EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 November 2020
EMA/CHMP/537088/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xofluza

International non-proprietary name: baloxavir marboxil

Procedure No. EMEA/H/C/004974/0000

Note

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

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List of abbreviations

[^{14}C]	carbon-14, a radioactive isotope of carbon
AADAC	arylacetamide de-acetylase
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
Alu	aluminium
AS	active substance
AST	aspartate aminotransferase
$AUC_{0\text{-inf}}$	the area under the plasma concentration curve from time 0 to infinity
$AUC_{0\text{-last}}$	the area under the concentration-time curve from 0 to the time point of the last quantifiable concentration after dosing
baloxavir	the active metabolite of baloxavir marboxil
BA	bioavailability
BE	bioequivalence
BfArM	German Federal Institute for Drugs and Medical Devices
BID	twice daily
BMI	body mass index
bxm	baloxavir marboxil
C_{24}	plasma concentration at 24 hours post dose
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CL/F	apparent total clearance, calculated as Dose/$AUC_{0\text{-inf}}$ (baloxavir only)
CLcr	creatinine clearance
CMAs	critical material attributes
C_{max}	maximum plasma concentration
CPPs	critical process parameters
CQAs	critical quality attributes
CSR	Clinical Study Report
CTAB	cetyltrimethylammonium bromide
CTD	Common Technical Document
CV	coefficient of variation
CYP	cytochrome P450 enzymes

DDI	drug-drug interaction
DMSO	dimethyl sulfoxide
EC_{50}	concentration which produces 50% of maximum effect
EC_{90}	concentration which produces 90% of maximum effect
eCDC	European Centre for Disease Prevention and Control
F	absolute oral bioavailability
FDA	Food and Drug Administration
FE	food effect
GC	gas chromatography
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HPLC	high performance liquid chromatography
HR	high risk of developing influenza complications
IC_{50}	50% inhibitory concentration
ICH	International Conference on Harmonisation
ICP-MS	inductively coupled plasma mass spectrometry
IDSA	Infectious Disease Society of America.
IND	Investigational New Drug
IR	infra-red spectroscopy
ITTI	Intention-to-Treat Infected
Ka	absorption rate constant
LDPE	low-density polyethylene
MAA	Marketing Authorisation Application
MHRA	UK Medicines and Healthcare Products Regulatory Agency
MPA	Swedish Medicinal Products Agency
NAIs	neuraminidase inhibitors
NDA	New Drug Application
NORs	normal operating ranges
OPA	oriented polyamide
oselt.	oseltamivir
OwH	otherwise healthy
PA	polymerase acidic protein
PARs	proven acceptable ranges

pbo	placebo
PD	pharmacodynamics
PEP	post-exposure prophylaxis
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PK	pharmacokinetics
PopPK	population pharmacokinetics
PPS	Per-Protocol Set
PSD	particle size
PVC	polyvinyl chloride
QbD	quality by design
QC	quality control
Q/F	apparent inter-compartmental clearance
QTc	corrected QT interval
QTcF	QTc corrected by Fridericia's method
QTPP	Quality Target Product Profile
RH	relative humidity
RNA	ribonucleic acid
RT-PCR	reverse transcriptase-polymerase chain reaction
SAE	serious adverse event
SBP	Summary of Biopharmaceutic Studies and Associated Analytical Methods
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology Studies
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics
sNDA	supplemental New Drug Application
Tbil	total bilirubin
$TCID_{50}$	50% tissue culture infective dose
TTAS	time to alleviation of influenza symptoms
TTIS	time to improvement of influenza symptoms
UGT	uridine diphosphate glucuronosyltransferases
UHPLC	ultra high performance chromatography
USPI	United States Package Insert

UV	Ultraviolet spectrometry
Vc/F	apparent central volume of distribution
Vp/F	apparent peripheral volume of distribution
Vz/F	apparent volume of distribution in the terminal elimination (baloxavir only)
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Roche Registration GmbH submitted on 6 November 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Xofluza, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 January 2018.

The applicant applied for the following indication:

"Treatment of influenza

Xofluza is indicated for the treatment of influenza in patients aged 12 and above, including patients at high risk of developing influenza-related complications.

Prophylaxis of influenza

Xofluza is indicated for post-exposure prophylaxis of influenza in individuals aged 12 and above (see section 5.2)."

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is

composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0300/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0300/2019 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant 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.

Applicant's requests for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance baloxavir marboxil contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received the following Scientific advices on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
23 February 2018	EMA/CHMP/SAWP/97367/2017	Dr Marion Haberkamp and Dr Sheila Killalea
15 November 2018	EMA/CHMP/SAWP/785580/2018	Dr Ewa Balkowiec-Iskra and Dr Sheila Killalea

The Scientific advice pertained to the following *Quality* aspects:

- *Designation of regulatory starting materials for drug substance manufacture*
- *Mutagenic impurities control strategy for the drug substance*
- *Proposed dissolution test method for the drug product*
- *Proposed release and shelf-life specification parameters for drug substance and drug product*
- *Proposed stability protocols for drug substance and drug product*

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kirstine Moll Harboe Co-Rapporteur: Jayne Crowe

The application was received by the EMA on	6 November 2019
The procedure started on	28 November 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	17 February 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	17 February 2020

The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	3 March 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 March 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	10 July 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	24 August 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	4 September 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	17 September 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	8 October 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	28 October 2020
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	12 November 2020

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 (Harmon et al. 2019, Tregoning et al. 2018). 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 and risk factors

Natural history of the indicated condition in the (untreated) population

Morbidity and Mortality: The morbidity and mortality caused by seasonal influenza outbreaks continue to be substantial. Worldwide, these annual epidemics are estimated to result in about 3 to 5 million cases of severe illness, and about 290,000 to 650,000 respiratory deaths (WHO 2018b). The cost of primary care physician visits due to influenza for all EU 25 countries in 2005 was estimated at €267.2 million and the cost of hospital visits at €11.5 billion. An increase in the number of deaths caused by pneumonia and influenza is generally a late observation in an outbreak. Secondary bacterial pneumonia can follow acute influenza. The most common bacterial pathogens in this setting are *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenza*. Mortality among individuals with chronic metabolic, renal, and certain immunosuppressive diseases has also been elevated, although lower than that among patients with chronic cardiopulmonary diseases. Pandemics

provide the most dramatic evidence of the impact of influenza. However, illnesses that occur between pandemics account for greater total mortality and morbidity, albeit over a longer period.

Risk factors for the disease

Hospitalization and death occur mainly among high-risk (HR) groups. Complications of influenza occur most frequently in patients ≥ 65 years old and in those with certain chronic disorders, including cardiac or pulmonary diseases, diabetes mellitus, hemoglobinopathies, renal dysfunction, and immunosuppression. Pregnancy in the second or third trimester also predisposes the mother to complications with influenza. Furthermore, residents of nursing homes and other long-term facilities, people with weakened immune system due to disease or medications, people younger than 19 years old on chronic or long-term aspirin therapy, people with extreme obesity and people of American Indian and Alaskan Natives also are at higher risk for influenza complications. The CDC provides a complete list of people at high risk of developing influenza-related complications. These characteristics make influenza in these patients a "potentially severe disease," which should be distinguished from the "common cold syndrome." The most prominent HR conditions are chronic cardiac and pulmonary diseases, and age (≥ 65 years and < 2 years). Primary influenza viral pneumonia is more common in individuals with cardiac disease, particularly those with congenital heart disease, congestive heart failure, coronary artery disease, diabetes, but has also been reported in OwH young adults as well as in older individuals with chronic pulmonary obstructive disease and asthma.

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 and diagnosis

Illness caused by influenza is characterized by an abrupt onset of high fever, chills, prostration, fatigue, sore throat/pharyngitis, headache, myalgia, dry cough, rhinitis, cervical lymphadenopathy, and conjunctivitis. Conjunctivitis, rhinitis, and gastrointestinal symptoms are more common in infants and young children than in adults. Influenza infection severity can be defined as acute uncomplicated, referring to ambulant patients with a relatively benign self-limiting disease course, or "serious" or complicated infection requiring hospitalization.

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.

Through interplay between host immune defence and influenza virulent factors, the underlying disease can cause a wide spectrum of complications. The most significant complication of influenza is

pneumonia: "primary" influenza viral pneumonia, secondary bacterial pneumonia, or mixed viral and bacterial pneumonia. Other pulmonary complications associated with influenza include worsening of chronic obstructive pulmonary disease (COPD) and exacerbation of chronic bronchitis or asthma and even acute respiratory distress syndrome (ARDS). Sinusitis as well as otitis media (the latter occurring particularly often in children) may also be associated with influenza. In addition to the pulmonary complications of influenza, a number of extrapulmonary complications may occur. These include Reye's syndrome, myositis, rhabdomyolysis, and myoglobinuria. Although myalgias are very common in influenza, true myositis is rare. Myocarditis and pericarditis are rare. Electrocardiographic changes during acute influenza are common among patients with cardiac disease, but have been attributed most often to exacerbations of the underlying cardiac disease rather than to direct involvement of the myocardium with influenza virus. Central nervous system (CNS) complications, including encephalitis and encephalopathy, transverse myelitis, and Guillain-Barré syndrome, have been reported during influenza infection with the influenza virus being considered as causal. Toxic shock syndrome associated with *S. aureus* or group A streptococcal infection following acute influenza infection has also been reported. In addition to complications involving the specific organ systems described above, influenza outbreaks include a number of cases in which elderly and other high-risk individuals develop influenza and subsequently experience a gradual deterioration of underlying cardiovascular, pulmonary, or renal function – changes that occasionally are irreversible and lead to death. These fatalities contribute to the overall excess mortality associated with influenza A outbreaks.

