 7 (41.2%)	n=24 4 (16.7%)
Day 4 [f]	n=52 13 (25.0%)	n=20 14 (70.0%)	n=26 8 (30.8%)
Day 6	n=101 21 (20.8%)	n=32 21 (65.6%)	n=42 25 (59.5%)
Day 9	n=101 7 (6.9%)	n=32 2 (6.3%)	n=42 12 (28.6%)

[a] Death, hospitalization, radiologically confirmed pneumonia, bronchitis, sinusitis, and otitis media. A few patients experienced an influenza-related complication (2 patients with bronchitis in Study T0822; 1 patient with bronchitis and 2 patients with otitis media in Study T0833; and 2 patients with bronchitis and 1 patient with otitis media in Study T0835) after receiving baloxavir marboxil but no patients experienced other influenza-related complications commonly seen in pediatric patients. .

[b] Subset of patients who were positive for influenza virus titer at baseline.

[c] Patients whose virus titer/RNA had not reached cessation by the last observation time point were censored at the last time point.

[d] The upper limit of the 95% CI could not be calculated.

[e] Subset of patients who were positive by RT-PCR at baseline.

[f] Patients visited the site on either Day 3 or Day 4.

The time to alleviation of influenza illness was comparable across the three studies; 44.6 hours (95% CI: 38.9, 62.5) in Study T0822, 45.3 hours (95% CI: 28.5, 64.1) in Study T0833, and 37.8 hours (95% CI: 27.5, 46.7 hours) in Study T0835.

TTAS was longer in the pivotal study CP40563 (138.1 hours [95% CI: 116.6, 163.2]). However, the post-hoc sensitivity analysis (which excluded the 'return to normal health and activity') revealed a lower TTAS compared with the original TTAS definition; 69.8 hours [95% CI: 54.8, 86.9], which is still longer, but comparable to the results of the supportive studies.

Overall, the results of the three studies can be considered supportive, even though the difference in design, season, dosing regime, population and endpoints between the studies, makes interpretation difficult.

Clinical efficacy in the post-exposure-prophylaxis indication

The second part of the clinical efficacy section will present data and an assessment of the efficacy of baloxavir marboxil when used for the **post exposure prophylaxis (PEP)** of influenza virus infection in subjects 1 to < 12 years who were household members of influenza infected patients.

The proposed PEP indication is as follows:

- Xofluza is indicated for the post-exposure prophylaxis of influenza in individuals aged 1 year and above.

The efficacy evaluation for the PEP population is based on data from one large pivotal Phase 3 study 1719T0834 (also known as BLOCKSTONE, hereafter referred to as T0834) conducted in Japan.

- Study T0834 was a randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of a single oral dose of baloxavir marboxil in the prevention of influenza in approximately 750 subjects who were household members of influenza-infected patients. An overview of the study is presented in Table 25.

Table 25: Overview of the Pivotal Phase 3 Post-Exposure Prophylaxis Study T0834

Study No.	Study Design	Dose and Regimen	Study Objectives	No. Subjects
Post-Exposure Prophylaxis Study:				
1719T0834 (Phase 3)	Multicenter (Japan only), randomized, double-blind, parallel-group, placebo-controlled comparative study in subjects who are household members of influenza-infected index patients	• Single dose of baloxavir marboxil: ○ ≥ 12 years: ▪ < 80 kg: 40 mg (tablet) ▪ ≥ 80 kg: 80 mg (tablet) ○ < 12 years: ▪ < 10 kg: 1 mg/kg (2% granule) ▪ 10 to < 20 kg: 10 mg (2% granule) ▪ 20 to < 40 kg: 20 mg (tablet) ▪ ≥ 40 kg: 40 mg (tablet) • Placebo	• To confirm the efficacy of a single dose of baloxavir marboxil in the prevention of influenza • To determine the PK of baloxavir in subjects treated with baloxavir marboxil for prophylaxis • To evaluate the safety of a single oral dose of baloxavir marboxil for prophylaxis	**Randomized:** N = 752 bxm: 375; pbo: 377 **mITT Population:** N = 749 bxm: 374; pbo: 375 **< 12 Years Subgroup Population:** N = 142 bxm: 71; pbo: 71 **≥ 12 Years Subgroup Population:** N = 607 bxm: 303; pbo: 304

bxm = baloxavir marboxil; mITT = modified Intention-to-Treat population; pbo = placebo; PK = pharmacokinetics.

This assessment will focus on the age group 1 to <12 years, since the study has been evaluated and approved in the European Union post-exposure prophylaxis of influenza in individuals 12 years of age and older.

2.6.5.5. Dose response studies

The baloxavir marboxil single dose administrations used in study T0834 are the approved doses used for treatment of influenza virus infection outside EU: individuals weighing < 10 kg body weight: 1

mg/kg (2% granules), 10 kg to < 20 kg body weight: 10 mg (2% granules), 20 kg to < 40 kg body weight: 20 mg (one 20 mg tablet) and ≥ 40 kg body weight: 40 mg (two 20 mg tablets).

The rationale for using the above baloxavir marboxil dosage regimens in PEP Study T0834 was based on the results of a nonclinical pharmacology study and predictions from human population PK models as outlined below:

- Clinical influenza is caused by the immune response to virus replication in infected people, and baloxavir is considered to exert its preventive effect by suppressing viral replication. In mice, the plasma baloxavir concentrations 24-hour post-infection associated with prolonged survival relative to vehicle control were ≥ 0.444 and ≥ 2.35 ng/mL for influenza A and B virus, respectively. By maintaining plasma baloxavir concentrations at a level at least as high as these concentrations, baloxavir was expected to also exert its preventive effect against influenza A and B viruses in humans.

- Human population PK modelling predicted that plasma baloxavir concentrations could be maintained at the above noted preventative levels for 22 days (influenza A) and 14 days (influenza B) in Japanese adults and adolescents, for 15 to 22 days (influenza A) and 9 to 13 days (influenza B) in children weighing ≥ 10 kg, and for 13 to 15 days (influenza A) and 8 to 10 days (influenza B) in children aged ≤ 12 months

Based on the results of the nonclinical pharmacology study and the predictions from the human population PK model, it was expected that baloxavir marboxil would exert its preventive effect against influenza virus infection in humans for approximately 10 days without any safety concerns and at a level of exposure similar to that observed in therapeutic studies.

The recommended baloxavir marboxil dose for PEP of influenza in individuals ≥1 year of age is the same as for the treatment of uncomplicated influenza: 2 mg/kg for individuals weighing <20 kg, 40 mg for individuals weighing ≥20 kg, and 80 mg for individuals weighing ≥80 kg, administered as a single oral dose. It should be noted that the dosing regimen used in Study CP40563 is the proposed PEP dose in children, which differs from the paediatric dosing regimen used in Study T0834.

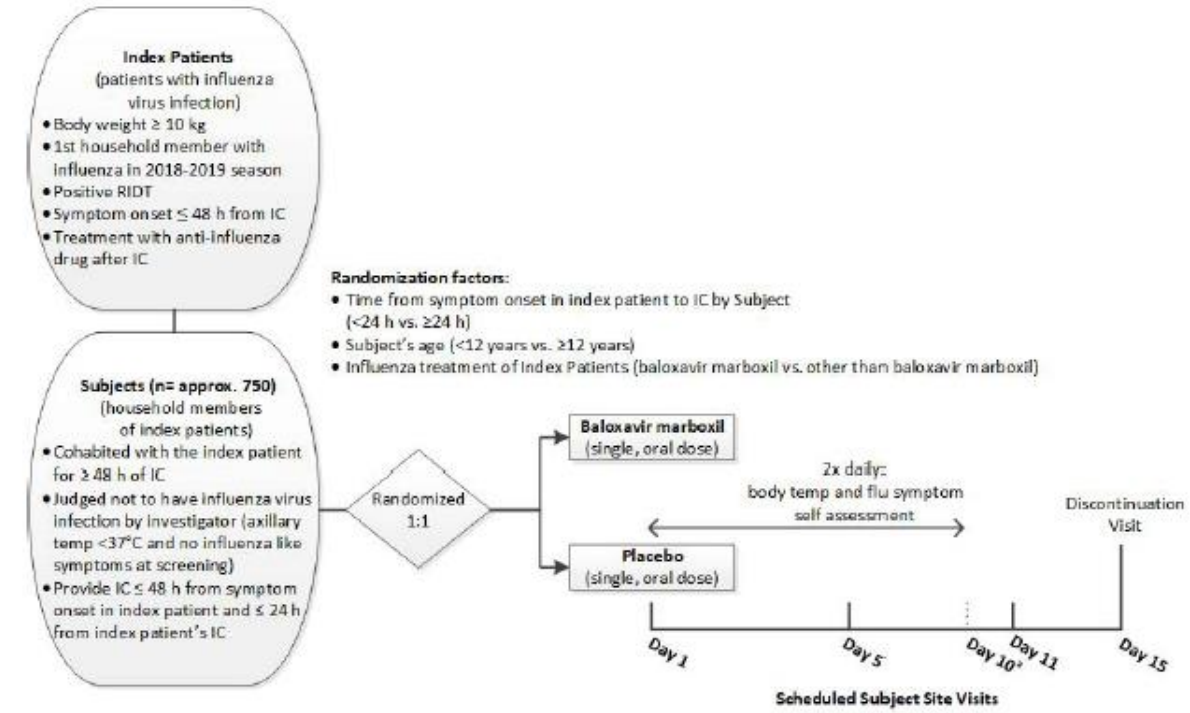
The positive T0834 PEP results observed in Japanese subjects are considered to be successfully bridged to non-Asian subjects ≥1 years of age based on an exposure-matching approach with the recommended dose.

The doses used in study T0384 are considered appropriate. It is noted that the dosing regimen used in Study CP40563 is the proposed PEP dose in children, which differs from the paediatric dosing regimen used in Study T0834. Since baloxavir T1/2 is shorter in paediatrics with lower body weight, the use of the recommended 2 mg/kg for <20 kg and 40 mg for ≥20 kg dosing regimen also for Asians will provide exposure in paediatrics similar to that seen in the adult population. Therefore, the recommended dose of 2 mg/kg for <20 kg and 40 mg for ≥20 kg, regardless of the ethnic group, is expected to be appropriate in a PEP setting in subjects aged ≥1 to <12 years.

2.6.5.6. Main study in post-exposure prophylaxis indication

Study T 0834 (BLOCKSTONE): A phase 3 randomized, double-blind, placebo-controlled study to confirm the efficacy of a single dose of baloxavir marboxil in the prevention of influenza virus infection

An overview of the study design is provided in Figure 12.



h = hour; IC = informed consent; RIDT = rapid influenza diagnostic test.

[a] Subjects made a visit when they experienced a body temperature (axillary) of ≥ 37.5°C or influenza-like symptoms between Day 1 and Day 10.

Figure 12: Overview of Post-Exposure Prophylaxis Study T0834 Design

Methods

The method section of study T0834 has previously been assessed in the initial application. This assessment will summarise the methods and focus on the age group 1 to < 12 years.

Study Participants

Inclusion criteria

Patients with Influenza Virus Infection **(Index Patients)**

Patients who fulfilled all of the following criteria were included in the study as index patients:

1. For adult patients, written informed consent had to be obtained from the patients, who participated voluntarily in the study, prior to Screening. For patients under legal age, written informed consent had to be obtained from the parent/legal representative of the patients; written informed assent also had to be provided in the case of patients aged ≥ 12 years, and should be provided in the case of patients aged < 12 years when feasible.

2. The first patient in a household with influenza virus infection in the 2018-2019 influenza season (November 2018 to April 2019).

3. Patients diagnosed as having influenza with a positive rapid influenza diagnostic test by nasopharyngeal (if difficult, nasal or throat) swabs.

4. Patients with onset of symptoms within 48 hours at the time of informed consent. The onset of symptoms was defined as the time when body temperature first rose to 37.5°C or higher.

5. Patients who were to receive any treatment with anti-influenza drugs after informed consent was obtained.

6. Patients with a body weight of at least 10 kg at Screening.

Household members of index patients **(Subjects)**

Subjects who fulfilled all of the following criteria were included in the study:

1. For subjects under legal age, written informed consent had to be obtained from the parent/legal representative of the subjects; written informed assent should be provided in the case of subjects aged < 12 years when feasible.

2. Subjects who had lived with the index patient for 48 hours or more prior to the time of informed consent.

3. Subjects who met all of the following criteria and were judged not to have influenza virus infection by the investigator or subinvestigator.

- Subjects who had a body temperature (axillary) < 37.0°C at Screening
- Subjects who had no influenza-like symptoms (cough, sore throat, headache, nasal discharge/nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) at Screening

4. Subjects under 12 years of age whose guardian was capable of evaluating influenza symptoms by using a subject diary.

5. Subjects who were able to provide informed consent within 48 hours from the onset of symptoms in index patients and within 24 hours from the time of informed consent in index patients.

*Exclusion criteria **(only for subjects)***

1. Subjects who had been diagnosed with influenza during the 2018-2019 influenza season (November 2018 to April 2019).

2. Subjects who were unable to live with the index patient from Screening until Day 10.

3. Subjects who lived with a household member who had any influenza-like symptom(s) (body temperature of > 37.5°C, cough, sore throat, headache, nasal discharge/nasal congestion, feverishness or chills, muscle or joint pain, or fatigue) other than the index patient on the day of Screening.

4. Subjects living with household members other than the index patient who were diagnosed with or strongly suspected to have influenza during the 2018-2019 influenza season (November 2018 to April 2019).

5. Subjects who had any underlying diseases requiring systemic (oral or injectable), or nasal treatment of antipyretics/analgesics, corticosteroids, or immunosuppressive agents.

6. Subjects who were immunocompromised (including subjects receiving systemic immunosuppressant agents or subjects with human immunodeficiency virus infection).

7. Subjects who had received baloxavir marboxil (Xofluza®), peramivir (Rapiacta®), laninamivir (Inavir®), oseltamivir (Tamiflu®), zanamivir (Relenza®) or amantadine (Symmetrel®) within 30 days prior to Screening (including prophylaxis).

8. Subjects with a known allergy and/or history of significant intolerance against baloxavir marboxil.

9. Subjects with severe (Grade 3 or higher of Common Terminology Criteria for Adverse Events [CTCAE] ver. 5 [7]) underlying diseases.

10. Subjects who had been exposed to an investigational drug within 30 days or 5 half-lives of the drug prior to Screening.

12. Subjects with any condition or circumstance that, in the opinion of the investigator or subinvestigator, would compromise the safety of the subject or the quality of the study data.

Treatments

The dose and formulation of baloxavir marboxil/placebo administered to each subject was dependent on their age and body weight at screening:

- **baloxavir marboxil group** (single oral dose of baloxavir marboxil on Day 1):
    - < 12 years:
        - < 10 kg body weight: 1 mg/kg (2% granules)
        - 10 kg to < 20 kg body weight: 10 mg (2% granules)
        - 20 kg to < 40 kg body weight: 20 mg (one 20 mg tablet)
        - ≥ 40 kg body weight: 40 mg (two 20 mg tablets)
- **placebo group** (single oral dose of baloxavir marboxil placebo on Day 1): same dosing scheme as the baloxavir marboxil group but with the equivalent placebo formulation.

The use of the following drugs and over-the-counter drugs with equivalent efficacy was prohibited from the time of informed consent until completion of assessments on Day 11 (or until completion of assessments at study withdrawal).

- Antipyretics/analgesics [a]
- Anti-influenza drugs [b]
- Corticosteroids [a]
- Immunosuppressive agents [a]
- Influenza vaccines
- Other study drugs

a Only systemic (oral, injection, rectal or enema) and nasal formulations were prohibited.
b Including herbal medicines with indication for influenza virus infection such as Mao-to.

The use of anti-influenza drugs and antipyretics/analgesics was permitted when a subject was diagnosed with influenza virus infection, had influenza-like symptoms, or experienced AE(s) and the investigator or subinvestigator judged its necessity.

The recommended baloxavir marboxil dose for PEP of influenza in individuals ≥1 year of age is the same as for the treatment of uncomplicated influenza: 2 mg/kg for individuals weighing <20 kg, 40 mg for individuals weighing ≥20 kg, and 80 mg for individuals weighing ≥80 kg, administered as a single oral dose. It is noted that the dosing regimen used in Study CP40563 is the proposed PEP dose in children, which differs from the paediatric dosing regimen used in Study T0834. This has been evaluated in the dose-response section.

Objectives

The primary objective of study T0834 was to evaluate the efficacy of a single oral dose of baloxavir marboxil compared with placebo in the prevention of influenza virus infection in subjects who were household members (subjects) of influenza-infected patients (index patients).

The secondary objectives of study T0834 were:

- To evaluate the efficacy of a single oral dose of baloxavir marboxil compared with placebo in the prevention of influenza virus infection by measuring the secondary endpoints in subjects.
- To determine the pharmacokinetics (PK) of the active form of baloxavir marboxil, ie, baloxavir in subjects treated with baloxavir marboxil for prophylaxis.
- To evaluate the safety of a single oral dose of baloxavir marboxil for prophylaxis.

Outcomes/endpoints

Primary Endpoint

Proportion of subjects who are infected with influenza virus (RT-PCR positive), and present with fever and at least one respiratory symptom in the period from Day 1 to Day 10.

– Defined as the proportion of subjects having body temperature (axillary) ≥ 37.5°C, having symptom of "cough" or "nasal discharge/nasal congestion" with a severity of "2, Moderate" or "3, Severe" assessed in the subject diary, and influenza virus positive assessed by RT-PCR.

Secondary Endpoints

1) Time from study treatment to the time when fever, at least one respiratory symptom, and influenza virus infection were observed.

– Defined as the later timepoint of the following:

- Timepoint when body temperature (axillary) rises first to ≥ 37.5°C
- Timepoint when symptom of "cough" or "nasal discharge/nasal congestion" was first assessed as "2, Moderate" or "3, Severe" in the subject diary

If a subject does not have a body temperature (axillary) of ≥37.5°C or respiratory symptom was not assessed as "2, Moderate" or "3, Severe" in the period from Day 1 to Day 10, the subject will be handled as a censored case.

2) Proportion of subjects who are infected with influenza virus (RT-PCR positive), and present with fever or at least one influenza symptom (respiratory symptom or systemic symptom) in the period from Day 1 to Day 10.

– Defined as the proportion of subjects having body temperature (axillary) ≥ 37.5°C or having at least one symptom of influenza with a severity of "2, Moderate" or "3, Severe" assessed in the subject diary, and influenza virus positive assessed by RT-PCR.

3) Time from study treatment to the time when fever or at least one influenza symptom (respiratory symptom or systemic symptom), and influenza virus infection are observed.

– Defined as the timepoint of the following, whichever is earlier:

- Timepoint when body temperature (axillary) rises first to ≥ 37.5°C
- Timepoint when an influenza symptom was first assessed as "2, Moderate" or "3, Severe" in the subject diary

If a subject does not have a body temperature (axillary) of ≥37.5°C and influenza symptoms (respiratory symptoms and systemic symptoms) were not assessed as "2, Moderate" or "3, Severe" in the period from Day 1 to Day 10, the subject will be handled as a censored case.

4) Proportion of asymptomatic influenza-infected (RT-PCR positive) subjects in the period from Day 1 to Day 10

– Defined as the proportion of subjects having body temperature (axillary) < 37.5°C, influenza symptoms all assessed as "0, Absent" or "1, Mild", and influenza virus positive assessed by RT-PCR.

5) Proportion of subjects with influenza virus infection in the period from Day 1 to Day 10

– Defined as the proportion of subjects having influenza virus positive assessed by RT-PCR regardless of body temperature or influenza symptoms.

Other Endpoints

Amino acid substitutions in the PA gene of virus isolated from household subjects with RT PCR-confirmed influenza at any time during the study are summarized. Amino acid substitutions are based on differences from the corresponding reference strain.

Subgroup Analysis

The primary endpoint was analysed by the following subgroups.

- Time from onset of influenza virus infection of index patient to informed consent of subject (< 24 hours or ≥ 24 hours)
- Treatment for influenza virus infection of index patient (baloxavir marboxil or other than baloxavir marboxil)
- Age of subject (< 12 years or ≥ 12 years)
- High risk factor of subject (Presence or Absence)
- Current smoking habit of subject (Yes or No)
- Vaccination status of subject (Yes or No)
- Age of index patient (< 12 years or ≥ 12 years)
- Age of index patient (< 6 years, ≥ 6 years to < 12 years or ≥ 12 years)
- Smoking habit of index patient (Yes or No)
- Vaccination status of index patient (Yes or No)
- Virus titre of index patient at Day 1 (< median value or ≥ median value)
- Influenza virus subtype based on RT-PCR of index patients (A/H1N1pdm, A/H3NX or B)

The primary endpoint is clinically relevant. Prevention of asymptomatic influenza would not be seen as a benefit to the individual, though it could prevent viral shedding and therefore have value in a public health perspective.

The fact that the study was confined to Japan has been addressed and both the internal and external validity of the trial has been clarified in the initial assessment of the study for individuals ≥ 12 years. This can be extrapolated to the <12 years population.

Sample size

The sample size calculation was based on the pooled risk ratio of 0.4 to meet the estimated treatment effect size, using a modified Poisson regression model with a two-sided significance level of 5%. 748 subjects were planned to have a power of 90%. 2 subjects were assumed to be excluded from the

mITT population, which made the sample size of 750 subjects. The sample size calculation is considered adequate.

According to CSR, 19% under 12-years old subjects were involved in the study.

Randomisation and blinding (masking)

Subjects who were qualified for entry in the study were randomised to either the baloxavir marboxil group or the placebo group in a 1:1 ratio, using stochastic minimization method for balancing the 3 stratification factors.

The study was conducted in a double-blind fashion by using matching indistinguishable placebo in appearance, labelling, and packaging.

Statistical methods

Analysed population

The mITT population will include all randomized subjects who have post-baseline efficacy data available (virology testing data assessed by RT-PCR, body temperature or influenza symptom score) among household members of index patients. Subjects will be analyzed according to the treatment to which they were randomized.

This population will be the primary efficacy analysis population.

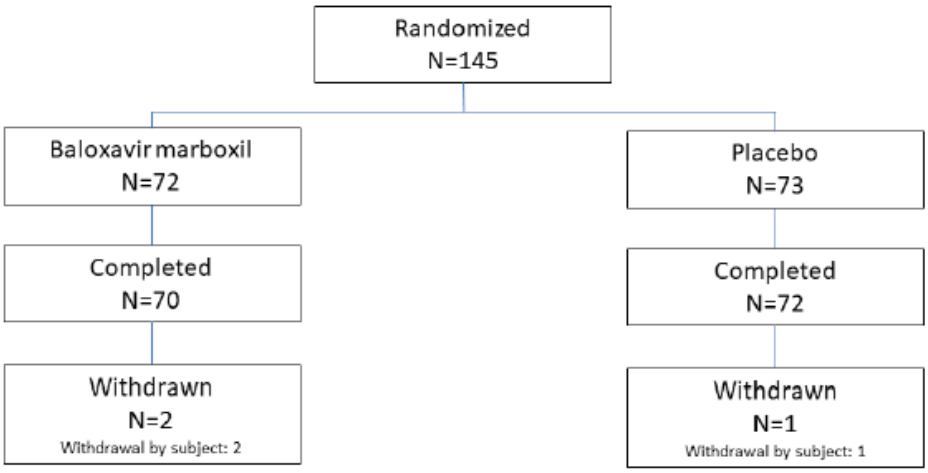
The modified Poisson regression approach was employed to estimate the risk ratio for primary endpoint, using the sandwich variance estimator. It is understood as the covariates were adjusted in the poison regression model. Subgroup analysis with relevant age cut offs were also provided.

Clopper-Pearson method was used to measure the 95% CI of the proportion of influenza-infected subjects.

Results

Participant flow

A total of 145 subjects (72 in the baloxavir marboxil group and 73 in the placebo group) were randomized as household members of 117 index patients. Of these, 70 (18.7%) and 72 (19.1%) subjects completed the study while 2 (0.5%) and 1 (0.3%) subjects were withdrawn from the study in the baloxavir marboxil and placebo groups respectively. The reason for all withdrawals was recorded as 'withdrawal by subject' on the eCRF. This is considered adequate for evaluating efficacy in subjects aged 1 to < 12 years. According to the PIP at least 40 paediatric subjects should be evaluated in the primary analysis.



Source: t_ds_rand_eu

Figure 13: Subject Disposition (subjects aged 1 to <12 years)

Recruitment

The study was conducted at 52 sites in Japan. The studied period was 5 months between 09 Nov 2018 (first subject signed informed consent form) and 25 Mar 2019 (last patient completed). The majority of sites were primary care centers. Investigators confirmed the eligibility of index patients and subjects for participation in the study, before study drug administration on Day 1.

Conduct of the study

The sponsor or designee monitored the study to ensure that the study was conducted in accordance with ICH GCP requirements and protocol.

The original protocol (dated 26 July 2018) was amended once (on 15 October 2018).

Major changes to the protocol amendment 1 included addition of exploratory assessment for prophylaxis effect and change in the exclusion criterion 10.

The analysis plan was not changed after database lock.

Protocol deviations

For 1-<12-year-olds, important protocol deviations were reported in 1 (0.3%) and 4 (1.1%) subjects in the baloxavir marboxil and placebo groups, respectively.

Baseline data

Subjects (< 12 Years mITT Population)

The demographics and baseline disease characteristics for the < 12-year-old subgroup were generally similar between the baloxavir marboxil and placebo groups (Table 26).

Table 26: Demographics and Baseline Characteristics of Subjects <12 Years in Study T0834 (mITT Population)

	Baloxavir Marboxil N=71 n (%)	Placebo N=71 n (%)
Median Age, years[a]	8.0 (1–11)	7.0 (1–11)
Median Weight, kg[a]	24.50 (10.3–57.8)	22.30 (8.0–46.2)
Sex		
Male	34 (47.9%)	32 (45.1%)
Female	37 (52.1%)	39 (54.9%)
Relation to index patient		
Parent	1 (1.4%)[b]	0
Sibling	68 (95.8%)	64 (90.1%)
Child	2 (2.8%)	7 (9.9%)
Influenza vaccination within the previous 6 months	24 (33.8%)	22 (31.0%)
High-risk factor present	18 (25.4%)	22 (31.0%)
Time from onset of influenza virus infection of index patient to informed consent of subject (hours)		
<24	48 (67.6%)	48 (67.6%)
≥24	23 (32.4%)	23 (32.4%)
Influenza virus subtype based on RT-PCR		
Positive	4 (5.6%)	11 (15.5%)
A/H1N1pdm	1 (1.4%)	4 (5.6%)
A/H3NX	2 (2.8%)	6 (8.5%)
A/ND	1 (1.4%)	1 (1.4%)
B	0	0
Mixed infection	0	0
Negative	67 (94.4%)	60 (84.5%)

BMI = body mass index; ND = not determined; RT-PCR = reverse transcription polymerase chain reaction

[a] Data presented as median (minimum–maximum)

[b] Subject identified to have relationship to the index patient as 'parent' is a suspected data capture error, both the index patient and household contact are <10 years old, and therefore should be captured as siblings.

Source: SCE t_dm_hhc_xv41428

A summary of age categories for the mITT population is presented in Table 27.

Table 27: Summary of Age Categories for Subjects <12 Years in Study T0834 (mITT Population)

Age Group, Years	Baloxavir Marboxil N = 374 n (%)	Placebo N = 375 n (%)
<1 years	0	0
1 year	1 (0.3%)	5 (1.3%)
2 years	1 (0.3%)	2 (0.5%)
3 years	6 (1.6%)	7 (1.9%)
4 years	6 (1.6%)	6 (1.6%)
5 years	2 (0.5%)	3 (0.8%)
6 years	9 (2.4%)	8 (2.1%)
7 years	7 (1.9%)	13 (3.5%)
8 years	12 (3.2%)	3 (0.8%)
9 years	11 (2.9%)	5 (1.3%)
10 years	14 (3.7%)	13 (3.5%)
11 years	2 (0.5%)	6 (1.6%)

source: SCE t_dm_age_xv41428

Overall, the baloxavir and placebo subject groups are comparable. However, only two subjects aged <3 years were included in the baloxavir marboxil group in study T0834. However, since the application in <12 years is to a large extend based on extrapolation from older subjects, this will not be pursued.

Index Patients with a Subject Included in < 12 years mITT Population

The demographic and baseline disease characteristics of the index patients with a subject included in the < 12 year old mITT population are summarized by the subject's treatment group in Table 28 and were generally similar between the baloxavir marboxil and placebo groups.