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. 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.

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.

Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was due to the fact that while it was agreed that there is a public interest in getting more and better treatment options for influenza, the presented results on clinical parameters were not convincingly better than available treatment options. Further, the potential benefit in case of resistance to available treatment options remains a theoretical benefit, as currently rates of oseltamivir resistance remain low. Thus, there were no solid grounds for concluding that baloxavir is of major public interest or that baloxavir constitutes a major therapeutic innovation.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as immediate-release film-coated tablets for oral administration containing 20 mg or 40 mg of baloxavir marboxil as the active substance.

Other ingredients in the tablet core are: lactose monohydrate, croscarmellose sodium (E468), povidone (K25), microcrystalline cellulose (E460) and sodium stearyl fumarate.

Other ingredients in the film coating are: hypromellose, talc (E553b) and titanium dioxide (E171).

The film-coated tablets are available in oriented polyamide (OPA)/aluminium foil/polyvinyl chloride (PVC) laminate blisters with a PVC based heat seal coated aluminium.

2.2.2. Active Substance

General information

The chemical name of baloxavir marboxil is ({(12a*R*)-12-[(11*S*)-7,8-difluoro-6,11-dihydrodibenzo[b,e] thiepin-11-yl]-6,8-dioxo- 3,4,6,8,12,12a-hexahydro-1*H*-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazin-7-yl}oxy)methyl methyl carbonate. It corresponds to the molecular formula $C_{27}H_{23}F_2N_3O_7S$, its relative molecular mass is 571.55 g/mol and it has the chemical structure shown in Figure 1.

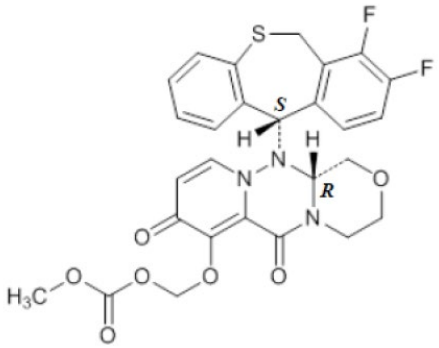


Figure 1. Structure of baloxavir marboxil.

The structure of the active substance (AS) was elucidated by a combination of elemental analysis, mass spectrometry (MS), IR spectroscopy, ^{1}H-NMR and ^{13}C-NMR spectrometry, UV spectrometry, and by single crystal x-ray crystallography.

Baloxavir marboxil appears as a white to light yellow, non-hygroscopic, crystalline powder. It is practically insoluble in water, and aqueous buffer solutions with pH 1 - pH 9 (4.4-6.1 µg/mL); in pH 11 buffer, solubility is 24.8 µg/mL but this value represents the solubility of baloxavir which is formed at this pH by conversion of the AS. It is sparingly soluble in acetone, slightly soluble in methanol, and ethanol (99.5 %), very slightly soluble 2-propanol, and 1-octanol. No acid dissociation constant pKa can be determined; its partition coefficient was found 5.80.

Baloxavir marboxil molecule has 2 asymmetric carbon atoms and exhibits stereoisomerism. In addition to the desired (*R,S*) configuration, the enantiomer (*S,R*) and 2 diastereomers (*R,R* and *S,S*) exist. The enantiomer and the two diastereomers can be differentiated from the active substance (AS) and are controlled in the AS specification.

Polymorphism has been observed for baloxavir marboxil. It is produced as Form I, which was found to be the most stable form. The manufacturing process is capable of consistently producing Form I. All forms can be distinguished by x-ray diffraction.

Manufacture, characterisation and process controls

The active substance manufacturer has been stated.

The manufacturing process consists of ten steps and was adequately described. The starting materials have been selected in line with the considerations of ICH Q11 and are considered acceptable. Adequate details have been provided of suppliers, manufacturing flow charts, specifications and batch data. The isolated intermediates were defined and are controlled by acceptable specifications. Reagents, solvents, catalysts and auxiliary materials used in the synthesis are also controlled by acceptable specifications.

All the synthetic steps and the milling step are considered critical steps and are controlled by appropriate in-process controls. A major objection had been raised on the manner in which the proven acceptable ranges (PARs) were presented because it was unclear whether the PARs were intended to be used in a multivariate or univariate way. It was clarified that the process is run in a univariate way and the described proven acceptable ranges (PARs) are not used in a multivariate way. No design space is claimed. The PARs are considered fully justified as they have been derived through a rigorous and stepwise risk assessment during development. Extensive discussion has been provided to justify the PARs and also the impurity control strategy (genotoxic and otherwise) and how the process is capable of purging them. Genotoxic substances involved in the synthesis are appropriately controlled.

No holding times are proposed. The manufacturing process is run at set points/target values and within normal operating ranges (NORs). The PAR ranges are now listed unambiguously, and the ranges provided are consistent with the PARs determined during process development. The control of the process is now acceptable and the tight control of process parameters, with other complementary parts of the control strategy, provides assurance for the consistent manufacture of future batches.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

An elaborated impurity discussion and control strategy has been presented covering starting materials, reagents and solvents used in the synthesis, as well as elemental impurities, carry over of intermediates and synthetic by-products. The mutagenic impurity evaluation thus included 150 substances. The control strategy is based on knowledge of the synthesis, purging factors (originating from purging studies or theoretical estimations), and batch data of starting materials, intermediates and active substance. Mutagenic impurities are controlled by appropriate specifications on the relevant materials or by controls applied during the manufacturing process. Overall, the control strategy for impurities has been presented in detail and is considered satisfactory.

The stereochemistry of the active substance is ensured by the process and is also sufficiently controlled.

The AS was designed to be readily hydrolysed upon administration to the active form, and for this purpose the methoxycarbonyloxymethyl group has been chosen as a side chain.

A history of the synthetic route evolution was provided. Different versions of the process have been clearly designated and a summary of the changes has been presented, which involve changes in sites, scale, and some changes in process parameters.

The active substance is packaged in double low-density polyethylene (LDPE) bags tightly closed with plastic ties placed into a secondary container, e.g. metal or fibre. A satisfactory specification for the LDPE bag is provided. The LDPE complies with the requirements of Regulation (EU) No. 10/2011 and Regulation (EU) No. 2017/752 and with Ph. Eur. 3.1.3 "Polyolefins".

Specification

The AS specification includes appropriate tests and limits for description (visual), identification (UV, IR), assay (HPLC), related substances (HPLC), stereoisomer content (chiral HPLC), residual solvents (GC), water content (Ph. Eur.), residue on ignition (Ph. Eur.) and particle size (laser diffraction). The specifications are in line with ICH Q6A and are acceptable. The unwanted enantiomer and diastereomers are controlled as impurities to the ICH Q3A qualification threshold. The limits for related substances are set based on toxicological studies and batch data. An acceptable toxicological justification has been provided for those impurity limits above the ICH Q3A qualification threshold. The control strategy for genotoxic impurities, residual solvents and polymorphism is satisfactory. The assay limit is also acceptable.

The specification limit for particle size is defined based on batch data (including clinical) and the limit has been set in relation to finished product critical quality attributes (CQAs).

During stability studies, microbial contamination and the water activity was monitored. No changes were observed and with a water activity on 0.6, there is no microbiological risk for the active substance and thus a microbial limit test was not deemed necessary.

In line with ICH Q3D, batches of active substance have been tested for elemental impurities by a properly validated ICP-MS method. The risk of elemental impurities contamination exceeding the PDE value was reduced by introducing appropriate controls in relevant intermediates and by employing suitable purification means and processes. Therefore, a control in the active substance specification is not deemed necessary.

Batch data were provided for 5 commercial scale batches manufactured with the proposed synthetic route. The results comply with the proposed specification and demonstrate consistent manufacture and quality of the AS. Data from another 9 batches, ranging in batch size from pilot to commercial scale, including the non-clinical and clinical batches and covering the different manufacturing processes used throughout the development were presented. Differences in impurity limits and methods for earlier batches have been adequately explained and there are no concerns. The data support the process being under control and the comparable quality between batch sizes and different versions of the manufacturing process.

Stability

Stability data has been provided for three pilot scale batches manufactured with the previous process at the proposed site. This manufacturing process is fully representative of and simulating the manufacturing process to be applied to a full production scale batch. These primary stability batches were packaged in the proposed container closure system. Stability data were provided for up to 24 months stored at long term conditions (30°C / 65% RH) and for up to 6 months at accelerated conditions (40°C / 75% RH) according to the ICH guidelines.

Samples were tested for description, identification, assay, related substances, water content, crystalline form, particle size, and microbial limit. Related substances increased at accelerated condition but remained well within the proposed acceptance criteria. Regardless of the storage condition, all results comply with the specification limits; no trends were observed.

Additionally, stability data were generated for the three first commercial scale batches, per the current process at the proposed manufacturing site, and stored for up to 12 months under long term and for 6 months under accelerated conditions. Batches were packaged in the proposed container closure system and were stored protected from light. Samples were tested for description, identification, related substances, stereoisomers, water, assay, crystalline form, particle size, water activity and microbial limit. Related substances increased under accelerated conditions but remained well within the proposed acceptance criteria. Regardless of the storage condition, all results comply with the specification limits; no trends were observed.

Data from one additional technical batch, manufactured by the current process at the proposed manufacturing site and stored under accelerated conditions for 6 months, were provided as supportive information. The related substances increased but remained well within the proposed acceptance criteria.

Stress testing was carried out on a pilot scale batch. The conditions investigated were:

- 60°C/ Ambient RH, protected from light in an amber glass bottle for three months.
- 25°C/ 85% RH, protected from light in an open petri dish for three months.
- 40°C/ 75% RH, protected from light in an open petri dish for three months.

The parameters tested were the same as for the formal stability studies. No significant changes were noted except a minor increase in one impurity. Regardless of the stress condition, no additional trends were observed.

Photostability testing was carried out on one pilot batch in as per ICH Q1B. There were no significant changes in any tested parameter, except that the appearance changed from white powder to pale

yellow powder. The AS is not considered photosensitive but because of the colour change it is, accepted to include the warning "protect from light".

Forced degradation testing was carried out on a pilot scale batch under the following conditions in solid state: 80°C/ ambient, protected from light; 60°C / 75% RH, protected from light; 25°C / 60% RH, D65 lamp (4000 lx). Parameters tested were description, assay, related substances, stereoisomers, and water. Except for the appearance change from white powder to pale yellow powder due to light exposure, no significant change was observed.

Forced degradation testing in solution state in a range of solubilising solutions and pHs, temperatures and storage period was also performed. Parameters tested were clarity and colour of solution, assay, related substances, and stereoisomers. Certain impurities increased under different storage conditions. Based on the results of the forced degradation studies, the analytical methods for assay and related substances are stability indicating.

Based on the available stability data, the proposed retest period of 24 months for the AS when stored below 30°C protected from light, is acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is an immediate release film-coated tablet for oral administration, presented in two strengths, containing 20 mg or 40 mg of baloxavir marboxil.

The 20 mg tablets are oblong, white to light yellow film-coated tablets debossed on one side with the manufacturer's trademark and the identifier code "772", and on the other side with "20".

The 40 mg tablets are oblong, white to light yellow film-coated tablets debossed on one side with "BXM" and on the other side with "40".

The qualitative and quantitative composition of Xofluza film-coated tablets has been stated; the list of excipients is presented in section 2.2.1 of this report and in SmPC 6.1.

Formulation development
The AS is a prodrug which is metabolised into the active form after administration. The key AS physical/chemical properties which could impact are in accordance with ICH Q6A guideline. It was demonstrated that the proposed specification ensures satisfactory finished product dissolution, stability, blend uniformity, appearance and processability.

The chosen excipients are commonly used in immediate release film-coated tablets and are described in Ph. Eur., except the film coating mixture, which consists of pharmacopoeial ingredients. The choice and function of each excipient has been presented. Compatibility with the AS has been investigated and drove the selection of excipients and coating. The quantity of each excipient has been discussed with reference to some tablet CQAs such as dissolution, hardness and appearance.

The choice of pharmaceutical form/strength adequately addresses the proposed dosing regime, i.e. one single dose of 40 mg or 80 mg. A paediatric formulation has been developed and paediatric studies are ongoing. The paediatric formulation is not part of the present application. The history of formulations used for clinical studies and the compositions of the various formulations used during development were presented. The Phase 3 clinical studies utilised a 20 mg tablet formulation and the doses being studied are 40 mg and 80 mg. A 10 mg tablet has also been used for clinical studies. The particle size of AS was classified as a critical material attribute (CMA) and is controlled in the active substance

specification in line with clinical batches. The impact of AS particle size on finished product quality in terms of dissolution, stability, blend uniformity, appearance, and processability was investigated.

The applicant has clearly laid out the different formulations used for each clinical study (20 mg strength). Only small changes have been made since Phase 2 and the rationale for each is provided. Comparative dissolution studies demonstrated no significant difference. The proposed commercial formulation of the 20 mg tablet has been used for phase 3 clinical trials. The 40 mg strength was subsequently developed. Linear pharmacokinetics are claimed. In support of waiver of clinical/ bioequivalence studies for the 40 mg strength, comparative dissolution profiles between the 20 mg clinical batches and the 40 mg strength have been presented. The dissolution studies were carried out in media with three different pHs (pH 1.0, 4.5 and 6.8) with and without surfactant and demonstrated over 85% dissolution at 15 min and/or f2 values over 50 for each pH. The strength biowaiver is therefore acceptable.

The AS is a prodrug and is mainly hydrolysed to the active form in the small intestine. Therefore, the most appropriate pH of dissolution media to ensure complete and rapid dissolution of the product is that of intestinal fluid, rather than that of gastric fluid. The dissolution medium was selected based on the solubility of the AS and dissolution profiles of the 20 mg and 40 mg tablets. The discriminatory power of the method was sufficiently demonstrated by showing differentiation of tablets with meaningful variations in AS attributes, or other relevant changes in composition and/ or manufacturing process

Overall, the development of the dissolution method proposed for QC testing is acceptable and the discriminatory properties are demonstrated.

Manufacturing process development
The Quality by Design (QbD) principles outlined in ICH guidelines (Q8, Q9 and Q10) have been adopted in developing the manufacturing process. The Quality Target Product Profile (QTPP) and critical quality attributes (CQA) were established and presented. CQAs were identified based on their impacts on patient safety, efficacy and usability. Preliminary studies identified high risk potential critical process parameters (CPPs) based on process experience (i.e. potential impact on CQAs and further investigation needed). Control ranges for CPPs and CMAs were established based on experiments intended to provide a better understanding of the manufacturing process and develop a suitable control strategy.

A bulk hold study was carried out on two commercial-scale batches of each strength. The amount of degradant increased slightly but no other changes were noted, thus supporting the proposed bulk hold time.

Container closure system
Xofluza film-coated tablets are packaged in cold formed oriented polyamide (OPA) / aluminium foil / polyvinyl chloride (PVC) laminate blisters with a PVC based heat seal coated aluminium. Blisters will be placed in a secondary container (fibre carton folding box). Details are provided for each component and satisfactory specifications were provided. The product-contact side of the blister foil and lidding foil comply with Regulation (EU) No.10/2011 subsequent revisions. The proposed packaging is considered suitable for packaging of the finished product based on the stability studies.

Manufacture of the product and process controls

The finished product manufacturer has been stated. The manufacturing process is a standard wet granulation process and consists of blending, granulation, drying, sizing, blending, lubrication, compression, coating and packaging. The same blend is used to produce both strengths. The level of details in the description of the manufacturing process is acceptable.

Critical steps were identified and clearly presented. Appropriate in-process controls have been established based on the manufacturing process development studies. As discussed above, the defined PARs are not operated in a multivariate way; no design space is claimed. The proposed bulk hold time is justified as discussed above.

The manufacturing process is a standard process. Nevertheless, full process validation data were provided for three batches of each strength. The data indicate that the process is capable of manufacturing product of consistent quality.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for description (visual), identification (UHPLC, UV), assay (UHPLC), related substances (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur., UV), water content (Ph. Eur.) 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 was provided. The justification for the impurity limits can be followed and takes ICH Q3B into account. Toxicological justification has been provided for impurity levels above the ICH Q3B qualification threshold. The dissolution limit is justified based the dissolution profile of several batches including the biobatch and stability data for the 40 mg biowaiver batch. It has been demonstrated that the polymorphic form does not change during manufacture or storage of the finished product. It has been satisfactorily justified that there is no need to test residual solvent in the finished product specification. Based on batch data it was concluded that the risk of the AS converting to stereoisomers in the product is low and thus control of stereoisomers is not necessary.

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 ten 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, in line with the "Questions and answers on Information on nitrosamines for marketing authorisation holders" and the "Information on nitrosamines for marketing authorisation holders" published on the EMA website, has been presented for both the finished product manufacturing process and the active substance with respect to potential formation of nitrosamine impurities. The outcome of the risk assessment confirms that there is no risk for nitrosamine impurities formation and no risk for cross-contamination with other products.

The analytical methods used have been adequately described and validated in accordance with ICH Q2 guideline. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis results are presented for three full scale primary stability batches and three full scale process validation batches of each strength, manufactured at the proposed commercial scale at the proposed manufacturing site. In addition, batch analysis data from some smaller clinical batches was presented. All results complied with the specifications in place at the time (old methods provided) and the data are consistent. The results showed that the finished product meets the proposed specifications and confirm the batch-to-batch consistency.

Stability of the product

Stability data from three full scale primary stability batches of each strength, manufactured and packed at the proposed manufacturing site, and stored for up to 36 months under long term conditions (25ºC / 60% RH and 30ºC / 75% RH) and for up to six months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

Stability data were also presented from three batches of each strength intended for commercial use manufactured and packed at the proposed manufacturing site and stored for up to 6 months under long term conditions (25ºC / 60% RH and 30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines.