Table 28: Demographics and Baseline Characteristics of Index Patients Associated with Subjects <12 Years of Age in Study T0834 (mITT Population)

	Baloxavir Marboxil N=71	Placebo N=71
Median (min-max) Age, years	6.00 (1.0–38.0)	7.00 (1.0–45.0)
Age group (yr)		
<10	58 (81.7%)	47 (66.2%)
≥ 10 to < 20	11 (15.5%)	17 (23.9%)
≥30 to <40	2 (2.8%)	4 (5.6%)
≥40 to <50	0	3 (4.2%)
Sex		
Male	43 (60.6%)	39 (54.9%)
Female	28 (39.4%)	32 (45.1%)
Influenza vaccination within the previous 6 months		
Yes	23 (32.4%)	24 (33.8%)
No	48 (67.6%)	47 (66.2%)
Household size group		
2	0	1 (1.4%)
3	4 (5.6%)	1 (1.4%)
≥4	67 (94.4%)	69 (97.2%)
Influenza virus subtype based on RT-PCR		
Positive	71 (100%)	70 (98.6%)
A/H1N1pdm	33 (46.5%)	40 (56.3%)
A/H3NX	38 (53.5%	30 (42.3%)
Negative	0	1 (1.4%)
Virus titer [$log_{10}(TCID_{50}/mL)$]		
n	71	71
mean (SD)	5.61 (1.75)	5.47 (2.03)
Median	5.50	5.50
Min - Max	0.7 - 8.5	0.7 - 8.5

	Baloxavir Marboxil N=71	Placebo N=71
Actual treatment for influenza virus infection		
Baloxavir Marboxil	35 (49.3%)	33 (46.5%)
Oseltamivir	25 (35.2%)	27 (38.0%)
Zanamivir	3 (4.2%)	3 (4.2%)
Laninamivir	5 (7.0%)	6 (8.5%)
Peramivir	3 (4.2%)	2 (2.8%)

Source: SCE t_dm_ips_xv41428

Overall, the baloxavir and placebo index groups are comparable. It is noted that all index patients received anti-influenza treatment, the impact of this treatment has been clarified during the initial assessment for the adult and adolescent population.

All subjects and index patients in both groups were Asian.

Numbers analysed

Of the 749 paediatric household members (subjects) in the overall study population (mITT), subjects aged 1- < 12 years accounted for 19% (142 paediatric subjects, 71 subjects each in the baloxavir marboxil and placebo groups).

Outcomes and estimation

Primary Endpoint: Proportion of Subjects with Influenza Virus Infection, Fever, and at Least One Respiratory Symptom

In the < 12 year subgroup analyses, the proportion of subjects with influenza virus infection (RT-PCR positive), fever, and at least one respiratory symptom during the period from Day 1 to Day 10 was lower in the baloxavir marboxil group than in the placebo group (4.2% vs. 15.5%; adjusted risk ratio 0.27 [95% CI: 0.08, 0.90], p = 0.0339), These results are consistent with the primary analysis in the full mITT population (Table 29).

Table 29: Primary Endpoint and Subgroup Evaluation by Subject Age in Study T0834 (mITT Population)

			Comparison with Placebo		
	Baloxavir Marboxil	Placebo	Adjusted risk ratio [b]	95%CI for adjusted risk ratio [b]	P-value [b]
Primary Endpoint (all ages)					
n	374	375			
Subjects with influenza infection, fever and at least one respiratory symptom	7	51	0.14	0.06, 0.30	< 0.0001
Proportion of subjects with influenza infection, fever and at least one respiratory symptom	1.9%	13.6%			
95% confidence interval [a]	0.8%, 3.8%	10.3%, 17.5%			
Primary Endpoint Subgroup:					
Subject ≥ 12 years					
n	303	304			
Subjects with influenza infection, fever and at least one respiratory symptom	4	40	0.10	0.04, 0.28	< 0.0001
Proportion of subjects with influenza infection, fever and at least one respiratory symptom	1.3%	13.2%			
95% confidence interval [a]	0.4%, 3.3%	9.6%, 17.5%			
Subject < 12 years					
n	71	71			
Subjects with influenza infection, fever and at least one respiratory symptom	3	11	0.27	0.08, 0.90	0.0339
Proportion of subjects with influenza infection, fever and at least one respiratory symptom	4.2%	15.5%			
95% confidence interval [b]	0.9%, 11.9%	8.0%, 26.0%			

[a] Clopper-Pearson method

[b] Modified Poisson regression approach of a binary response (whether all of the following are confirmed for a subject or not; occurrence of fever, at least one respiratory symptom, and influenza virus infection) on a study treatment for subject with randomization factors (time from onset of influenza virus infection of index patient to informed consent of subject [< 24 hours or ≥ 24 hours], treatment for influenza virus infection of index patient [baloxavir marboxil, other than baloxavir marboxil or no treatment when index patients didn't take any treatment] and age of subject [continuous variable]) as covariates.

Note: All statistical tests were performed at the two-sided significance level of 0.05. No multiplicity adjustments were made in this study.

Source: Table 14.2.1.1 and 14.2.1.4.3 CSR T0834

For the primary endpoint, the proportion of subjects with influenza virus infection, fever, and at least one respiratory symptom during the period from Day 1 to Day 10 was lower in the baloxavir marboxil

group than in the placebo group (4.2% vs. 15.5%; adjusted risk ratio 0.27 [95% CI: 0.08, 0.90], p = 0.0339). The proportion of subjects who were infected with influenza virus (RT-PCR positive) and presented with fever and at least one respiratory symptom from Day 1 to Day 10 was lower in the baloxavir marboxil group than in the placebo group for both subgroups of subjects younger and older than 12 years, but the adjusted risk ratio was higher in the youngest age group, however, numbers are limited for the age group < 12 years.

Further, an analysis of the primary endpoint on all randomized household subjects of influenza infected index patients were performed. There were two subjects, one in each treatment group, who were excluded from the mITT population as they did not receive any study drug and one subject withdrew due to GCP noncompliance in the placebo group. For this analysis, these subjects were included and conservatively set as failure, i.e. they were considered as influenza-infected subjects.

The addition of the three subjects using an NC = F analysis, did not have any impact on the conclusions of the primary efficacy endpoint (risk ratio: 0.14, p-value: <0.0001).

Results by Age subgroup

Table 30: Analysis of Proportion of subjects infected with Influenza and Present with Fever and at least One Respiratory Symptom by Age subgroup (mITT population)

	Baloxavir Marboxil	Placebo	Comparison with Placebo		
			Adjusted risk ratio [b]	95%CI for adjusted risk ratio [b]	P-value [b]
Subject <5 years					
n	14	20			
Subjects with influenza infection, fever and at least one respiratory symptom	1	4	0.32	0.04, 2.53	0.2827
Proportion of subjects with influenza infection, fever and at least one respiratory symptom	7.1%	20.0%			
95% confidence interval [a]	0.2%, 33.9%	5.7%, 43.7%			
Primary Endpoint Subgroup: Subject 5–<12 years					
n	57	51			
Subjects with influenza infection, fever and at least one respiratory symptom	2	7	0.28	0.06, 1.25	0.0946
Proportion of subjects with influenza infection, fever and at least one respiratory symptom	3.5%	13.7%			
95% confidence interval [a]	0.4%, 12.1%	5.7%, 26.3%			
Subject ≥ 12 years					
n	303	304			
Subjects with influenza infection, fever and at least one respiratory symptom	4	40	0.10	0.04, 0.28	<0.0001
Proportion of subjects with influenza infection, fever and at least one respiratory symptom	1.3%	13.2%			
95% confidence interval [b]	0.4%, 3.3%	9.6%, 17.5%			

[a] Clopper-Pearson method

[b] Modified Poisson regression approach of a binary response (whether all of the following are confirmed for a subject or not; occurrence of fever, at least one respiratory symptom, and influenza virus infection) on a study treatment for subject with randomization factors (time from onset of influenza virus infection of index patient to informed consent of subject [< 24 hours or ≥ 24 hours], treatment for influenza virus infection of index patient [baloxavir marboxil, other than baloxavir marboxil or no treatment when index patients didn't take any treatment] and age of subject [continuous variable]) as covariates.

Note: All statistical tests were performed at the two-sided significance level of 0.05. No multiplicity adjustments were made in this study.

Source: t_prop_infl_prim_endpt_mitt_age_eu_xv41428

The Applicant presented data for the subgroups <5 years, 5 - <12 years and ≥ 12 years. Only 7 subjects in the baloxavir marboxil group met the primary endpoint across all age cut-offs, hence data should be interpreted with caution. The results support that efficacy is not age depending.

Secondary Efficacy Endpoints

The results of the analyses of the secondary efficacy endpoints in the < 12 year mITT population were generally supportive of the primary endpoint results in the < 12 year mITT population (Table 31). In addition, results of the post-hoc evaluation of key secondary clinical endpoints in the < 12 year

subgroup were generally in agreement with secondary clinical endpoints in the overall mITT population (Table 32).

Table 31: Post-Hoc Evaluation of Secondary Endpoints in <12 Year Subgroup in Study T0834 (mITT Population)

	Baloxavir Marboxil (n=71)	Placebo (n=71)	Adjusted Risk Ratio (95% CI)	*P*-value
Proportion of Subjects with Influenza Virus Infection and Fever or at least One Influenza Symptom	6/71 8.5%	20/71 28.2%	0.30 (0.13, 0.70)	0.0052
Proportion of Subjects with Influenza Virus Infection Regardless of Symptoms	17/71 23.9%	24/71 33.8%	0.73 (0.43, 1.24)	0.2451
Proportion of Subjects with Asymptomatic Influenza Virus Infection	11/71 15.5%	3/71 4.2%	4.17 (1.15, 15.09)	0.0295

Source: SCE t_eff_sec2_xv41428, t_eff_sec4_xv41428, and t_eff_sec5_xv41428

Table 32: Secondary Efficacy Endpoints in Study T0834 (Overall mITT Population)

	Baloxavir Marboxil (n=374)	Placebo (n=374)	Adjusted Risk Ratio (95% CI)	*P*-value
Proportion of Subjects with Influenza Virus Infection and Fever or at least One Influenza Symptom	20/374 5.3%	84/375 22.4%	0.24 (0.15, 0.38)	<0.0001
Proportion of Subjects with Influenza Virus Infection Regardless of Symptoms	49/374 13.1%	114/375 30.4%	0.43 (0.32, 0.58)	<0.0001
Proportion of Subjects with Asymptomatic Influenza Virus Infection	29/374 7.8%	29/375 7.7%	1.00 (0.61, 1.64)	0.9917

Source: Tables 11-8, 11-10, and 11-11 of CSR T0834

The secondary efficacy endpoint results overall support the primary endpoint results.

It is noted that the proportion of subjects with asymptomatic influenza virus infection, was higher in the baloxavir marboxil group compared to the placebo group in the < 12 years population. As described by the Applicant, these results demonstrate that baloxavir marboxil prevents incoming virus from establishing a clinically meaningful symptomatic infection and prevents household members from developing symptomatic influenza, which is the aim of PEP.

Ancillary analyses

Treatment-Emergent I38X Substitutions

Overall, compared with reference strains, amino acid changes at position 38 of the PA gene (PA/I38X) were detected in virus from 10 baloxavir marboxil-treated subjects. Of these 10 subjects with I38X substitutions, 3 were < 12 years of age and 2 of these 3 paediatric subjects developed clinical influenza (as described for the primary endpoint).

Amino acid substitutions

No amino acid substitutions were found at position 38 in virus collected from RT-PCR positive placebo-treated subjects (36 at baseline and 87 postdose), with the exception of 2 subjects (one paediatric patient [6 years] and one adult) who received baloxavir marboxil as rescue medication on Day 3; PA/I38X was detected in virus at Day 5 from these 2 subjects.

The possible clinical impact of the gene changes cannot be properly evaluated due to a low number of patients, who were infected with a virus that expressed the gene changes.

- **Summary of main efficacy results (PEP indication)**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 33: Summary of efficacy for trial T0834. Data presented for the subgroup < 12 years of age.

Title: A phase 3 randomized, double-blind, placebo-controlled study to confirm the efficacy of a single dose of baloxavir marboxil in the prevention of influenza virus infection		
Study identifier	1719T0834 (T0834), XV41428, BLOCKSTONE	
Design	A randomized, double-blind, multicenter, parallel-group, placebo-controlled comparative study to evaluate the efficacy and safety of a single oral dose of baloxavir marboxil in the prevention of influenza virus infection in approximately 750 subjects who were household members of influenza-infected index patients. Eligible subjects were randomly assigned with the stochastic minimization method in a 1:1 ratio to receive a single weight-based dose of baloxavir marboxil or placebo. There were a maximum of 5 study visits during the 15-day period, for 11 days of efficacy evaluation and 15 days of safety evaluation.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	15 days Not applicable Not applicable
Hypothesis	Superiority	
Treatments groups	Baloxavir marboxil	• Baloxavir marboxil (subjects < 12 years of age) ○ 1 mg/kg (weight < 10 kg) ○ 10-mg (weight 10 to < 20 kg) ○ 20-mg (weight 20 to <40 kg) ○ 40-mg (weight ≥ 40 kg) • 1 day duration • N = 71

Title: A phase 3 randomized, double-blind, placebo-controlled study to confirm the efficacy of a single dose of baloxavir marboxil in the prevention of influenza virus infection			
Study identifier	1719T0834 (T0834), XV41428, BLOCKSTONE		
	Placebo		• Baloxavir matching Placebo. • 1 day duration • N = 71
Endpoints and definitions	Primary endpoint	Proportion symptomatic infected	Proportion of subjects who are infected with influenza virus (RT-PCR positive), and present with fever and at least one respiratory symptom in the period from Day 1 to Day 10. Defined as subjects having a body temperature (axillary) of ≥ 37.5°C, having symptom of "cough" and/or "nasal discharge/nasal congestion" with a severity of "2, Moderate" or "3, Severe" assessed in the subject diary, and influenza virus positivity assessed by RT-PCR.
Database lock	22nd April 2019		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Modified intention-to-treat (mITT) Efficacy was assessed over 11 days The mITT population included all randomized subjects who received the study drug and had post-baseline efficacy data available among household members of influenza-infected index patients. The mITT population was analyzed as randomized.		
Descriptive statistics and estimate variability	Treatment group	Baloxavir marboxil	Placebo
	Number of subject	71	71
	Proportion symptomatic infected (%)	4.2	15.5
	95% confidence interval using the Clopper-Pearson method (%)	0.9, 11.9	8.0, 26.0
Effect estimate per comparison	Primary endpoint – Proportion symptomatic infected	Comparison groups	Baloxavir marboxil and Placebo
		Risk ratio using modified Poisson regression approach of a binary response	0.27
		95% confidence interval using modified Poisson regression approach of a binary response	0.08, 0.90
		P-value using modified Poisson regression approach of a binary response	0.0339
Notes	Covariates used in the modified Poisson regression approach were: time from onset of influenza in the index patient to informed consent of subject (< 24 hours or ≥ 24 hours), treatment for influenza virus infection in the index patient (baloxavir marboxil, other than baloxavir marboxil or no treatment when index patients did not take any treatment) and age of the subject (continuous variable). No multiplicity adjustments were made in this study.		

2.6.5.7. Clinical studies in special populations

Gender

Table 34 shows the proportion of subjects who were infected with influenza virus (RTPCR positive) and presented with fever and at least one respiratory symptom from Day 1 to Day 10 by gender.

Table 34: Analysis of Proportion of Subjects Who are Infected with Influenza Virus and Present with Fever and At Least One Respiratory Symptom (Subgroup: Gender) for 1 - < 12 year age group – mITT Population

Subgroup		Baloxavir Marboxil	Placebo
Gender			
Male	Summary statistics		
	- n	34	32
	- Subjects with influenza virus infection, fever and at least one respiratory symptom	2	5
	- Proportion of subjects with influenza virus infection, fever and at least one respiratory symptom (%)	5.9	15.6
	- 95% confidence interval (%) [a]	0.7, 19.7	5.3, 32.8
	Comparison with Placebo		
	- Risk ratio [b]	0.34	---
	- 95% confidence interval for risk ratio [b]	0.07, 1.55	---
	- P-value [b]	0.1624	---
Female	Summary statistics		
	- n	37	39
	- Subjects with influenza virus infection, fever and at least one respiratory symptom	1	6
	- Proportion of subjects with influenza virus infection, fever and at least one respiratory symptom (%)	2.7	15.4
	- 95% confidence interval (%) [a]	0.1, 14.2	5.9, 30.5
	Comparison with Placebo		
	- Risk ratio [b]	0.18	---
	- 95% confidence interval for risk ratio [b]	0.02, 1.44	---
	- P-value [b]	0.1055	---

[a] Clopper-Pearson method
[b] modified Poisson regression approach of a binary response (whether all of the following are confirmed for a subject or not; occurrence of fever, at least one respiratory symptom, and influenza virus infection) on a study treatment for subject with randomization factors (time from onset of influenza virus infection of index patient to informed consent of subject [<24 hours or >=24 hours] and treatment for influenza virus infection of index patient [baloxavir marboxil, other than baloxavir marboxil or no treatment when index patients didn't take any treatment] as covariates.

Adapted from t_prop_infl_prim_endpt_mitt_gen_vx_eu_xv41428

The results from the <12 year-old population are generally in line with the results based on the total study population, showing that baloxavir marboxil is efficacious in PEP regardless of gender.

Influenza Vaccination Status

Table 35 shows results by vaccination status of subjects (household contacts [HHCs]).

Table 35: Analysis of Proportion of Subjects Who are Infected with Influenza Virus and Present with Fever and At Least One Respiratory Symptom (Subgroup: Vaccination Status) for 1 - < 12 year age group – mITT Population

Subgroup		Baloxavir Marboxil	Placebo
Vaccination Status			
Yes	Summary statistics		
	- n	24	22
	- Subjects with influenza virus infection, fever and at least one respiratory symptom	1	3
	- Proportion of subjects with influenza virus infection, fever and at least one respiratory symptom (%)	4.2	13.6
	- 95% confidence interval (%) [a]	0.1, 21.1	2.9, 34.9
	Comparison with Placebo		
	- Risk ratio [b]	0.36	---
	- 95% confidence interval for risk ratio [b]	0.05, 2.38	---
	- P-value [b]	0.2872	---
No	Summary statistics		
	- n	47	49
	- Subjects with influenza virus infection, fever and at least one respiratory symptom	2	8
	- Proportion of subjects with influenza virus infection, fever and at least one respiratory symptom (%)	4.3	16.3
	- 95% confidence interval (%) [a]	0.5, 14.5	7.3, 29.7
	Comparison with Placebo		
	- Risk ratio [b]	0.27	---
	- 95% confidence interval for risk ratio [b]	0.06, 1.26	---
	- P-value [b]	0.0958	---

[a] Clopper-Pearson method
[b] modified Poisson regression approach of a binary response (whether all of the following are confirmed for a subject or not; occurrence of fever, at least one respiratory symptom, and influenza virus infection) on a study treatment for subject with randomization factors (time from onset of influenza virus infection of index patient to informed consent of subject [<24 hours or >=24 hours] and treatment for influenza virus infection of index patient [baloxavir marboxil, other than baloxavir marboxil or no treatment when index patients didn't take any treatment] as covariates.

Adapted from t_prop_infl_prim_endpt_mitt_gen_vx_eu_xv41428

Table 36 shows results by vaccination status of index patients (IPs).

Table 36: Proportion of Subjects who are infected with Influenza and present with Fever and ≥ 1 Respiratory Symptom, Vaccination Status of Index Patients, 1 - < 12 years age group (mITT population)

Analysis of Proportion of Subjects Who are Infected with Influenza Virus and Present with Fever and At Least One Respiratory Symptom (Subgroup: Vaccination Status of the Index Patient) for 1 - < 12 year age group - mITT Population
Project: 1719T0834 (XV41428)

Subgroup		Baloxavir Marboxil	Placebo
Vaccination Status of the Index Patient			
Yes	Summary statistics		
	- n	23	24
	- Subjects with influenza virus infection, fever and at least one respiratory symptom	1	4
	- Proportion of subjects with influenza virus infection, fever and at least one respiratory symptom (%)	4.3	16.7
	- 95% confidence interval (%) [a]	0.1, 21.9	4.7, 37.4
	Comparison with Placebo		
	- Risk ratio [b]	0.30	---
	- 95% confidence interval for risk ratio [b]	0.05, 1.68	---
	- P-value [b]	0.1697	---
No	Summary statistics		
	- n	48	47
	- Subjects with influenza virus infection, fever and at least one respiratory symptom	2	7
	- Proportion of subjects with influenza virus infection, fever and at least one respiratory symptom (%)	4.2	14.9
	- 95% confidence interval (%) [a]	0.5, 14.3	6.2, 28.3
	Comparison with Placebo		
	- Risk ratio [b]	0.32	---
	- 95% confidence interval for risk ratio [b]	0.07, 1.54	---
	- P-value [b]	0.1541	---

[a] Clopper-Pearson method
[b] modified Poisson regression approach of a binary response (whether all of the following are confirmed for a subject or not; occurrence of fever, at least one respiratory symptom, and influenza virus infection) on a study treatment for subject with randomization factors (time from onset of influenza virus infection of index patient to informed consent of subject [<24 hours or>=24 hours] and treatment for influenza virus infection of index patient [baloxavir marboxil, other than baloxavir marboxil or no treatment when index patients didn't take any treatment] as covariates.

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Output: root/clinical_studies/RO7191686/CDT70160/XV41428/data_analysis/CSR/prod/output/t_prop_infl_prim_endpt_mitt_vxip_eu_xv41428.out
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In adults, there was no apparent difference in efficacy in the subgroup analysis of vaccination status in either index patient or subject. In subjects < 12 years, the small number of subjects meeting the

primary endpoint in each group, makes it difficult to draw conclusions; however, these results are generally in line with the results of the total study population.

Renal or Hepatic Impairment

In the popPK model, creatinine clearance, alanine aminotransferase, aspartate aminotransferase and bilirubin were not significant covariates. In the initial application, the MAH showed that in 8 subjects with moderate hepatic impairment, the mean Cmax was lower (20% decrease) and the AUC0-inf was higher (12% increase) than in 8 subjects with normal hepatic function. However, the differences were small and not considered clinically relevant, and no dose adjustment is considered necessary in adolescents and adults with mild or moderate hepatic impairment. The same can be expected for the paediatric population, in light of the metabolism and clearance of baloxavir. Hence, impaired renal function, mild or moderate hepatic impairment is not considered to impact the PK, safety or efficacy in paediatric subjects.

The PK of baloxavir in patients with severe hepatic impairment has not been evaluated.

Overall, the subgroup analyses and discussion on subgroups suggested similar efficacy in subjects 1 to < 12 year old, regardless of gender, vaccination status and renal or hepatic impairment.

2.6.6. Discussion on clinical efficacy

TREATMENT INDICATION

Design and conduct of clinical studies

The efficacy of baloxavir marboxil has previously been established in two pivotal randomized Phase 3 studies in adults and adolescents. The treatment indication for baloxavir in adults and adolescents was approved in the EU in January 2021.

Demonstration of clinical efficacy of baloxavir marboxil in the proposed indication of **treatment** of influenza infection in children 1 to < 12 years in based on one pivotal study. The pivotal study CP405463 was a global Phase 3, multicenter, randomized, double-blind, active-controlled study to assess the safety, pharmacokinetics (PK), and efficacy of baloxavir marboxil granules compared with oseltamivir in otherwise healthy paediatric patients 1 to <12 years of age with influenza-like symptoms. The primary objective of the study was to compare the safety of baloxavir marboxil with the safety of oseltamivir. Evaluation of the clinical efficacy and virological activity of baloxavir marboxil compared with oseltamivir were secondary objectives. This is in accordance with the agreed paediatric investigational plan. Overall, the design is considered acceptable.

The inclusion- and exclusion criteria in the study selected a healthy population without either acute or chronic illnesses. The inclusion- and exclusion criteria are appropriate for the sought indication of treatment of uncomplicated influenza.

Patients were recruited in two cohorts based on age (1 to < 5 years of age and 5 to < 12 years of age) and subsequently randomized on a permuted block basis in a 2:1 ratio to receive either baloxavir marboxil and corresponding placebo or oseltamivir and corresponding placebo.

Baloxavir marboxil was provided as granules for oral suspension; administered orally as a single dose on Day 1 only. A dose was administered based on the body weight of the child (2 mg/kg for patients weighing < 20 kg, or 40 mg for patients weighing ≥ 20 kg). The dose used in study CP40563 are

considered appropriate. The baloxavir marboxil matching placebo was provided as granules for oral suspension and was administered orally on Day 1 only.

The choice of oseltamivir as active comparator is considered relevant as an approved medicinal product in EU for the sought indication. Oseltamivir was administered orally BID (morning and evening) for 5 days. A dose was administered based on the body weight of the child. The oseltamivir matching placebo powder was an oral suspension and was administered orally BID for 5 days.

The study medication is adequately described and the choice of paracetamol as rescue medication is acceptable. On request, the MAH has conducted a sensitivity analysis using a composite endpoint of TTAS without rescue medication in order to address the risk of confounding by paracetamol use. In the SmPC it is stated that: "*Patients could receive paracetamol as required"*.

The key clinical efficacy endpoint in the study was time to persistent alleviation of influenza signs and symptoms (TTAS) (cough and nasal symptoms, time to return to normal health and activity and duration of fever). The other clinical efficacy endpoints in the study relate either to clinical improvement, such as time to alleviation/improvement of individual symptoms/fever and absence of complications. The virology efficacy endpoints in the study address the risk of transmission of the infection, such as viral shedding and virus titre and the additional endpoints are clinically relevant in a broader perspective in terms of developing resistance.

There was no formal statistical hypothesis testing and no formal sample size calculations have been performed in this study. 80 patients in the baloxavir marboxil treatment group and 40 patients in the oseltamivir treatment group were planned to be recruited to detect adverse events with a 3% incidence for at least 1 patient with a probability of ≥90%. This is acceptable.

The statistical analyses of efficacy endpoints were descriptive. The ITTI population was used for all efficacy analyses, comprising all treated subjects with a positive RT-PCR on day 1 or during the study period, as in prior treatment studies that have supported NAI approvals. This is endorsed. The data was summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables. Efficacy endpoints were based on the CARIFS questionnaire data which was recorded by parent/ caregiver using handheld device. Time-to event endpoints and duration endpoints was summarized using Kaplan-Meier plots and summaries of the median survival time.

Efficacy data and additional analyses

The demographic and baseline disease characteristics were well balanced between the two treatment groups in terms of demographics, subtype of influenza infection, and percentage of patients who received influenza vaccination. The two cohorts based on age reached the minimum of 15 patients 1 to < 5 years of age and minimum 30 patients 5 to < 12 years of age as agreed in the PIP. However, the number of patients within the two age groups are somewhat skewed. There is only one 1 year old and two 2 years old patients who were included in the baloxavir marboxil group in study CP40563 compared to three 1 year old and three 2 years old patients in the oseltamivir group. However, since the application in <12 years is to a large extend based on extrapolation from older subjects, this will not be pursued.

25 (30.9%) patients in the baloxavir marboxil group and 7 (16.3%) patients in the oseltamivir group were co-infected with another respiratory virus at baseline. TTAS was similar in the baloxavir marboxil group and oseltamivir group for patients with and without co-infection. Hence, there is no indication that baloxavir marboxil should be less effective in patients with co-infection with other respiratory viruses.

Major protocol deviations were low and in general comparable between the two treatment groups and is not considered impacting efficacy and safety of the study.

The main efficacy endpoint, TTAS based on the CARIFS questionnaire, was comparable in the two treatment groups. Of important clinical relevance, the incidence of influenza-related complications was low and similar in both treatment groups. Acknowledging that overall numbers are small, nonetheless these findings contrast to the results from the pivotal studies in adults (which are given in the SmPC as comparison vs. placebo only). The MAH has included the frequencies of influenza-related complication in both SmPC's.

Regarding virology endpoints, based on virus titer, the data were more favourable in the baloxavir marboxil group than in the oseltamivir group. Using RT-PCR methodology, the median time to cessation of viral shedding was similar in the two treatment groups. The observation reflects the different methodology with RT-PCR, which detects viable and nonviable virus or virus fragments, in contrast to virus titre, which is a culture-based assay and only detects intact virus capable of growing in tissue culture.

Overall, treatment of influenza with baloxavir marboxil and oseltamivir is comparable, based on TTAS. The other secondary endpoints were in line with the main analysis.

In the subgroup analyses for virus subtype, the median TTAS was comparable in the baloxavir marboxil and oseltamivir treatment groups for virus A/H3. For subtype A/H1N1, the median TTAS was longer in the oseltamivir group. However, no conclusions can be made, due to the low number of patients in this subgroup. The subgroup analyses for time to cessation of viral shedding by virus titer and RT-PCR were consistent with the results of the overall ITTI population. No reduced susceptibility of baseline viruses was detected for either baloxavir marboxil nor oseltamivir.

11 (19.3%) baloxavir marboxil-treated patients with paired samples had treatment-emergent I38X substitutions in the PA genes. TTAS for these patients was comparable to the oseltamivir group. A subgroup analysis by age found prevalence rates of I38X to be higher in children 1 to < 5 years) compared to children aged 5 to < 12 years. None of the selected patients had treatment-emergent amino acid substitutions in PB1 or PB2. The possible clinical impact of these gene changes cannot be properly evaluated due to a relatively low number of patients, who were infected with a virus that expressed the gene changes. Thus, it is noted that a change in virus genome may occur on treatment with baloxavir marboxil, this is in line with the results from the clinical trials in adults and adolescents.