Stability samples were tested for description, identification, related substances, stereoisomers, uniformity of dosage units, dissolution, assay, water, hardness and microbial limits. The methods were the same as for release. Some minor differences are the result of slight optimisations to the methods for dissolution and impurities introduced after start of the stability studies. These changes were discussed and are not expected to impact the results. Stereoisomer and hardness tests were also performed for some stability studies using validated methods.

A known degradation product increased slightly under both long term and accelerated conditions; no changes were observed for other related substances. No changes were observed for other tested parameters either. The same findings were observed in the commercial batches as for the primary stability study batches. A tendency for an increase in one of the degradation products was observed. All other parameters remained unchanged.

A photostability study in accordance with the ICH Q1B guideline was carried out on one batch of each strength. Based on the results the tablets are not considered to be sensitive to light.

Temperature cycling testing was conducted on one batch of each strength. The results demonstrate that the product is not affected by temperature cycling and support limited duration excursions from recommended storage conditions during product handling and distribution.

Stress testing was carried out on one batch of each strength for three months. A known degradation product-increased to a variable degree under the different test conditions. Under increased humidity, there was a tendency for a decrease in hardness and increase in water. No other changes were noted.

Forced degradation testing was carried out on both strengths to elucidate the degradation pathways and to support suitability of the stability-indicating power of the analytical methods. Both solid and solution phase degradation were investigated. Samples in the solid state were exposed to heat, heat and humidity, and light (in line with ICH photostability conditions). Samples in solution were exposed to water/acetonitrile, acid hydrolysis, base hydrolysis, and oxidation and have been compared to unstressed samples. Proposed degradation pathways were presented. The methods for testing assay and related substances of baloxavir marboxil are considered stability indicating.

Based on the submitted stability data the proposed shelf-life of 36 months with the storage condition "store in the original package in order to protect from moisture" is justified.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

No other materials derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The overall control strategy is adequately justified and is acceptable. The proposed strength biowaiver for the 40 mg strength has been sufficiently supported. 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.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable and consistent. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

GLP:

For the nonclinical part of the dossier, the safety pharmacology studies, the study of tissue distribution in pregnant rats, and the pivotal toxicity studies were conducted in compliance with Good Laboratory Practice (GLP) guidelines.

All studies were conducted under an extensive GLP audit program and in general appear to be GLP compliant.

2.3.2. Pharmacology

Baloxavir marboxil is a prodrug that is converted to the active form baloxavir through metabolism. The active form selectively inhibits the cap-dependent endonuclease (CEN), an influenza virus-specific enzyme in the polymerase acidic (PA) subunit of the viral RNA polymerase complex, which thereby inhibits influenza virus replication. Baloxavir marboxil, a prodrug form of baloxavir, did not have an inhibitory potency like baloxavir.

Primary pharmacodynamic studies

In vitro pharmacology

Baloxavir has a more potent virus replication inhibitory effect than the control drugs in the laboratory strains of influenza A and B viruses determined both as decrease in virus titer and number of plaques

in infected MDCK cells. EC50 was typically subnanomolar against influenza type A and approximately 2-7 nM against influenza virus type B. It appears that baloxavir is up to 50-200 times more potent than oseltamivir (Tamiflu) in these assays (study 1088864 and 1088871).

A similar picture was found when testing in clinical isolates from across the world, i.e. EC50 for baloxavir of 0.34 to 2.12 nmol/L for type A viruses, with the exception of the polymorphic variant A/Louisiana/49/2017-PA/I38M [H3N2], and 5.54 to 14.23 nmol/L for type B viruses (study 1088869, 1088915 and 1091646).

Furthermore, baloxavir decreased number of plaques of vaccine strains of influenza type A and B recommended by WHO. In addition, baloxavir showed similar potency against NA inhibitor-resistant viruses and its wild-type viruses of both A and B types (study 1088875).

Baloxavir is more potent against influenza type A compared to type B. This was explained by differences in molecular interactions in the hydrophobic pocket in which baloxavir is situated in the virus Polymerase Acidic Protein.

The combination-use of baloxavir and a NA inhibitor inhibited virus replication in MDCK cells synergistically (study 1088919 and 1094824) for both influenza A and B strains.

Overall, in vitro proof of concept is considered established for baloxavir.

In the baloxavir-resistant virus isolation assay, all influenza viruses with a reduced susceptibility were containing an isoleucine-to-threonine substitution at amino acid position 38 in PA (PA/I38T). The PA/I38T mutation resulted in a reduced virus replication capacity, compared with the wild-type virus. Hence, influenza A virus harbouring PA/I38T is considered unlikely to emerge in clinical settings. The same exercise was conducted with influenza virus type B. However, no mutations were identified which resulted in reduced susceptibility to baloxavir.

MDCK cells were infected with highly pathogenic avian influenza virus A/H5N1 isolated from patients in Hong Kong. Baloxavir showed a 10 times better potency than oseltamivir in inhibiting the replication of this avian influenza virus and has an inhibitory activity against the NA inhibitor-resistant highly pathogenic avian influenza virus comparable to that against the wild-type virus.

A similar picture was obtained when testing baloxavir against avian influenza virus A/H7N9. Baloxavir was also shown to be efficient against various influenza A virus isolated from pigs, chickens and ducks (H1N2, H5N2, H5N6, and H9N2, study 1088904).

In vivo pharmacology

In vivo studies were carried out in mouse non-lethal models of seasonal influenza infections to show the antiviral efficacy of baloxavir marboxil using virus titer in lungs as end-point.

Baloxavir marboxil was orally administered twice daily (BID) for 1 day to mice inoculated with an influenza A or B virus 5 days post-inoculation, and the virus titer in the lung was measured 24 hours after the first dose.

Baloxavir marboxil was compared to other established antiviral drugs at clinically equivalent doses. In all cases baloxavir marboxil was the most efficacious and most potent against influenza A virus compared to oseltamivir, favipiravir, zanamivir (nasal administration) and laninamivir. Baloxavir marboxil was also efficacious against influenza B virus, although less potently. As also shown in in vitro studies, baloxavir marboxil is efficacious against neuramidine inhibitor resistant influenza A virus with similar potency as for wild type influenza A virus.

The effect of baloxavir marboxil was dose dependent in a wide dose range of 0.5 to 50 mg/kg BID. This mouse model was supported with pharmacokinetic analysis of baloxavir marboxil at all doses

showing dose-linear AUC_{inf}, except at the highest dose, which showed less than dose linear AUC. At the highest dose of 50 mg/kg, absorption process(es) appeared to have reached saturation, since t_{max} was delayed from 0.5 hours to 2 hours between 15 and 50 mg/kg dose (study 1088858).

A time-course analysis of inhibitory effect of baloxavir marboxil on viral replication indicated that the treatments of 0.5 or 5 mg/kg of baloxavir marboxil 5 days post infection for 1 or 3 days reduced the virus titres of a non-lethal dose of strain A/Osaka/129/2009 during the period of viral shedding. The effect was superior to that of the treatment of 5 mg/kg of oseltamivir phosphate for 3 days in mice (study 1088861).

Baloxavir appeared to have beneficial effects on survival after viral infection both in combination with oseltamivir and after delayed treatment. It should be noted that oseltamivir showed surprisingly little effects in the mouse models of viral infection, whereas baloxavir marboxil showed consistent efficacy with virus titers significantly ($P<0.0001$) lower than in the control groups at the 5 mg/kg BID dose, although the higher dose levels of 15 and 50 mg/kg provided even lower virus titers than 5 mg/kg (study 1094926).

Furthermore, it was shown that the prophylactic effect of a single subcutaneous administration of baloxavir against a lethal infection of influenza virus A or mouse adapted B was optimal at 48 hours (study 1094814). The effect declined thereafter, which seems logical considering the half-life is 2-3 hours of baloxavir in the mouse. It is unclear why subcutaneous administration of baloxavir was used in this study instead of baloxavir marboxil by the oral route. It should be mentioned that this study was supported by exposure determination, however only from to 48 to 192 hours post dosing, i.e. long after t_{max}.