Post-hoc subgroup analyses were additionally addressing co-infection, age (1-5 years and 5-<12 years), gender and vaccination status, and no relevant differences were seen between subgroups. Subgroup analyses on race, region, renal and hepatic impairment were not conducted. The PK in those subgroups is addressed in the pharmacology section.

POST-EXPOSURE PROPHYLAXIS INDICATION

Design and conduct of clinical studies

Study T0834 has been included in the MAA to support the indication of baloxavir marboxil for post-exposure prophylaxis (PEP) of influenza in individuals aged 1 to < 12 years. The same study was evaluated and used for approval of the indication of post-exposure prophylaxis of influenza in individuals 12 years of age and older in EU.

Study T0834 is a household influenza prophylaxis placebo-controlled trial conducted in Japan in the 2018-2019 influenza season. Index patients were included less than 48 hours after onset of symptoms. Influenza infection in index patients was confirmed with a RT-PCR. Eligible and volunteer household

members of all age groups living with the index patients, were randomly assigned to a single dose of either baloxavir or placebo. Baloxavir marboxil dosing was dependent on age and body weight at screening. The fact that the study was confined to Japan has been addressed and both the internal and external validity of the trial has been clarified in the initial assessment of the study for individuals ≥ 12 years. This can be extrapolated to the <12 years population.

The baloxavir marboxil single dose administrations used in study T0834 are the approved doses used for treatment of influenza virus infection outside EU. Subjects < 12 years were administered weight-based dosing: 1 mg/kg in subjects < 10 kg, 10 mg in subjects 10 to < 20 kg, 20 mg in subjects 20 to < 40 kg and 40 mg in subjects ≥ 40 kg. The doses have been found to have an acceptable safety profile. Plasma baloxavir concentrations are predicted to be above the expected preventive levels (≥ 0.444 and ≥ 2.35 ng/mL for influenza A and B virus, respectively) for approximately 10 days. The doses used in study T0384 are considered appropriate.

The recommended baloxavir marboxil dose for PEP of influenza in individuals ≥1 year of age is the same as for the treatment of uncomplicated influenza: 2 mg/kg for individuals weighing <20 kg, 40 mg for individuals weighing ≥20 kg, and 80 mg for individuals weighing ≥80 kg, administered as a single oral dose. Since baloxavir $T_{1/2}$ is shorter in paediatrics with lower body weight, the use of the recommended 2 mg/kg for <20 kg and 40 mg for ≥20 kg dosing regimen also for Asians will provide exposure in paediatrics similar to that seen in the adult population. Therefore, the recommended dose of 2 mg/kg for <20 kg and 40 mg for ≥20 kg, regardless of the ethnic group, is expected to be appropriate in a PEP setting in subjects aged ≥1 to <12 years.

In contrast to standard of care in EU, all index patients received anti-influenza treatment, including baloxavir marboxil. This has previously been addressed and validity has been clarified in the initial application for individuals ≥ 12 years. This will not be pursued further.

The primary objective of study T0834 was to evaluate the efficacy of a single oral dose of baloxavir marboxil compared with placebo in the prevention of influenza virus infection in subjects who were household members (subjects) of influenza-infected patients ("index patients"). The primary efficacy endpoint was the proportion of subjects who were infected with influenza virus (reverse transcription polymerase chain reaction [RT-PCR] positive) and presented with fever and at least one respiratory symptom in the period from Day 1 to Day 10.

The primary endpoint is clinically relevant. Prevention of asymptomatic influenza would not be seen as a benefit to the individual, though it could prevent viral shedding and therefore have value in a public health perspective. The study was conducted in a double-blind fashion by using matching indistinguishable placebo in appearance, labelling, and packaging. The double-blind trial set-up is key as the primary endpoint is partly based on the individual subjects' self-evaluation of symptoms.

The sample size calculation was based on the pooled risk ratio of 0.4 to meet the estimated treatment effect size, using a modified Poisson regression model with a two-sided significance level of 5%. 748 subjects were planned to have a power of 90%. 2 subjects were assumed to be excluded from the mITT population, which made the sample size of 750 subjects. The sample size calculation is considered adequate. According to CSR, 19% under 12-years old subjects were involved in the study. This is acceptable.

Subjects who were qualified for entry in the study were randomised to either the baloxavir marboxil group or the placebo group in a 1:1 ratio, using stochastic minimization method for balancing the 3 stratification factors.

The mITT population was used for the primary efficacy analysis. All randomized subjects who had post-baseline efficacy data available (virology testing data assessed by RT-PCR, body temperature or influenza symptom score) among household members of index patients was included. This is endorsed.

The modified Poisson regression approach was employed to estimate the risk ratio for primary endpoint, using the sandwich variance estimator. It is understood as the covariates were adjusted in the poison regression model. Clopper-Pearson method was used to measure the 95% CI of the proportion of influenza-infected subjects. The RMST was estimated as the area under the KM curve which produces unadjusted estimates.

Overall, the design and size and conduct of study T0834 is considered adequate.

Efficacy data and additional analyses

Study T0834 met its primary endpoint and efficacy is supported by the supplementary analysis.

A total of 145 subjects (72 in the baloxavir marboxil group and 73 in the placebo group) were randomized as household members of 117 index patients. Of these, 70 (18.7%) and 72 (19.1%) subjects completed the study This is considered adequate for evaluating efficacy in subjects aged 1 to < 12 years. According to the PIP at least 40 paediatric subjects should be evaluated in the primary analysis.

Baseline and demographic data for subjects < 12 Years in the baloxavir and placebo groups were comparable. However, as for the treatment indication, there is a concern regarding the age categories, since only two subjects aged <3 years were included in the baloxavir marboxil group in study T0834. However, since the application in <12 years is to a large extend based on extrapolation from older subjects, this will not be pursued.

For the primary endpoint, the proportion of subjects with influenza virus infection, fever, and at least one respiratory symptom during the period from Day 1 to Day 10 was lower in the baloxavir marboxil group than in the placebo group (4.2% vs. 15.5%; adjusted risk ratio 0.27 [95% CI: 0.08, 0.90], p = 0.0339). The proportion of subjects who were infected with influenza virus (RT-PCR positive) and presented with fever and at least one respiratory symptom from Day 1 to Day 10 was lower in the baloxavir marboxil group than in the placebo group for both subgroups of subjects younger and older than 12 years, but the adjusted risk ratio was higher in the youngest age group, however, numbers are limited for the age group < 12 years.

The secondary efficacy endpoint results overall support the primary endpoint results.

It is noted that the proportion of subjects with asymptomatic influenza virus infection, was higher in the baloxavir marboxil group compared to the placebo group in the < 12 years population. As described by the Applicant, these results demonstrate that baloxavir marboxil prevents incoming virus from establishing a clinically meaningful symptomatic infection and prevents household members from developing symptomatic influenza, which is the aim of PEP. This is endorsed.

Compared with reference strains, amino acid changes at position 38 of the PA gene (PA/I38X) were detected in virus from 10 baloxavir marboxil-treated subjects. Of these 10 subjects with I38X substitutions, 3 were < 12 years of age and 2 of these 3 paediatric subjects developed clinical influenza. No amino acid substitutions were found at position 38 in virus collected from RT-PCR positive placebo-treated subjects (36 at baseline and 87 postdose), with the exception of 2 subjects (one paediatric patient [6 years] and one adult) who received baloxavir marboxil as rescue medication on Day 3; PA/I38X was detected in virus at Day 5 from these 2 subjects. The possible clinical impact of the gene changes cannot be properly evaluated due to a low number of patients, who were infected with a virus that expressed the gene changes.

Overall, the subgroup analyses and discussion on subgroups suggested similar efficacy in subjects 1 to < 12 year old, regardless of gender, vaccination status and renal or hepatic impairment.

2.6.7. Conclusions on the clinical efficacy

The study investigating the efficacy of baloxavir marboxil compared with oseltamivir in paediatric patients 1 to <12 years of age with influenza-like symptoms demonstrated similar time to alleviation of symptoms between baloxavir marboxil and oseltamivir. The other secondary endpoints and virology endpoints supported this finding.

The two cohorts based on age reached the minimum of 15 patients 1 to < 5 years of age and minimum 30 patients 5 to < 12 years of age as agreed in the PIP. However, the number of patients within the two age groups are somewhat skewed. There is only one 1 year old and two 2 years old patients who were included in the baloxavir marboxil group in study CP40563 compared to three 1 year old and three 2 years old patients in the oseltamivir group. However, since the application in <12 years is to a large extend based on extrapolation from older subjects, this will not be pursued.

The study investigating the post-exposure-prophylaxis of baloxavir marboxil compared with placebo in paediatric subjects 1 to <12 years of age met its primary endpoint.

Overall, both studies met their key secondary or primary endpoints, showing that baloxavir marboxil had comparable effect to oseltamivir for the treatment of influenza and superior to placebo for the post-exposure prophylaxis in household contacts. Both supported by the studied secondary endpoints.

2.6.8. Clinical safety

In 2019, an MAA was submitted for the treatment of influenza and post exposure prophylaxis in adolescents ≥ 12 years and adults, and safety was evaluated in the relevant population. The post exposure prophylaxis study T0834 was submitted for that the initial application and has therefore already been evaluated, however for the present application, the focus is on children from 1-12 years of age.

2.6.8.1. Patient exposure

The safety evaluation is based on a global pivotal study in paediatric patients 1 - <12 years of age (Study CP40563, n=115 exposed to baloxavir marboxil granules for oral suspension), 3 supportive studies including Japanese patients < 12 years of age (Studies T0822, T0833 and T0835, n=185 exposed to baloxavir marboxil), and a pivotal study in healthy household members of influenza infected patients (Study T0834, n=71 children form 1-12 years exposed to baloxavir marboxil).

The formulation and dose used in the pivotal study is similar to the proposed dose and formulation in the SmPC. The dose used in the Japanese paediatric studies are overall lower, however, the exposure is overall similar to the non-Japanese population included in the pivotal trial due to lower clearance and lower volume of distribution.

The PEP study is also conducted din Japanese subjects, where the dose is half the dose used in non-Japanese subjects. The PEP study (study T0834) was evaluated in the initial application. In this evaluation a special focus on the paediatric population is applied.

Overall, the safety database consists of 371 children below the age of 12 years exposed to baloxavir marboxil.

CP40563

A total of 173 patients received at least one dose of study drug, 115 in the baloxavir marboxil group and 58 in the oseltamivir group (Table 37).

Table 37: Study Drug Exposure in Study CP40563 (Safety Population)

	Baloxavir Marboxil (N=115)	Oseltamivir (N=58)
Baloxavir Exposure		
Compliance Rate (%)		
n	115	58
Mean (SD)	94.8 (20.3)	97.0 (16.3)
Median	100.0	100.0
Min - Max	10 - 100	10 - 100
Compliance Rate (Category)		
< 80%	7 (6.1%)	2 (3.4%)
>= 80%	108 (93.9%)	56 (96.6%)
Oseltamivir Exposure		
Duration (Days)		
n	115	58
Mean (SD)	5.3 (0.6)	5.3 (0.7)
Median	5.0	5.0
Min - Max	3 - 9	1 - 6
Compliance Rate (%)		
n	115	58
Mean (SD)	99.5 (9.8)	97.8 (12.1)
Median	100.0	100.0
Min - Max	40 - 170	10 - 100
Compliance Rate (Category)		
< 80%	3 (2.6%)	1 (1.7%)
>= 80%	112 (97.4%)	57 (98.3%)

Duration of treatment exposure [days] for oseltamivir is calculated as {(final dose date) - (initial dose date)+1}. Compliance rate [%] for oseltamivir is calculated as: {(actual frequency of treatment exposure / expected frequency of treatment exposure)*100}
For baloxavir marboxil treatment duration is defined as 1 day. Compliance rate [%] in the baloxavir marboxil group is calculated as: {(actual treatment received / expected treatment received)*100}.

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Study T0822

A total of 107 patients received one dose of baloxavir marboxil tablet at doses of 5 mg (2 patients, 1.9%), 10 mg (31 patients, 29.0%), 20 mg (66 patients, 61.7%), or 40 mg (8 patients, 7.5%). All patients received the per-protocol assigned amount of study drug.

Study T0833

A total of 33 patients received one dose of baloxavir marboxil granules at doses of 4 mg (1 patient, 3.0%), 7 mg (4 patients, 12.1%), 8 mg (5 patients, 15.2%), 9 mg (2 patients, 6.1%) or 10 mg (21 patients, 63.6%). All patients received the per-protocol assigned amount of study drug except for 1 patient (4 years of age) who spat out the study drug (10 mg) before swallowing it completely. This patient is included in the safety population.

Study T0835

A total of 45 patients received one dose of baloxavir marboxil granules at doses of 14 mg (1 patient, 2.2%), 16 mg (6 patients, 13.3%), 18 mg (2 patients, 4.4%), and 20 mg (36 patients, 80.0%). All patients received the per-protocol assigned amount of study drug except for 2 patients (1 year and 3 years of age) who could not swallow the entire dose of the drug. These patients were still included in the safety population.

PEP Study T0834

Of the 749 subjects in the overall safety population of Study T0834, paediatric household members (subjects) aged 1 to < 12 years accounted for 19% (142 paediatric subjects, 71 in the baloxavir marboxil group and 71 in the placebo group) (Table 38).

Table 38: Overview of Baloxavir Marboxil Dosing in Subjects < 12 Years in Study T0834

	Baloxavir marboxil	Placebo
Safety Population, n	71	71
Actual dose of baloxavir marboxil received, n (%)		
< 10 mg (2% granules)	0	–
10 mg (2% granules)	19 (26.8%)	–
20 mg (one 20 mg tablet)	47 (66.2%)	–
40 mg (two 20 mg tablets)	5 (7.0%)	–

SCS t_ae_dose_agelt12_SE_xv41428

Age-distribution:

In the pivotal study CP40563, 36 paediatric subjects in the age group 1 to <5 years and 79 subjects in the age group 5 to < 12 years were exposed to baloxavir marboxil (Table 39). In the PEP study, 14 subjects in the age group 1 to <5 years were exposed to baloxavir marboxil (Table 40), and in the supportive studies, 81 subjects in the age group 0- to < 5 years were exposed to baloxavir marboxil (Table 39). The included subjects were equally distributed across age groups, hence 9 subjects of 1 year were included in the pivotal study.

Table 39: Summary of Age Categories – Studies CP40563, T0822, T0833 and T0835 (Safety Population)

	Study CP40563		Studies T0822, T0833 and T0835
Age Group, Years	Baloxavir Marboxil N=115 n (%)	Oseltamivir N=58 n (%)	Baloxavir Marboxil N=185 n (%)
< 1 years	0	0	11 (5.9%)
1 year	9 (7.8%)	7 (12.1%)	16 (8.6%)
2 years	6 (5.2%)	3 (5.2%)	18 (9.7%)
3 years	9 (7.8%)	6 (10.3%)	18 (9.7%)
4 years	12 (10.4%)	3 (5.2%)	18 (9.7%)
5 years	13 (11.3%)	7 (12.1%)	20 (10.8%)
6 years	12 (10.4%)	6 (10.3%)	14 (7.6%)
7 years	14 (12.2%)	3 (5.2%)	16 (8.6%)
8 years	14 (12.2%)	8 (13.8%)	11 (5.9%)
9 years	11 (9.6%)	6 (10.3%)	16 (8.6%)
10 years	5 (4.3%)	3 (5.2%)	16 (8.6%)
11 years	10 (8.7%)	6 (10.3%)	11 (5.9%)

Source: SCS t_dm_age_cp40563_se; t_dm_age_se

Table 40: Summary of Age Categories for Subjects < 12 Years in Study T0834 (Safety Population)

Age Group, Years	Baloxavir Marboxil N = 374 n (%)	Placebo N = 375 n (%)
< 1 years	0	0
1 year	1 (0.3%)	5 (1.3%)
2 years	1 (0.3%)	2 (0.5%)
3 years	6 (1.6%)	7 (1.9%)
4 years	6 (1.6%)	6 (1.6%)
5 years	2 (0.5%)	3 (0.8%)
6 years	9 (2.4%)	8 (2.1%)
7 years	7 (1.9%)	13 (3.5%)
8 years	12 (3.2%)	3 (0.8%)
9 years	11 (2.9%)	5 (1.3%)
10 years	14 (3.7%)	13 (3.5%)
11 years	2 (0.5%)	6 (1.6%)

Source: SCS t_dm_age_xv41428_se

2.6.8.2. Adverse events

Incidence of adverse events

The incidence of adverse events in subjects <12 years exposed to baloxavir marboxil for the treatment of influenza differed from 34.6% to 54.5% with the highest incidence in study T0833 (Table 41, Table 42, Table 43, Table 44). In the pivotal study, where a comparator arm was present, the frequency of adverse events was lower in the baloxavir marboxil group (46.1%) than the oseltamivir group (53.4%) (Table 41).

In subjects exposed to baloxavir marboxil due to post exposure prophylaxis, the frequency of adverse events was lower (25.4%) and comparable to the placebo group (Table 45), and no ADR were identified in the baloxavir marboxil group.

No serious adverse events were seen in neither the treatment studies nor the post exposure prophylaxis studies.

In patients ≥ 12 years with influenza treated with baloxavir marboxil (studies T0831 and T0821), the frequency of patients with any adverse events was 21.4% (lower than placebo and oseltamivir) whereas it was 46.1% in the pivotal study CP40563 although also lower than the oseltamivir group.

Table 41: Safety Summary of Pivotal Study CP40563 (Safety Population)

	Baloxavir Marboxil (N=115)	Oseltamivir (N=58)	All Patients (N=173)
Total number of patients with at least one AE	53 (46.1%)	31 (53.4%)	84 (48.6%)
Total number of AEs	80	42	122
Total number of deaths	0	0	0
Total number of patients withdrawn from study due to an AE	0	0	0
Total number of patients with at least one			
AE with fatal outcome	0	0	0
Serious AE	0	0	0
Serious AE leading to withdrawal from treatment	0	0	0
Serious AE leading to any dose modification/interruption	0	0	0
Related Serious AE	0	0	0
AE leading to withdrawal from treatment	2 (1.7%)	0	2 (1.2%)
AE leading to dose modification/interruption	1 (0.9%)	0	1 (0.6%)
Related AE	3 (2.6%)	5 (8.6%)	8 (4.6%)
Related AE leading to withdrawal from any treatment	2 (1.7%)	0	2 (1.2%)
Related AE leading to dose modification/interruption	0	0	0
Severe AE (at greatest intensity)	1 (0.9%)	2 (3.4%)	3 (1.7%)
AE of special interest	0	0	0

Investigator text for AEs encoded using MedDRA version 22.0. Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple
occurrences of the same AE are counted separately.

Program:
root/clinical_studies/RO7191686/CDT30202/CP40563/data_analysis/Final_CSR/prod/program/t_ae_sum.sas
Output:
root/clinical_studies/RO7191686/CDT30202/CP40563/data_analysis/Final_CSR/prod/output/t_ae_sum_SE.out
09JUL2019 19:48

Table 42: Safety Summary of Supporting Study T0822 (Safety Population)

	Baloxavir marboxil N = 107 n (%)
Total number of patients with at least one AE	37 (34.6)
Total number of AEs	49
Total number of deaths	0
Total number of patients with at least one	
AE with fatal outcome	0
Serious AE	0
Treatment-related AE	4 (3.7)
Treatment-related Serious AE	0
Severe AE (≥ Grade 3)	0

AE = adverse event.
Source: CSR T0822 Tables 14.3.1.1, 14.3.2.1, 14.3.2.2, and 14.3.3.1

Table 43: Safety Summary of Supporting Study T0833 (Safety Population)

	Baloxavir marboxil N = 33 n (%)
Total number of patients with at least one AE	18 (54.5)
Total number of AEs	24
Total number of deaths	0
Total number of patients with at least one	
AE with fatal outcome	0
Serious AE	0
Treatment-related AE	1 (3.0)
Treatment-related Serious AE	0
Severe AE (≥ Grade 3)	0

AE = adverse event.
Source: CSR T0833 Tables 14.3.1.1, 14.3.2.2, and 14.3.3.1

Table 44: Safety Summary of Supporting Study T0835 (Safety Population)

	Baloxavir marboxil N = 45 n (%)
Total number of patients with at least one AE	24 (53.3)
Total number of AEs	38
Total number of deaths	0
Total number of patients with at least one	
AE with fatal outcome	0
Serious AE	0
Treatment-related AE	3 (6.7)
Treatment-related Serious AE	0
Severe AE (≥ Grade 3)	0

AE = adverse event.
Source: CSR T0835 Tables 14.3.1.1, 14.3.2.2, and 14.3.3.1

Table 45: Overall Summary of Adverse Events (Overall, < 12 Year, ≥ 12 Year Subgroups in Study T0834) (Safety Population)

	Overall Population		<12 Years		≥12 Years	
Subject with:	Baloxavir marboxil N=374 n (%)	Placebo N=375 n (%)	Baloxavir marboxil N=71 n (%)	Placebo N=71 n (%)	Baloxavir marboxil N=303 n (%)	Placebo N=304 n (%)
Any AE	83 (22.2)	77 (20.5)	18 (25.4)	18 (25.4)	65 (21.5)	59 (19.4%)
No. AEs, n	102	99	25	20	77	79
SAEs	0	1 (0.3)	0	0	0	1 (0.3)
No. AEs, n	0	1	0	0	0	1
Deaths	0	0	0	0	0	0

AE = adverse event; SAE = serious adverse event.
Source: CSR T0834 Table 14.3.1.1, SCS t_aesum_xv41428

Common adverse events

By preferred term in study CP40563, the most common AEs (≥ 2%) in baloxavir marboxil-treated patients were vomiting (6.1%), diarrhea (5.2%), upper respiratory tract infection (4.3%), medication error (4.3%), rhinorrhea (3.5%), otitis media (2.6%), bronchitis (2.6%), accidental overdose (2.6%),

and cough (2.6%). Besides for diarrhoea that had the highest incidence in the baloxavir marboxil group, the adverse events by preferred term were overall similar across the two treatment groups (Table 46). Vomiting was highest in the oseltamivir group.

In the supporting studies, the same adverse events although with a higher frequency were seen.

For post exposure prophylaxis, nasopharyngitis was the most frequently occurring adverse event by preferred term and similar in the placebo group (8.5%). Headache, cough and pyrexia occurred in 2.8% of the children in the baloxavir marboxil group, but not in the placebo group.

Table 46: Summary of Adverse Events Occurring in > 2% of Patients in at least One Treatment Group (Safety Population

MedDRA System Organ Class MedDRA Preferred Term	Baloxavir Marboxil (N=115)	Oseltamivir (N=58)	All Patients (N=173)
Gastrointestinal Disorders			
Total number of patients with at least one adverse event	12 (10.4%)	10 (17.2%)	22 (12.7%)
Total number of events	13	11	24
Vomiting	7 (6.1%)	9 (15.5%)	16 (9.2%)
Diarrhoea	6 (5.2%)	1 (1.7%)	7 (4.0%)
Infections And Infestations			
Total number of patients with at least one adverse event	9 (7.8%)	7 (12.1%)	16 (9.2%)
Total number of events	11	8	19
Otitis Media	3 (2.6%)	4 (6.9%)	7 (4.0%)
Upper Respiratory Tract Infection	5 (4.3%)	2 (3.4%)	7 (4.0%)
Bronchitis	3 (2.6%)	1 (1.7%)	4 (2.3%)
Injury, Poisoning And Procedural Complications			
Total number of patients with at least one adverse event	8 (7.0%)	3 (5.2%)	11 (6.4%)
Total number of events	9	3	12
Medication Error	5 (4.3%)	2 (3.4%)	7 (4.0%)
Accidental Overdose	3 (2.6%)	1 (1.7%)	4 (2.3%)
Respiratory, Thoracic And Mediastinal Disorders			
Total number of patients with at least one adverse event	5 (4.3%)	2 (3.4%)	7 (4.0%)
Total number of events	7	2	9
Rhinorrhoea	4 (3.5%)	1 (1.7%)	5 (2.9%)
Cough	3 (2.6%)	1 (1.7%)	4 (2.3%)
Ear And Labyrinth Disorders			
Total number of patients with at least one adverse event	1 (0.9%)	2 (3.4%)	3 (1.7%)
Total number of events	1	2	3
Ear Pain	1 (0.9%)	2 (3.4%)	3 (1.7%)
Metabolism And Nutrition Disorders			
Total number of patients with at least one adverse event	0	2 (3.4%)	2 (1.2%)
Total number of events	0	2	2
Vitamin D Deficiency	0	2 (3.4%)	2 (1.2%)

Investigator text for AEs encoded using MedDRA version 22.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program:
root/clinical_studies/RO7191686/CDT30202/CP40563/data_analysis/Final_CSR/prod/program/t_ae_2per.sas
Output:
root/clinical_studies/RO7191686/CDT30202/CP40563/data_analysis/Final_CSR/prod/output/t_ae_2per_SE.out
t
19SEP2019 17:19

Adverse drug reactions

In study CP40563, 10 adverse events were considered treatment related by the MAH and occurred in 3 out of 115 patients in the baloxavir marboxil group and 5 out of 58 patients in the oseltamivir group.

In the baloxavir marboxil group, flushing, rash morbilliform, rash, and accidental overdose of oseltamivir placebo occurred. Immune system disorders (anaphylaxis, anaphylactic reactions, hypersensitivity) and skin and subcutaneous disorders (urticaria, angioedema) are stated as adverse

drug reactions with unknown frequency (besides for urticaria) in the SmPC. Rash has been included as an ADR in a separate table for paediatric patients.

In the supportive studies, the MAH considered 8 adverse events as treatment related. Of those, 5 patients with diarrhoea, 1 patient with soft faeces, 1 patient with elevated alanine aminotranferase, and 1 patient with elevated platelet count. In the pivotal trial, 5.2% of patients had diarrhoea but this adverse event was not considered treatment related by the MAH, even though the incidence was only 1.7% in the oseltamivir group. Furthermore, post marketing data also have reports on diarrhoea as serious adverse event. Diarrhoea has been included as an ADR in a separate table for paediatric patients.

In the pivotal trial, vomiting occurred with a frequency of 6.1% in the baloxavir marboxil group and in 15.5% in the oseltamivir group. Furthermore, post marketing data has reports on vomiting as serious adverse event. Vomiting has been included as an ADR in a separate table for paediatric patients.

Adverse events by severity

In the baloxavir marboxil group only one grade 3 adverse event was observed. This was abdominal pain on day 8 in a girl that on the following day was diagnosed with pneumonia.

Outcome of adverse events

The majority of adverse events had resolve at day 29 besides for 9 cases in the baloxavir marboxil group. Those constituted upper respiratory tract infection, oropharyngeal pain, ear infection, dental caries, dry skin. ligament sprain and blood in urine.

Time of adverse events

The onset of adverse events was highest during the first 7 days after drug administration.

Adverse events by dose and exposure

Patients with a bodyweight below 20 kg were dosed with a weight-based dose (2 mg/kg), whereas patients with a bodyweight higher than 20 kg were dosed with a flat dose of 40 mg. Overall, the frequency of adverse events was higher in the patents dosed with a weight-based dose (57.4%), in contrast to the group dosed with a flat dose (40 mg) (Table 47). This could be due to a relative higher exposure in the weight-based dose group compared to the flat dose group, as patients with a higher bodyweight than 20 kg have received a smaller weight-based dose and thereby a lower exposure. However, data on exposure-safety does not support this theory (Table 48). It is more likely that the youngest patients report more adverse events.

Five medication errors occurred in the weight-based dose group, which comprised 10% of the group. The patients were dosed with a lower dose than expected. The MAH has clarified that the medication errors occurred at a single site, and that the site was sat on hold and the staff retrained. In order to reduce the risk of medication errors the MAH has included the volumes to be administered.