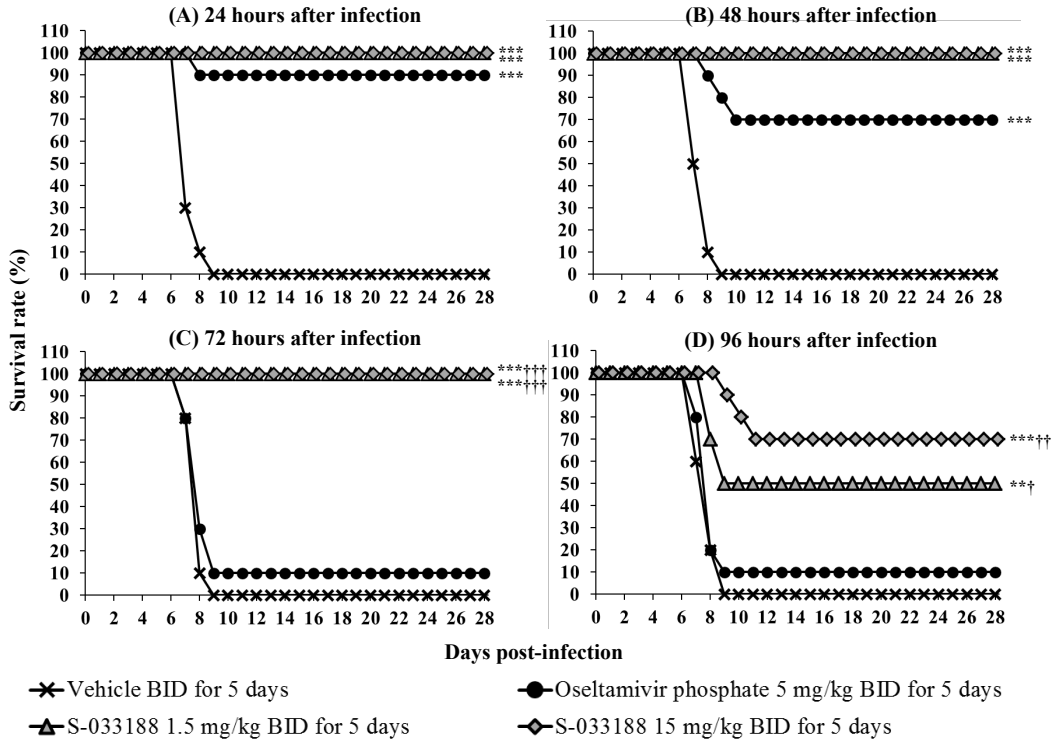
PK/PD analyses were performed based on the inhibitory effect on virus replication in the lung and plasma concentrations of baloxavir in the mouse infection model. The plasma concentration at the end of dosing interval after the first dose (C_T) was shown to be the PK parameter best correlated with the virus titer in the lung 24 hours after the first dose. The C_T of baloxavir that met the above efficacy target was 6.85 ng/mL from the nonclinical investigation (study 1088859). PK/PD relationship is considered established.

Finally, it was shown in vitro (MDCK cells) that human serum at 12.5 or 25% did not shift EC90 of baloxavir to a significant degree (study 1088859). A small shift in EC90 was observed from 7 nM at 25% to 11 nM at 50%. Protein binding was not determined in the mouse. Overall, to make up for the uncertainty of the significance of protein binding, protein binding could be considered not to reduce the efficacy of baloxavir marboxil to a degree of more than 3 times. Hence, a plasma concentration of baloxavir at C_T is above approximately 20 ng/mL (3 times 6.85 ng/mL) should be adequate for clinically relevant effect. For comparison; the data, submitted in Clinical study report 1510T0811 state that $AUC_{0\text{-}72h}$ after a 40 mg dose = 3475 ng/mL*hr. This corresponds to a mean plasma concentration of 48 ng/mL across the first 72 hours and C_{24h} is 57.6 ng/mL.

Baloxavir marboxil demonstrated pharmacological effect in mouse non-lethal models. Applicant also investigated the effect of baloxavir marboxil in lethal mouse models in comparison with oseltamivir. In one study, baloxavir marboxil (BID for 1 day) or oseltamivir phosphate (BID for 5 days) was orally administered to mice inoculated with influenza A/H1N1 or B virus immediately after inoculation to determine the survival rate of mice for 14- or 21-days post-inoculation. Baloxavir marboxil provided complete survival in mice infected with the A virus at the dose 0.5 mg/ BID for one day. Oseltamivir did not show complete survival at 5 mg/kg BID for 5 days. A dose of 5 mg/kg baloxavir marboxil was necessary against the B virus, however the potency against B virus was still better than for oseltamivir (studies 1088916 and 1088872).

A more clinically relevant model was the delayed treatment model in which mice were inoculated with a lethal dose of virus (A/PR/8/34) and treated with baloxavir marboxil or oseltamivir at 24, 48, 72 or 96 hours after. See Figure 2 Here it was demonstrated that treatment initiation 72 hours after inoculation, the dose of 1.5 mg/kg baloxavir marboxil BID for 5 days, provided full survival, whereas oseltamivir at 5 mg/kg BID showed 90% mortality at that time of treatment initiation (study 1088911). It should be noted that at 96 hours, survival was 50% for 1.5 mg/kg and 70% for 15 mg/kg of baloxavir marboxil, hence timing of initiation of treatment seems to be crucial for clinically relevant effect. The posology of baloxavir marboxil in patients is a single dose of 40 mg (minimum 0.5 mg/kg corresponding to a mouse equivalent single dose of 6.25 mg/kg), which should be taken within 48 hours of symptom onset. The time for maximal plasma concentration is 4 hours and half-life of baloxavir marboxil is 79 hours in humans (SmPC). From a nonclinical point of view, the posology in patients seems plausible.

Figure 2 Improvement in Mortality by Delayed Administration of Baloxavir Marboxil in Mice Infected with A/PR/8/34 Strain



The following P values were calculated by log-rank test and the fixed-sequence procedure:

** P<0.01; *** P<0.0001 vs vehicle.

† P<0.05; †† P<0.01; ††† P<0.0001 vs oseltamivir phosphate 5 mg/kg BID.

Since timing of treatment appear to be crucial and that treatment with high doses of baloxavir marboxil 96 hours after inoculation could not provide full survival in the mouse lethal model, a study of the combination treatment of baloxavir marboxil and oseltamivir was conducted (study 1088914). Baloxavir marboxil and oseltamivir phosphate was orally administered BID for 5 days to mice inoculated with a lethal dose of influenza A/H1N1 virus 96 hours post-inoculation. Doses of 1.5 mg/kg of baloxavir marboxil and 10 or 50 mg/kg oseltamivir BID for 5 days provided full survival even 96 days after inoculation.

Baloxavir marboxil showed relevant clinical effect in a ferret model of non-lethal influenza A infection. Baloxavir marboxil administered at 10 or 30 mg/kg BID for one day provided reduction in virus titers in nasal washes and reduction in temperature change in the days following the infection. This study was also supported with pharmacokinetic data, however showed that AUC increased more than dose-proportionally between 10 and 30 mg/kg with AUC_{inf} of 460 and 3300 ng/mL*h, respectively. This is an increase in exposure of 7 with an increase in dose of 3.33. HED of 10 and 30 mg/kg in the ferret is 1.9 and 5.7 mg/kg, somewhat higher than the clinical maximum dose of approximately 1 mg/kg in patients (80 mg to e.g. 81 kg body weight or 40 mg to e.g. 39 kg body weight). It should be noted that doses higher than 80 mg have not been intentionally administered to humans and there is apparently linear kinetics between 6 and 80 mg, hence the clinical relevance of the nonlinear pharmacokinetics in the ferret may not be known.

Baloxavir marboxil showed dose-dependent decrease in virus titers in nasal washes of immunocompromised mice inoculated 5 days earlier with a non-lethal dose of the influenza A/PR/8/34 strain. The dose 1.5 mg/kg BID for 5 days was more effective than 50 mg/kg BID for 5 days of oseltamivir.

In a mouse lethal model inoculated with a highly pathogenic avian influenza virus (A/H5N1, Hong Kong/483/97 strain), baloxavir marboxil (BID for 1 or 5 days) or oseltamivir phosphate (BID for 5 days) was orally administered to mice immediately after inoculation. Baloxavir marboxil provided complete survival when dosed at 5 or 50 mg/kg BID for both 1 day or 5 days. Oseltamivir provided 70% survival after 14 days when dosed 50 mg/kg BID for 5 days (study 1088870). When treatment is initiated right after inoculation with a highly pathogenic avian influenza virus, baloxavir marboxil appear efficient although a higher dose was necessary than for e.g. influenza virus A/H1N1 (0.5 mg/kg, 1088916). No virus with reduced susceptibility to baloxavir emerged during treatment with baloxavir marboxil (study 1088910).

A similar study was conducted with avian influenza virus A/H7N9 in which the mice again were treated with baloxavir marboxil or oseltamivir right after inoculation and throughout 28 days (study 1088905). In this study dosing of baloxavir marboxil 5 mg/kg BID for one day and 0.5 mg/kg BID for 5 days and above provided full survival after 28 days.

Baloxavir marboxil showed effect against two strains of avian influenza virus, however only in a model of treatment immediately after inoculation. On the other hand, since baloxavir have shown effect after delayed treatment with other influenza A viruses (up to and including 72 hours post infection with baloxavir marboxil alone and up to 96 hours in combination with oseltamivir), it is considered plausible that a similar picture will appear for avian influenza strains, although perhaps requiring higher doses.

Secondary pharmacodynamic studies

Applicant investigated cellular toxicity of baloxavir in vitro. This was carried out in cell-lines used for potency testing (study 1088988). Finally, a selectivity index was calculated and compared with ribavirin and favipiravir (study 1088990). It would have been more informative if the same exercise was performed with oseltamivir, which should be considered the most relevant comparator. Nevertheless, baloxavir appear to provide a large selectivity index with low cytotoxic potential.

Applicant also tested the cytotoxic potential in cell-lines of human origin both in the proliferation phase and in the non-proliferating phase (study 1088991). It is agreed that baloxavir show low potential for cytotoxicity in human tissue.

Both baloxavir and baloxavir marboxil was evaluated for potential for mitochondrial toxicity in an assay in which HepG2 cells were made more susceptible by incubation with galactose instead of glucose. The

study was supported with a range of positive controls. Neither baloxavir nor baloxavir marboxil showed any sign of mitochondrial toxicity.