Table 47: Adverse Events by Dose of Baloxavir Marboxil Occurring in ≥ 2 Patients in Any Dose Subgroup in Study CP40563 (Safety Population)

Preferred Term	2 mg/kg N = 47 n (%)	40 mg N = 68 n (%)
Patients with any AE	27 (57.4)	26 (38.2)
Vomiting	3 (6.4)	4 (5.9)
Diarrhoea	1 (2.1)	5 (7.4)
Medication error	5 (10.6)	0
Upper respiratory tract infection	3 (6.4)	2 (2.9)
Rhinorrhoea	1 (2.1)	3 (4.4)
Otitis media	2 (4.3)	1 (1.5)
Bronchitis	2 (4.3)	1 (1.5)
Cough	2 (4.3)	1 (1.5)
Accidental overdose	1 (2.1)	2 (2.9)
Rash	2 (4.3)	0
Headache	0	2 (2.9)

Source: SCS t_ae_dose_SE (CP40563)

Table 48: Adverse Events by Exposure (AUC_{0-inf} and C_{max}) of Baloxavir Occurring in ≥2 Patients in Any Exposure Subgroup in Study CP40563 (Safety Population)

Preferred Term	Low N = 48 n (%)	High N = 47 n (%)
AUC_{0-inf}		
Patients with any AE	22 (45.8)	15 (31.9)
Vomiting	3 (6.3)	4 (8.5)
Diarrhoea	5 (10.4)	1 (2.1)
Accidental overdose	2 (4.2)	1 (2.1)
Bronchitis	2 (4.2)	0
Upper Respiratory Tract Infection	2 (4.2)	0
Headache	2 (4.2)	0
Nausea	0	2 (4.3)
Rhinorrhoea	0	2 (4.3)
C_{max}		
Patients with any AE	22 (45.8)	15 (31.9)
Vomiting	4 (8.3)	3 (6.4)
Diarrhoea	4 (8.3)	2 (4.3)
Accidental Overdose	1 (2.1)	2 (4.3)
Bronchitis	2 (4.2)	0
Upper Respiratory Tract Infection	2 (4.2)	0
Headache	2 (4.2)	0
Nausea	0	2 (4.3)
Rhinorrhoea	0	2 (4.3)

Note: N values are the same for AUC and C_{max}, but do not reflect the same patients, therefore the number of AEs may change for some events.

Median AUC_{0-inf}: 4145.69 ng•hr/mL

Median C_{max}: 91.02 ng/ml

Source: SCS t_ae_soc_pt_auc_cp40563 and t_ae_soc_pt_cmax_cp40563

The volume to be ingested is considered large for small children (up to 20 ml) – especially if the taste is bitter. This is further supported by the reflection paper, Formulations of choice for the paediatric population: "The dose volume is a major consideration for the acceptability of a liquid formulation. Typical target dose volumes for paediatric liquid formulations are < 5 ml for children under 5 years and < 10 ml for children of 5 years and older. However, the more palatable the formulation, the higher the dose volume which will be tolerated. Large volume doses may be inconvenient for both patient and carer."

With regard to justification for the suitability of amounts of up to 20 ml in children, the Applicant argued that a volume of up to 20 mL is acceptable given that generally children older than >5 years of age will receive a volume of 20 mL and will receive it sequentially in volumes of 10 ml. Furthermore, if the children are able to swallow tablets, the tablet formulation could be used in children with a bodyweight above 20 kg.

Overall, the provided data indicates an adequate acceptability and palatability with baloxavir marboxil GfOS in the paediatric population. The MAH has agreed to submit the palatability results from Study CP40559 and Study MV40618 as soon as possible after the end of study dates. Furthermore, acceptability data should also be submitted. In accordance with the paediatric legislation, data on paediatric studies should be submitted as soon as possible after the end of study dates, hence it is

expected that the MAH complies with the legislation and submit all data after end of study and not only the palatability results.

2.6.8.3. Serious adverse event/deaths/other significant events

No deaths or serious adverse events were reported.

ALT or AST elevation in combination with elevated bilirubin or clinical jaundice or suspected transmission of an infectious agent by the study drug were considered adverse event of special interest. No AESI were reported.

2.6.8.4. Laboratory findings

In the pivotal study, no significant elevations in liver parameters were observed based on the data that the MAH has provided. In one of the supporting studies, marginally elevated ALT related to treatment was observed with an onset on day 5 and resolved at day 11.

2.6.8.5. Safety in special populations

No new information regarding special populations has been provided.

No pregnancies were reported in pivotal Study CP40563 or supporting studies T0822, T0833, and T0835.

2.6.8.6. Safety related to drug-drug interactions and other interactions

No new information related to drug-drug interaction were provided.

2.6.8.7. Discontinuation due to adverse events

No adverse events associated with baloxavir marboxil treatment lead to discontinuation of the study drug.

2.6.8.8. Post marketing experience

An estimated number of subjects < 12 years exposed to baloxavir marboxil is 963,501. Those children come from Japan and Taiwan and also from other countries where the medicinal product has been used off-label. A total of 1901 adverse events in 1016 subjects have been reported post marketing. Of those, 124 adverse events were reported as serious, of which vomiting (n=11), seizure (n=9), abnormal behaviour (n=9) and diarrhoea (n=5) were most frequently reported. The age-distribution in 1-year intervals in the post-marketing study as shown in Table 49.

Table 49: Age Distribution in Japanese Post-Marketing Study

Age (Years)	Number of study participants*
0-1	0
1-2	13
2-3	11
3-4	37
4-5	37
5-6	80
6-7	108
7-8	133
8-9	130
9-10	107
10-11	121
11-12	119

*Safety analysis population in post marketing study

The MAH has been requested to provide the most updated data on AE reporting post marketing as the most recent PSUR is covering the period from 23 February 2021 to 22 August 2021. Due to the COVID-19 pandemic and the resulting lack of flu seasons, the MAH was not able to provide more recent data than data from the flu season 2018-2019.

In the total age distribution including adults, 1454 serious AE has been reported with the highest frequency of infections and infestations and gastrointestinal disorders. Vomiting and diarrhoea were also seen in the pivotal study, hence a request of including those adverse events in the SmPC has been made.

The MAH has during the assessment period submitted a prospective post marketing study in 896 children, of which 178 children were younger than 6 years. In this study, the frequency of AE is higher in children from 6-12 years compared to children below 6 years. This is somewhat reassuring. But it does not address the question regarding adverse events in the youngest age group below 6 years.

An overview of post-marketing exposure and post marketing adverse events in 1-year intervals showed that overall across age-groups, the most frequent AEs, except for the AEs that indicates off-label use, were vomiting and diarrhoea which have been included in the SmPC. Abnormal behaviour was also frequently reported and may be associated with fever. No age-related pattern was seen in the presented AE's from post-marketing data. A tendency towards a higher frequency of reported AE in the older age-groups were observed. The hypersensitivity events (anaphylactic reaction, anaphylactic shock, urticaria, face-, eyelid- and lip swelling) seen in the data from post marketing experience is reflected in the SmPC.

2.6.9. Discussion on clinical safety

In 2019, an MAA was submitted for the treatment of influenza and post exposure prophylaxis in adolescents ≥ 12 years and adults, and safety was evaluated in the relevant population. The safety of baloxavir marboxil for the current application for the treatment and post exposure prophylaxis (PEP) in children from 1 to 12 years is based on 5 paediatric studies: the pivotal study CP40563 (n=115 exposed to baloxavir marboxil), 3 supportive studies (T0822, T0833 and T0835, n=185 exposed to baloxavir marboxil) and the PEP study T0834 (n=71 children form 1-12 years exposed to baloxavir marboxil). The PEP study (study T0834) was evaluated in the initial application. In this evaluation a special focus on the paediatric population is applied.

The pivotal study is the only study in which the proposed dose and formulation (granules for oral suspension) to be marketed have been used. In the PEP study and the supporting studies, a lower dose has been used due to the different pharmacokinetics (lower clearance and lower volume of distribution) in the Asian population, however, the exposure in the Asian and non-Asian population is comparable, hence the safety data from the supportive studies is considered applicable to the non-Asian population.

Overall, the safety database of 371 children below the age of 12 years exposed to baloxavir marboxil is considered adequate, and the methodology to collect safety data is considered appropriate.

The total safety population <12 years was equally distributed across age groups. As such, 131 subjects below 5 years were included. In the pivotal trial, the number of patients in each 1-year age strata varied from 5-13 subjects, and in the youngest age group of 1 year, the number of subjects were 9. Hence, the safety database is considered to sufficiently covering the age range in the proposed target population.

In the pivotal trial, the frequency of patients experiencing adverse events were 46.1% and lower in the baloxavir marboxil group than the oseltamivir group. When comparing with placebo in the PEP study, the incidence was the similar between the treatment groups (25.4%) and lower than in the treatment population. Overall, the frequency of adverse events was higher in children < 12 years than subjects ≥ 12 years, however, comparable or lower than placebo or oseltamivir in the pivotal studies, which is considered acceptable.

The most common adverse events in the pivotal trial were vomiting, diarrhoea, upper respiratory tract infection and medication error occurring in 4-6 % of the subjects. Diarrhoea was more frequently occurring in the baloxavir marboxil group and vomiting was more frequently occurring in the oseltamivir group. For other adverse events, the frequency was almost similar between treatment groups. Vomiting and diarrhoea were reported as treatment related adverse events in the supportive studies and is therefore included as ADRs in a separate table for paediatric patients. Furthermore, rash and flushing occurred in 3 out of 115 patients in the baloxavir marboxil group and were considered treatment related and is considered an adverse drug reaction and is included in the SmPC section 4.8.

No serious adverse events or deaths were reported in neither the treatment studies nor the post exposure prophylaxis studies. Furthermore, the severity of the adverse events was grade 1 and grade 2, besides for one adverse event that were grade 3 (abdominal pain). For the majority of the adverse events, they had resolved by day 29 post dose.

No exposure related safety issues were identified. However, six medication errors occurred in the weight-based dose group, which comprised 10% of the group. Those medication errors occurred in a single site, and the site was sat on hold and the staff retrained. In order to reduce the risk of medication errors the MAH has included examples of dosing in ml for weight groups in random intervals in the SmPC. In order to ease the reading of the dosing, the MAH has provided information on the volume to be administered.

The volume to be ingested is considered large for small children (up to 20 ml) – especially if the taste is bitter. This is further supported by the reflection paper, Formulations of choice for the paediatric population: "The dose volume is a major consideration for the acceptability of a liquid formulation. Typical target dose volumes for paediatric liquid formulations are < 5 ml for children under 5 years and < 10 ml for children of 5 years and older. However, the more palatable the formulation, the higher the dose volume which will be tolerated. Large volume doses may be inconvenient for both patient and carer."

With regard to justification for the suitability of amounts of up to 20 ml in children, a volume of up to 20 mL is acceptable given that generally children older than >5 years of age will receive a volume of

20 mL and will receive it sequentially in volumes of 10 ml. Furthermore, if the children are able to swallow tablets, the tablet formulation could be used in children with a bodyweight above 20 kg.

Overall, the provided data indicates an adequate acceptability and palatability with baloxavir marboxil GfOS in the paediatric population. Further data will be submitted post-marketing.

The laboratory variables have been summarised in the CSR and no safety issues were identified.

Baloxavir marboxil has been marketed in children in Japan and Taiwan. Furthermore, it has been marketed in other countries in adolescents and adults. Therefore, extensive post marketing data is available including children. An estimated number of subjects < 12 years exposed to baloxavir marboxil is 963,501. Those children come from Japan and Taiwan and also from other countries where the medicinal product has been used off-label. A total of 1901 adverse events in 1016 subjects have been reported post marketing. Of those, 124 adverse events were reported as serious, of which vomiting (n=11), seizure (n=9), abnormal behaviour (n=9) and diarrhoea (n=5) were most frequently reported.

In the post-marketing data, across age-groups, the most frequent AEs, except for the AEs that indicates off-label use, were vomiting and diarrhoea which has been included in the SmPC. Abnormal behaviour was also frequently reported and may be associated with fever. No age-related pattern was seen in the presented AE's from post-marketing data. A tendency towards a higher frequency of reported AE in the older age-groups were observed.

The hypersensitivity events (anaphylactic reaction, anaphylactic shock, urticaria, face-, eyelid- and lip swelling) seen in the data from post marketing experience is reflected in the SmPC.

In the total age distribution, 1454 serious AE has been reported with the highest frequency of infections and infestations and gastrointestinal disorders. Vomiting and diarrhoea were also seen in the pivotal study, hence a request of including those adverse events in the SmPC has been made (see previous sections).

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

The safety of baloxavir marboxil in the treatment of influenza in children from 1-12 years has been evaluated in 1 pivotal trial and in 3 supportive studies and for the post exposure prophylaxis in 1 single trial that has previously been evaluated. A total of 371 children below 12 years have been exposed to baloxavir marboxil, of which 115 children have been exposed to the proposed dose and formulation to be marketed. Overall, the safety database for the paediatric indication is considered acceptable.

The CHMP considers the following measures necessary to address issues related to safety:

Acceptability/ palatability: the results from study CP40559 and study MV40618 should be submitted as soon as possible after the finalisation.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

2.7.2. Pharmacovigilance plan

Routine pharmacovigilance activities are considered by the Applicant to be sufficient to obtain and analyse relevant post-marketing safety data for all safety concerns with the aim to fully assess the safety of the product.

No additional pharmacovigilance activities are necessary

2.7.3. Risk minimisation measures

None

2.7.4. Conclusion

The CHMP considered that the risk management plan version 2.0 is acceptable.

2.7.5. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.6. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Labelling exemptions

None

2.8.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Xofluza (baloxavir marboxil) is included in the additional monitoring list as new active substance (refer to initial assessment report on baloxavir marboxil).

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed indications are as follows:

- *Xofluza is indicated for the treatment of uncomplicated influenza in patients aged 1 year and above.*
- *Xofluza is indicated for post-exposure prophylaxis of influenza in individuals aged 1 year and above.*

Baloxavir marboxil has been approved in the European Union in January 2021 for the treatment and post-exposure prophylaxis of influenza in individuals 12 years of age and older.

Influenza is an acute respiratory infection with influenza virus types A and B that occur in outbreaks of varying severity almost every winter in temperate climates and year-round in tropical climates. Influenza viruses are highly contagious with efficient person-person spread within communities and with the potential for pandemics with severe morbidity and mortality presenting significant public health challenges.

Children play a central role in the dissemination of influenza in the community as children infected with influenza virus can have a longer shedding time compared to adults and by virtue of their relative serosusceptibility and consequently higher illness attack rates. They are also frequently exposed to each other in collective settings such as school and daycare, which plays a role in the prevalence and transmission of influenza.

The clinical manifestations of influenza in healthy paediatric patients are similar to those seen in adults; however, the rate of severe influenza infection and complications is higher than in their adult counterparts.

The MAH claims an unmet need for a drug that is more efficacious especially for influenza type B, has improved viral kinetics, and an easily administered antiviral drug for both treatment and prophylaxis for influenza in children.

3.1.2. Available therapies and unmet medical need

The major public health control measure for prevention of influenza is vaccination and in the overall management of influenza, treatment and prevention with anti-influenza virus drugs is not a substitute for, but a complement to, vaccination. Limitations of influenza vaccines exist, such as the target strains being different from epidemic strains or, in the event of a pandemic, an effective vaccine may not be available in the early phase owing to the several months' lead time required to produce such a vaccine. A further limitation is that vaccination is contraindicated in some patients.