Applicant provided a receptor screening study. In this study, the inhibition of 66 receptors, ion channels, transporters, or enzymes by baloxavir was investigated. Baloxavir 10 µmol/L (4.83 µg/mL) did not inhibit the binding to any of them by more than 50%. The highest inhibition was observed for two Type L Ca channels (43 and 38% inhibition), GABA A chloride channel (36%) and opiate κ (39%). Since, baloxavir at the maximum dose show C_{max} of 253 ng/mL in humans corresponding to ~0.5 µM (Report 1510t0811, page 69), it is agreed that baloxavir is unlikely to cause adverse reactions mediated by these receptors, ion channels, transporters or enzymes (study 1088984).

Safety pharmacology programme

CNS

The effects of baloxavir marboxil on the central nervous system were evaluated in male Crl:CD(SD) rats aged 8 weeks by examining general behaviour and neurobehavioral function using a modified functional observational battery method (FOB) (study 1088993).

Baloxavir marboxil was suspended in 0.5 w/v% methylcellulose solution (vehicle) and was administered once orally to rats (6/group) at dose levels of 0 (vehicle), 200, 600, and 2000 mg/kg.

Whereas it is agreed that no difference between vehicle and active dose groups were observed for FOB, effects were observed on rectal temperature and urine volume. It is however agreed that the changes in both rectal temperature and urine volume may be of limited clinical relevance.

Cardiovascular effects

Baloxavir had no effect on action potential at 0.1, 0.3, or 1 µmol/L in male guinea pig papillary muscles (actual concentrations in organ bath: 0.82, 0.25 and 0.83 µmol/L). The highest dose of baloxavir tested was 400 ng/mL. Since median C_{max} at the highest dose is 253 ng/mL (~ 0.5 µM), the highest concentrations used in the guinea pig papillar muscle study is providing a safety margin - however limited.

Baloxavir were evaluated on the potassium currents, which are human ether-a-go-go-related gene (hERG) currents, in hERG transfected Chinese hamster ovary (CHO) cells using the patch clamp method (1088998). IC50 was 7.31 µg/mL for baloxavir and is considered not to be clinically relevant.

The effects of baloxavir marboxil (oral administration of single dose of 200 or 400 mg/kg) on the cardiovascular system was evaluated in 4 conscious male cynomolgus monkeys, using a telemetry system (study 1088994). Applicant (study director) concluded that there were no test substance-related changes in any cardiovascular parameter at 200 or 400 mg/kg. This is agreed even though subtle effects were observed as described below*.

**: Statistically significant increases were observed in systolic, diastolic, and mean blood pressure at 4 hours after dosing at 400 mg/kg when compared with the control substance dosing; however, these were not considered test substance related because the individual animal values were similar to the pre-dose values and differences from the time matched control value were 10 mmHg or below. Furthermore, heart rate was increased in 2 animals (Nos. 2 and 4) at 4 hours after dosing at 400 mg/kg when compared with the pre-dose values; however, this increase was not considered test substance related because the values were almost within the range of variation at control substance dosing.*

These findings could be related to the clinical signs of vomiting, retching (animal 4) and diarrhoea (animal 2 and 3), which were observed with higher prevalence in the highest dose compared to the low dose and control dosing events.

The study was supported with toxicokinetics. Maximal plasma concentration of baloxavir in the monkeys in this study were well above C_{max} at the highest dose in humans (median 253 ng/mL), i.e. the doses used are considered to provide an appropriate safety margin.

Respiratory effects

The effects of baloxavir marboxil on the respiratory system were evaluated in male Crl:CD(SD) rats aged 8 weeks by measuring respiratory rate, tidal volume, and minute volume using whole body plethysmography. Baloxavir marboxil suspended in 0.5 w/v% methylcellulose solution (vehicle) was administered as a single oral dose to rats (8/group) at dose levels of 0 (vehicle), 200, 600, and 2000 mg/kg. Respiratory function was measured before dosing, and at 1, 2, 4, 6, 8, and 24 hours after dosing.

It was concluded that baloxavir marboxil had no effect on respiratory rate, tidal volume, or minute volume at 200, 600, or 2000 mg/kg. This view is supported. Unfortunately, this study was not supported with toxicokinetics. It is expected that toxicokinetic data from study 1088993 can be used as supportive data

2.3.3. Pharmacokinetics

Bioanalytical methods

The bioanalytical method to support pivotal GLP-compliant repeat-dose studies in rat, monkey and rabbit were presented in report 1089187. Selectivity, carry-over, calibration curves, precision and accuracy, matrix effects and stability of working solutions and samples appear to be successfully evaluated.

One more validation study was conducted for a method in rat plasma (Report 1089188). This report (1089188) describes the validation of the bioanalytical method in rat plasma. In order to cover the bioanalysis in the Phototoxicity study, a bioanalytical method was also validated in mouse plasma. In all in vivo studies (pharmacology, pharmacokinetics, toxicology) units of ng/mL plasma has been used.

Absorption

Pharmacokinetic studies of baloxavir marboxil were conducted in mice, ferrets, rats and monkeys, with the latter two species informing the majority of nonclinical PK. Studies were also conducted in juvenile and pregnant rats. Efficacy-based PK was investigated in influenza A-infected mice. Based on the hydrolysis of baloxavir marboxil to baloxavir *in vivo*, absorption studies measured baloxavir concentrations in plasma (or blood) following single or repeated oral administrations. After single administrations baloxavir concentrations reached Cmax at approximately 0.5- 5 hours depending on the nonclinical species. Studies with radiolabelled baloxavir marboxil identified that 90% and 80% of radioactivity was representative of baloxavir in monkeys and rats, respectively. In all studies baloxavir marboxil was below the lower limit of quantification (BLQ) at almost all time points. Thus, the PK studies describe the ADME of the active moiety, baloxavir.

Pivotal studies align with the intended route of administration and proposed dosing regimen of a single oral dose. Dose-proportional baloxavir exposure was evident in both rats and monkeys up to 3 mg/kg and 10 mg/kg, respectively, indicating a linear PK profile. Linearity at doses up to 15 mg/kg was also observed in mice infected with influenza A.

Other PK parameters including Vd_{ss}, total clearance and $t_{1/2}$, were consistent across doses in both rats and monkeys. Bioavailability ranged between 9.77-14.7% in rats and monkeys and was not significantly affected by fasting. Key PK differences in adult rats include an extended Tmax in monkeys versus rats (5.33 vs. 1.25 hours) and a significant food effect in monkeys.

Administration of baloxavir marboxil under fasting conditions with metal ions (calcium, iron, and mixture of magnesium and aluminium) found reduced exposure of 14-15% in monkeys (Cmax and $AUC_{0\text{-}inf}$), closely mirroring observations from the food effect observed in humans. It was hypothesized that the food effect associated with baloxavir is due to chelate formation with metal ions in the gastrointestinal lumen, thereby reducing absorption. The findings in primates support this.

Administration of baloxavir marboxil in juvenile rats identified higher absorption of baloxavir (Cmax and $AUC_{0\text{-}inf}$) in animals aged 10 days-old compared to 20- or 30-day old rats, possibly due to relative immaturity of the gastrointestinal tract in rats, which is not considered to be relevant to paediatric dosing. Further discussion on this could be warranted; however, in light of the proposed indication for children aged 12 years or over juvenile PK is adequately assessed. The Cmax and $AUC_{0\text{-}24hr}$ values of baloxavir after repeated administration were lower than those after first administration in rats and rabbits, while higher than those after first administration in monkeys.

Distribution

Distribution of baloxavir was investigated in pigmented rats and pregnant rats. In pigmented rats the highest concentrations of radioactivity were identified in the intestinal mucosa and liver. There was no significant retention of baloxavir in melanin-containing tissue.

Placental transfer of baloxavir was observed at approximately 50% that of maternal tissues, again exposure in foetal bones was present at all of the time points and Cmax was achieved at 48 hours (last sampling time point). Relatively high radioactivity in blood cells of male rats and monkeys (non-fasting) was observed in samples up to 24 and 48 hours, respectively. At 24 hours, concentrations of baloxavir were low indicating retention in blood cells is unlikely. In monkeys, relatively high blood cell distribution was maintained, at a similar degree to plasma concentrations suggesting that baloxavir marboxil is unlikely to remain in blood cells.

Metabolism

Hydrolysis of baloxavir marboxil in the liver is similar across nonclinical species and humans; however, intestinal hydrolysis is more rapidly achieved in humans (81.8% vs. 51.1% in rat and 43% in monkey, 1 h post-dose). Hydrolysis of baloxavir marboxil to baloxavir is mediated by serine esterases, predominantly AADAC in humans. In metabolism studies, after a single oral administration of $^{[14C]}$baloxavir marboxil at 5 mg/kg to rats and at 3 mg/kg to monkeys under a non-fasting condition, baloxavir was detected as the major component in plasma. Additional metabolites were investigated using human hepatocytes. Baloxavir was found to undergo further metabolic reactions via oxidation and glucuronidation. Baloxavir glucuronide and two kinds of baloxavir sulfoxides were identified. Baloxavir glucuronide was present at AUC ratios exceeding 10% (16.4%) in the human mass balance study. Thus, based on this clinical evidence baloxavir glucuronide exceeded the safety specifications for ICH M3 R2, and was further evaluated; however, it was considered to be of low toxicological concern.

Abundance ratios were applied to absorption data from the 2-week repeat dose study in monkeys (based on metabolic profiling study in monkeys). An abundance ratio of 3% in monkeys and 16.4% in humans derives an estimated baloxavir glucuronide exposure of 672 ng.hr/mL and an actual human exposure of 628 ng.hr/mL from the mass balance study. The applicant considered that the safety of baloxavir glucuronide has been adequately addressed. This is supported. In summary, baloxavir glucuronide exposure at the NOAEL in the monkey study was approximately equivalent to the human exposure in the mass balance study, and as per ICH M3 R(2) exposure of 50% or greater in of the

metabolite in nonclinical species (relative to therapeutic exposure) is considered sufficient for safety evaluation. Also, the absence of histopathological correlates to the findings at the high dose of 200 mg/kg it is accepted that the exposure at this dose is acceptable and further contributes to the safety evaluation, suggesting low risk with this metabolite.

Based on human mass balance study the metabolism of baloxavir is predominantly via glucuronidation (via UGT1A3 enzyme). Oxidation to sulfoxide metabolites are mediated via CYP3A4. Baloxavir was found to inhibit CYP2B6, CYP2C8, and CYP3A4 enzymes in human liver microsomes. Baloxavir has some induction potential for CYP1A2, CYP2B6, and CYP3A4, although with lesser potency (<20% effect of positive controls), thus the potential for inducible effects of baloxavir is low. In liver microsomes isolated from rats dosed at 2000 mg/kg/day for 2 weeks, induction of CYP2B and CYP3A was observed with a pronounced effect for CYP3A induction in female rats (31-fold). Given the predominance of glucuronidation metabolism of baloxavir, a clinical DDI study was performed. Unexpectedly, plasma exposure of baloxavir was decreased in the presence of the pan-UGT inhibitor probenecid. This reduction of 21-25% suggests there is an unexplained effect.

Excretion

Faecal excretion accounted for 96.6% of radiolabelled baloxavir marboxil (0.4% urine) in bile-duct cannulated male rats (1 mg/kg dose oral). Based on urinary and bile excretion, the absorbed dose was approximately 19% in this study. After oral administration of radiolabelled baloxavir marboxil 80% of dose was not absorbed and no faecal baloxavir was detectable (due to hydrolysis in GI tract). Enterohepatic circulation of baloxavir is observed in rats (0.9% of radioactively) but was associated with minimal effects on PK. Baloxavir was detected in breast milk of nursing rats up to 8 hours and was undetected at 24 hours. In monkeys, faecal excretion accounted for 89.5% of administered radiolabelled baloxavir, the absorption ratio was approximately 10% in bile-duct cannulated male monkeys. Similar to rats, minimal baloxavir was measured in faeces following oral administration.

Pharmacokinetic drug interactions

In-vitro studies were conducted to investigate the potential for inhibition of metabolizing enzymes and inhibition and/or induction of drug transporters. Appropriate concentrations of baloxavir marboxil baloxavir were used and study conditions were in line with relevant guidance (CPMP/EWP/560/95/Rev. 1 Corr. 2**). Based on the studies conducted, baloxavir marboxil and baloxavir had low potential to inhibit human CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) and to induce CYP1A2, CYP2B6, and CYP3A4, suggesting that baloxavir marboxil and baloxavir are unlikely to affect the PK of drugs that are substrates for CYPs. Baloxavir marboxil and baloxavir were substrates of P-glycoprotein (P-gp), but not substrates of breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1, or OATP1B3. Baloxavir marboxil has a potential to inhibit the P–gp-mediated transport, but not to inhibit the BCRP-mediated transport. Baloxavir has a potential to inhibit the transport mediated by P-gp, BCRP, OATP1B1, organic cation transporter (OCT) 1, multidrug and toxin extrusion (MATE) 1, and MATE2-K, but not to inhibit the transport mediated by OATP1B3, organic anion transporter (OAT) 1, OAT3, OCT2, and bile salt export pump (BSEP). A clinical DDI study confirmed that baloxavir marboxil minimally altered PK of P-gp and BCRP substrates to a degree that is not considered to have an effect on drugs that are substrates for these transporters.

DDI studies have calculated the IC_{50} for substrate and transporter assessments. The use of IC50 was adequately justified.

2.3.4. Toxicology

Single dose toxicity

No single dose studies were conducted with baloxavir marboxil. Instead, acute toxicity was evaluated on basis of findings in the repeat dose studies in rats and monkeys.

Repeat dose toxicity

No mortality, moribund condition or acute clinical signs was observed in rats in doses up to 2000 mg/kg. In male monkeys dosed with 200 and 400 mg/kg loose stool, diarrhoea and vomiting was observed, however, in another study in monkeys, no deaths, moribund condition or clinical signs was observed in doses up to 200 mg/kg.

Baloxavir marboxil was investigated in repeat dose studies in monkeys and rats for 2 and 4 weeks. As the product is only intended for single dose use, the duration of the repeat dose studies are acceptable.

In the 2- and 4-week rat studies, prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT) were observed at 200 mg/kg/day or higher. This was attributed by the applicant to vitamin K deficiency due to fasting of the animals and autoclavation of the animal feed. This was further elucidated in a study investigating the impact of vitamin K supplementary as described below, which showed that prolongation of PT and APTT did not occur when rats where supplemented with vitamin K. Conditions for fasting in the 2- and 4-week repeat dose study was similar to the conditions used in the investigative study (i.e. all animals in the main study were fasted for at least 16 hours prior to necropsy. Under the fasted condition, metal grid floors were put in the cages).
Increased weight of liver, hypertrophy of hepatocytes, hyperplasia of follicular epithelium in the thyroid, decreased colloid in the thyroid, and hypertrophy of basophilic cells in the pituitary were also observed at all doses. The applicant proposed these findings are rat-specific compensatory changes caused by the increased clearance of T3/T4 that is associated with the increased activities of CYP2B and CYP3A accompanied by an increased total content of CYP, and an increased activity of UGT in the liver due to a lack of thyroxine binding globulin (TBG). This was considered mild in severity without any degenerative changes which the applicant considered is unlikely to be relevant to humans. The accelerated clearance of T3/T4 indeed appears to be a species-specific effect in rats. The applicant has postulated a number of potential factors that contribute to the heightened sensitivity to increased T4 clearance in rats compared to humans. This is supported. The most relevant discussion herein relates to any clinically meaningful effects of enhanced T3/T4 clearance in conditions with TBG-deficiency. In situations of partial or total TBG deficiency, the impact on bioactive free T4 does not appear to be altered and clinical manifestations of TBG deficiency are generally absent. Additionally, the intended posology of baloxavir marboxil as a single dose suggests that it is unlikely to induce prolonged alteration of thyroid hormones.

Observed changes in liver were also considered adaptive changes to the induction of CYP enzymes, not considered clinically relevant. Overall, it appears that the effects at 20 and 200 mg/kg/day were not clinically relevant and the NOAEL in the repeat dose studies in rats is established at 2000 mg/kg/day.

In monkeys, hepato-biliary changes were observed at most dose levels, including increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), glutamate dehydrogenase (GLDH), leucyl aminopeptidase (LAP), and gamma-glutamyl transferase (GGT). Changes was also observed in one female (out of 6 animals) at 3 mg/kg/day, however, as no changes were observed at 10 mg/kg this is considered incidental. Effects observed at the end of the dosing period in both the 2- and 4-week study

were fully or partly returned to normal after the recovery period. The NOAEL in the repeat dose studies in monkeys is considered to be 10 mg/kg/day.

Generally, the safety margins in the repeat dose toxicity and juvenile toxicity studies were low (1.7-5.4). It is furthermore noted that AUC stated by the applicant is at 40 mg/day and not 80 kg/day, which is the highest intended clinical dose. The indicated safety margins therefore do not reflect the assumedly highest AUC values in humans. However, the derived NOAELs from animals is based on repeated dosing, whereas the dosing in humans is only intended as a single dose. It is therefore assumed that a sufficient margin is achieved to human relevant doses. This is further discussed in the pharmacokinetic section under repeat dose absorption. In juvenile rats at the beginning of dosing at D10 exposures are high, however, this is considered due to age related kinetics, which is further discussed in the pharmacokinetic section. At the end of dosing at D30, exposures and safety margins are similar to the 2- and 4-week repeat dose studies.
In summary, on the basis of comparative exposure levels in the toxicity studies, adverse effects in general occurred above therapeutic plasma levels of baloxavir.

Genotoxicity

In vitro and in vivo tests performed with baloxavir marboxil and baloxavir showed no genotoxic potential.

Carcinogenicity

No studies investigating the carcinogenic potential of baloxavir marboxil have been submitted. However, treatment with baloxavir marboxil is only intended as single dose per influenza season, i.e. not less than 6 months in between. Furthermore, no genotoxic potential was established for baloxavir marboxil and it was not shown to accumulate or remain in any specific tissue. Therefore, it is accepted that no carcinogenic studies are submitted for baloxavir marboxil.