Before the approval of baloxavir marboxil, two different classes of influenza antiviral medications were available: M2 blockers (amantadine and rimantadine) and neuraminidase inhibitors (NAIs: oseltamivir, zanamivir and peramivir).

There is an unmet need for a drug that is more efficacious especially for influenza type B, has improved viral kinetics, and an easily administered antiviral drug for both treatment and prophylaxis for influenza in children, for the below reasons:

- M2 blockers (amantadine and rimantadine) is ineffective due to widespread, transmissible resistance

- neuraminidase inhibitors (NAIs: oseltamivir, zanamivir and peramivir) have shown limited efficacy against influenza type B

- Zanamivir is not licensed for treatment of influenza in very young children due to the difficulty with inhalation in this group

- Peramivir needs to be intravenously administered effectively restricting it to inpatient use

- Oseltamivir requires twice daily (BID) dosing orally for 5 days for treatment and once daily dosing orally for 10 days for prophylaxis of influenza

These are considered relevant improvements and additions to current standard of therapy.

3.1.3. Main clinical studies

Treatment indication

The efficacy evaluation of baloxavir marboxil used for treatment in paediatric patients with influenza is primarily based on extrapolation from older subjects supported by data from one pivotal randomized double-blind Phase 3 study conducted in the 2018/2019 influenza season. This is in accordance with the PIP. Study CP40563 was a global Phase 3, multicenter, randomized, double-blind, active-controlled study to assess the safety, pharmacokinetics, and efficacy of baloxavir marboxil granules compared with oseltamivir in otherwise healthy (OwH) paediatric patients 1 to <12 years of age with influenza-like symptoms.

Approximately 120 paediatric patients 1 to < 12 years of age with influenza-like symptoms were planned for enrolment in this study.

Patients were recruited in two cohorts based on age (1 to < 5 years of age and 5 to < 12 years of age) and subsequently randomized on a permuted block basis in a 2:1 ratio to receive either baloxavir marboxil or oseltamivir.

The primary objective of the study was to compare the safety of a single dose of baloxavir marboxil with the safety of 5 days of oseltamivir administered BID. Evaluation of the clinical efficacy and virological activity of baloxavir marboxil compared with oseltamivir were secondary objectives.

The three non-controlled, single arm, Japanese paediatric studies: T0822, T0833 and T0835, are considered supportive for the treatment indication.

Post-exposure-prophylaxis indication

The efficacy evaluation for the post-exposure prophylaxis (PEP) population is based on extrapolation from older subjects supported by data from one pivotal Phase 3 Study T0834 conducted in Japan in the 2018/2019 influenza season. This is in accordance with the PIP. Study T0834 was a Phase 3, randomized, double-blind, placebo-controlled, comparative study conducted to evaluate the efficacy and safety of a single dose of baloxavir marboxil in the prevention of influenza versus placebo. The CSR was previously submitted in the initial MAA, supporting the PEP indication in individuals ≥12 years of age. Subjects evaluated to post-exposure prophylaxis was household members to the index patients.

Baloxavir marboxil 20-mg tablets, 2% granules, or matching placebo were orally administered to subjects as a single dose on Day 1 with a dose based on body weight at screening.

Eligible subjects were randomly assigned in a 1:1 ratio to receive either baloxavir marboxil or placebo using the stochastic minimization method for balancing the following 3 randomization factors:

- time from onset of influenza virus infection of index patient to informed consent of the subject (< 24 hours vs. ≥ 24 hours)
- treatment for influenza virus infection of index patient (baloxavir marboxil vs. other than baloxavir marboxil)
- subject's age at screening (< 12 years vs. ≥ 12 years).

750 subjects were planned to be included in the study, 19% of the included subjects were < 12 years.

The primary objective of the study was to evaluate the efficacy of a single oral dose of baloxavir marboxil compared with placebo in the prevention of influenza in subjects as determined by the primary efficacy endpoint, i.e. the proportion of subjects who were infected with influenza virus and presented with fever and at least one respiratory symptom in the period from Day 1 to Day 10.

3.2. Favourable effects

Treatment indication

Time to alleviation of influenza signs and symptoms (TTAS) was comparable in the two treatment groups. The median time was 138.1 hours (95% CI: 116.6, 163.2) in the baloxavir marboxil group compared with 150.0 hours (95% CI: 115.0, 165.7) in the oseltamivir group. Further, duration of fever was comparable in the two treatment groups. The median time was 41.2 hours (95% CI: 24.5, 45.7) in the baloxavir marboxil group compared with 46.8 hours (95% CI: 30.0, 53.5.) in the oseltamivir group.

Overall, the duration of the events TTAS, fever and "duration of symptoms" was numerically shorter in the baloxavir marboxil group compared to the oseltamivir group, except for "time to return to normal health and activity". The median time here was 116.5 hours (95% CI: 94.9, 138.0) in the baloxavir marboxil group compared with 111.6 hours (95% CI: 80.8, 138.3) in the oseltamivir group.

Of important clinical relevance; the incidence of influenza-related complications was low and similar in both treatment groups; 6 (7.4%) patients in the baloxavir marboxil group and 3 (7.0%) in the oseltamivir group and the proportion of patients requiring antibiotics was similar in each treatment group; 4.9% in the baloxavir marboxil group and 4.7% in the oseltamivir group.

Regarding virology endpoints, based on virus titer, the data were more favourable in the baloxavir marboxil group than in the oseltamivir group. The median time to cessation of viral shedding determined by virus titer was 24.2 [23.5, 24.6] for baloxavir marboxil compared with 75.8 [68.9, 97.8] for oseltamivir. Using RT-PCR methodology, the median time to cessation of viral shedding was similar in the two treatment groups (242.5 [235.8, 262.8] for the baloxavir marboxil group and 238.9 [214.0, 286.7] for the oseltamivir group).

Overall, the results were in line with studies performed in adults and adolescents, which has shown a reduction in time for influenza-related symptoms and virus titre for the baloxavir marboxil compared to placebo and no difference between the baloxavir marboxil and the active comparator, oseltamivir, groups.

TTAS was longer in the pivotal study CP40563 (138.1 hours [95% CI: 116.6, 163.2]) compared to the three single arm Japanese paediatric studies; 44.6 hours (95% CI: 38.9, 62.5) in Study T0822, 45.3 hours (95% CI: 28.5, 64.1) in Study T0833, and 37.8 hours (95% CI: 27.5, 46.7 hours) in Study T0835. However, the post-hoc sensitivity analysis (which excluded the 'return to normal health and activity') revealed a lower TTAS compared with the original TTAS definition; 69.8 hours [95% CI: 54.8, 86.9], which is still longer, but comparable to the results of the supportive studies.

Post-exposure-prophylaxis indication

The proportion of subjects with influenza virus infection, fever, and at least one respiratory symptom during the period from Day 1 to Day 10 was significant lower in the baloxavir marboxil group than in the placebo group (4.2% vs. 15.5%; adjusted risk ratio 0.27 [95% CI: 0.08, 0.90], p = 0.0339) for the age group < 12 years.

The results of the secondary endpoints with different definitions of symptomatic influenza and all supplementary analyses of subgroups (≥12 or < 12 years, anti-influenza treatment) were consistent with the result in the overall mITT population.

3.3. Uncertainties and limitations about favourable effects

Treatment indication

The number of patients < 3 years were very limited and skewed in study CP40563 (3 patients in the baloxavir marboxil group and 6 in the oseltamivir group). Therefore, there is limited efficacy data in this population.

Post-exposure-prophylaxis indication

The proportion of subjects who met the primary endpoint (infected with influenza virus (RT-PCR positive) was lower in the baloxavir marboxil group than in the placebo group for both subgroups of subjects younger and older than 12 years, but the adjusted risk ratio was higher in the youngest age group, indicating the effect could be lower in the age group < 12 years. However, numbers are limited for the age group < 12 years and therefore precaution should be taken with the conclusions.

No clinical data are available for the efficacy or safety of retreatment in the PEP setting. Therefore, retreatment is not recommended. The maximum interval between first contact with the symptomatic index case and intake of baloxavir marboxil was 48 hours, efficacy beyond this timeframe is not known. This has been addressed in the initial application for adults and adolescents and incorporated in the SmPC.

3.4. Unfavourable effects

In the pivotal trial, the frequency of patients experiencing adverse events were 46.1% and lower in the baloxavir marboxil group than the oseltamivir group. When comparing with placebo in the PEP study, the incidence was the similar between the treatment groups (25.4%) and lower than in the treatment population. Overall, the frequency of adverse events was higher in children < 12 years than subjects ≥ 12 years, however, comparable or lower than placebo or oseltamivir in the pivotal studies.

The most common adverse events in the pivotal trial were vomiting, diarrhoea, upper respiratory tract infection and medication error occurring in 4-6 % of the subjects. Diarrhoea was more frequently occurring in the baloxavir marboxil group and vomiting was more frequently occurring in the oseltamivir group. For other adverse events, the frequency was almost similar between treatment groups.

No serious adverse events or deaths were reported in neither the treatment studies nor the post exposure prophylaxis studies. Furthermore, the severity of the adverse events was grade 1 and grade 2, besides for one adverse event that were grade 3 (abdominal pain). For the majority of the adverse events, they had resolved by day 29 post dose. No exposure related safety issues were identified.

Extensive post marketing data is available including children. An estimated number of subjects < 12 years exposed to baloxavir marboxil is 963,501. Those children come from Japan and Taiwan and also from other countries where the medicinal product has been used off-label. A total of 1901 adverse events in 1016 subjects have been reported post marketing. Of those, 124 adverse events were reported as serious, of which vomiting (n=11), seizure (n=9), abnormal behaviour (n=9) and diarrhoea (n=5) were most frequently reported.

3.5. Uncertainties and limitations about unfavourable effects

The volume to be ingested is considered large for small children (up to 20 ml) – especially if the taste is bitter which is the case for the active substance, however the provided data indicates an adequate acceptability and palatability with baloxavir marboxil GfOS in the paediatric population.

3.6. Effects Table

Table 50: Effects Table for baloxavir marboxil for treatment and prophylaxis of influenza.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects: treatment of influenza						
TTAS Key secondary efficacy endpoint	Time to alleviation of influenza signs and symptoms based on CARIFS and tympanic temperature	Median Hours (95% CI)	Baloxavir marboxil 138.1 (116.6, 163.2)	Oseltamivir 150.0 (115.0, 165.7)	Descriptive, no comparison analysis or regression analysis on age	SCE table 10
Duration of fever Secondary efficacy endpoint	Duration of fever (time to return to afebrile state [tympanic temperature ≤ 37.2°C] and remaining so for at least 21.5 hours)	Median Hours (95% CI)	Baloxavir marboxil 41.2 (24.5, 45.7)	Oseltamivir 46.8 (30.0, 53.5)	Descriptive, no comparison analysis or regression analysis on age	SCE table 10
Time to cessation of viral shedding by virus titer		Median Hours (95% CI)	24.2 (23.5, 24.6)	75.8 (68.9, 97.8)	Descriptive, no comparison analysis or regression analysis on age	SCE table 12
Time to cessation of viral shedding by RT-PCR		Median Hours (95% CI)	242.5 (235.8, 262.8)	238.9 (214.0, 286.7)	Descriptive, no comparison analysis or regression analysis on age	SCE table 12
Favourable Effects: Prevention of influenza						
Proportion of subjects with influenza infection, fever, and at least one respiratory symptom Primary endpoint	Influenza events in household members to index patients mITT <12 years only	% (n/N) Adjusted risk ratio (95% CI)	Baloxavir marboxil 4.2% (3/71) 0.27 (0.08, 0.90)	Placebo 15.5% (11/71)	P-value 0.0339	SCE Table 30

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Proportion of subjects with influenza infection and fever or at least one influenza symptom Secondary endpoint	Symptomatic influenza events in household members to index patients mITT <12 years only	% (n/N) Adjusted risk ratio (95% CI)	8.5% (6/71) 0.30 (0.13, 0.70)	28.2% (20/71)	P-value 0.0052	SCE Table 31
Proportion of subjects with influenza infection regardless of symptoms Secondary endpoint	Influenza events n household members to index patients mITT <12 years only	% (n/N) Adjusted risk ratio (95% CI)	23.9% (17/71) 0.73 (0.43, 1.24)	33.8% (24/71)	P-value 0.2451	SCE Table 31
Unfavourable Effects						
Vomiting	Incidence of vomiting	%	Baloxavir marboxil 6.1%	Oseltamivir 15.5%		(1)
Diarrhoea	Incidence of diarrhoea	%	Baloxavir marboxil 5.2%	Oseltamivir 1.7%		(1)
Upper respiratory tract infection	Incidence of Upper respiratory tract infection	%	Baloxavir marboxil 4.3%	Oseltamivir 3.4%		(1)
Medication error	Incidence of medication error	%	Baloxavir marboxil 4.3%	Oseltamivir 3.4%		(1)

Abbreviations:
Notes: (1) pivotal trial,

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

For the treatment indication, in the age group 1 to < 12 years, the effect of baloxavir marboxil in terms of time to alleviation of influenza signs and symptoms and duration of fever, were comparable to the active comparator oseltamivir and of important clinical relevance; the incidence of influenza-related complications was low and similar in both treatment groups.

For the post-exposure prophylaxis indication efficacy was shown for the age group < 12 years, supported by data from the adult and adolescent population.

The number of patients < 3 years is limited and skewed in study CP40563 (3 patients in the baloxavir marboxil group and 6 in the oseltamivir group). Therefore, there is limited efficacy data in this population. However, as the PK modelling has shown similar exposure in children down to 1 year of age and that efficacy can be partially extrapolated from adolescents and adults, baloxavir marboxil is considered efficacious in children from 1 to < 3 years of age.

The safety database for the population from 1 to 12 years were overall considered adequate. The unfavourable effects appear to be limited and clinically manageable in this population.

3.7.2. Balance of benefits and risks

The benefit/risk balance for the proposed indication for the age group 1 to < 12 years is considered positive for both the treatment and post-exposure prophylaxis indication

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall benefit/risk balance of Xofluza for the extension of the indications, to include the age group of 1 to < 12 years is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Xofluza with new formulation and strength (2 mg/ml granules for oral suspension) grouped with a type II variation (C.I.6.a) to include paediatric use (from 1 year and above) for all presentations, is favourable in the following indications:

Treatment of influenza

Xofluza is indicated for the treatment of uncomplicated influenza in patients aged 1 year and above.

Post-exposure prophylaxis of influenza

Xofluza is indicated for post-exposure prophylaxis of influenza in individuals aged 1 year and above.

Xofluza should be used in accordance with official recommendations.

The CHMP therefore recommends the grouped extension and variation of the marketing authorisation for Xofluza subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.