Reproduction Toxicity

Baloxavir marboxil was investigated for potential effects on male and female fertility at doses up to 1000 mg/kg. No treatment related deaths occurred. No treatment related adverse changes in macropathology, reproductive organ weights, number of sperm cells in testes in males or estrous cycle in females were observed. Additionally, no baloxavir marboxil-related changes in copulation index, fertility index, copulation interval, the numbers of corpora lutea, implantations, and live embryos, and pre- and post-implantation loss rate were confirmed in any groups. Toxicokinetics (TK) was not investigated in this study, however, plasma concentration measurements in dams from the embryo-foetal development study in rats indicated sufficient exposure at the same dose levels.

In rats, baloxavir marboxil was orally administered at doses up to 1000 mg/kg/day to investigate effects on embryo-foetal effects. No deaths occurred and no treatment related changes in pre- and post-implantation loss rate, number of live foetuses, sex ratio, foetal body weight as well as skeletal morphology in live foetuses were observed. Sufficient exposure was shown in the TK investigations with an exposure margin of 4.2 to human relevant doses.

In rabbits, baloxavir marboxil was administered orally in doses of 30, 100 and 1000 mg/kg/day to investigate effects on embryo-foetal effects. No deaths occurred, however, two of 19 animals in the 1000 mg/kg/day group and 1 of 20 animals in the control group aborted on G25 or G26. A decrease in body weight accompanied by marked decrease in food consumption was observed in the 2 animals that aborted in the 1000 mg/kg/day. In foetuses, the incidence of thoracolumbar full supernumerary rib (11.42%) at 1000 mg/kg/day was lower than that in the control group (51.86%) and the historical

control data (26.83% to 73.06%). It is agreed that this finding does not seem to be of toxicological concern.
The incidence of an extra cervical rib (33.70%) at 1000 mg/kg/day was, however, significantly higher than that in the control group (0%) and the historical control data (0% to 2.73%) and occurred in all litters. Other than the findings stated above, no maternal toxicity was observed at any dose levels. In humans, a cervical rib can cause symptoms known as thoracic outlet syndrome and the finding may therefore be clinically relevant. Public literature indicates that a large prevalence of cervical ribs can be observed in animal studies, which may differ between the species and strain and has been associated with maternal stress during the gestational period, and furthermore, that the cervical ribs seem to be resorbed postnatally. Though a large incidence of cervical ribs has also observed in human foetuses, it is assumed that they are resorbed in a similar manner postnatally, as the prevalence of cervical ribs in adults are very limited, thus resulting in limited clinical relevance. NOAEL was established at 100 mg/kg/day based on the skeletal findings and abortions.

To investigate embryo-foetal developmental toxicity, baloxavir marboxil was administered orally to pregnant rats at dose levels of 20, 200 and 2000 mg/kg. No maternal toxicity was observed in F0 dams. In F1 pups, no treatment-related changes were observed except for a small number of observations of anterior chamber hyphaema resulting in unilaterally enlargement of the eyeball with dark red discoloration, which was first observed at opening of eyes at day 16 to 20 after birth (2 of 176 F1 pups (1.1%) and 4 of 168 F1 pups (2.4%) at 200 and 2000 mg/kg, respectively). The applicant argues that the incidence level is low and that the observed hyphaema only occurred unilaterally. No abnormal findings were seen in the eyeballs of pups in the historical control data, however, the applicant suspects that lack of appropriate routine examinations may be the cause of the lack of findings. The applicant argues that the morphologic structure of the eyes was intact, so it is unlikely that the observed haemorrhage was caused by dysmorphogenesis during prenatal development. Additionally, in the historical control data regarding spontaneous lesions in the eyes of Sprague Dawley rats, adhesion of tissues in the anterior chamber of the eye occurred in rats aged 6 weeks at an incidence of 0% to 1.74%, which indicates a similar mechanism of bleeding in the anterior segment of the eye that was found in this PPND study. Thus, the applicant considers these ocular findings to be most likely incidental and of no known toxicological consequence, despite the statistical significance in the high dose group. This is accepted and the ocular findings in the PPND study is considered of limited clinical concern. TK was not investigated in this study, however, plasma concentration measurements in dams from the embryo-foetal development study in rats indicated sufficient exposure at the same dose levels.

In the juvenile toxicity study, rats were dosed with 20, 200 and 1000 mg/kg. No mortalities occurred and only few effects were observed. Changes to body weight, body weight gain (200 mg/kg or higher) and in food consumption (all doses) were observed, however, the changes were considered transient and slight and thus not considered toxicologically significant. In haematological examinations changes were observed in red blood cell distribution width, prolongation of APTT/increase in PLT and albumin/globulin content. The changes were considered transient and no related clinical or histopathological changes were observed. Effects on APTT has already been discussed in the assessment of the 2- and 4-week repeat dose study in rats. Investigational studies have shown that prolonged APTT may be attributed to the lack of vitamin K due to fasting and/or in the feed. In the juvenile study, the feed was removed overnight before blood sampling for haematology and blood chemistry, thus indicating that the rats were not fasted for as long as in the investigational and repeat dose studies. Furthermore, it is not mentioned whether a grid is placed on the floor prior to blood sampling to prevent access to faeces and whether the animal feed were autoclaved in this study. Follicular cell hypertrophy in the thyroid was observed in males and females at 200 mg/kg/day or higher combined with an increase in thyroid weight. The same effects were observed in the 2- and 4-week repeat dose studies in rats, in which it was accepted that the effects are not considered clinically

relevant due to the rat specific induction of liver microsomal enzymes resulting in compensatory morphological changes in the thyroid and pituitary.
It appears that no toxicologically significant effects are observed in juvenile rats, and the NOAEL for the study is established at 1000 mg/kg. High plasma concentrations of baloxavir were measured at the beginning of dosing at D10 of age, however, the levels normalised at the end of the study where plasma concentrations in rats at D30 and D49 of age were comparable to concentrations in rats at similar age in 2- and 4-week repeat-dose studies. Thus, an age-related change in the toxicokinetics of baloxavir marboxil is observed. This is further discussed in the pharmacokinetic section.

Toxicokinetic data

Toxicokinetics are discussed in the pharmacokinetic section under repeat-dose absorption.

Local Tolerance

Local tolerance was investigated as part of the repeat-dose toxicity and safety pharmacology studies and no further local tolerance studies have been submitted

Other toxicity studies

A large number of impurities were identified for baloxavir marboxil stemming from the route of synthesis. The substances have been evaluated according to the ICH M7 guideline concerning their mutagenic potential using in silico modelling, investigated in GLP compliant Ames tests as well as referenced from published literature. Discussions of the genotoxic classification according to ICH M7 appear to be adequate. Measures to ensure adequate control of the genotoxic impurities are discussed in the quality part of the assessment.

Four related substances and baloxavir as well as three sterioisomers have been included in the drug substance specification. All impurities have shown negative mutagenic potential in in silico modelling and experimental testing, which is accepted. The three sterioisomers are included in the specifications at a limit of 0.15%, thus not triggering the requirement for qualification of the impurities according to ICH Q3A. However, the four related impurities are included in levels above 0.15%, and the applicant has thus performed a qualification of the impurities.

The specification limit is considered to be covered by the impurity content in the toxicological batches. The applicant states that one of the related substances is converted to baloxavir during degradation. By comparing impurity content in the batches used in the toxicological investigations during the course of the study, it is observed that the amount of that related substance is decreased and baloxavir is increased, respectively, from study start until the end of the study. The amounts of impurity measured at the end of the toxicological study in monkeys in the relevant batches are thus lower than the specified amount for baloxavir and the related substance mentioned above. However, baloxavir is considered the main active metabolite of baloxavir marboxil (83% conversion during 24h in monkeys) and thus baloxavir is considered qualified by toxicological testing.

Further, the four related substances are considered qualified by converting the NOAEL established in the 4-week monkey study (10 mg/kg/day). A NOAEL for the impurities was derived by estimating the relative NOAEL values for the impurities based on the impurity content in the toxicological batches by the end of the study. By deriving the daily dose corresponding to the upper specification limit, it seems that a sufficient margin from the upper dose specification limit to the impurity NOAELs can be established, and the four related substances are considered qualified by toxicological testing.

Five residual solvents have been included in the specification with limits in compliance with those stated in the ICH Q3C guideline.

In an investigation of phototoxic potential of baloxavir marboxil UV visible absorption was observed at two wavelengths, 261 and 304.6 nm, both with a molar extinction coefficient greater than 1000 L/mol/cm.

A photohaemolysis assay was conducted to investigate the phototoxic potential in vitro. Baloxavir marboxil was positive in photohaemolysis index, whereas baloxavir was negative in photohaemolysis index or met-haemoglobin formation.
A skin phototoxicity study on baloxavir marboxil in hairless mice was conducted via oral and intraperitoneal administration. Baloxavir marboxil was administered to female Hos:HR-1 mice (5 or 10 females/group) once at 0 (control group) or 1000 mg/kg orally, or at 10, 30, or 100 mg/kg intraperitoneally and animals were investigated for skin reactions after the exposure of UV light. No skin reactions indicative of phototoxicity occurred in any baloxavir marboxil-treated groups, whereas the positive control induced skin reactions indicative of phototoxicity.

The applicant has performed investigational studies in rats to elucidate the effect of fasting and vitamin K supplementary on PT and APTT, which were increased in the 2- and 4-week repeat dose studies in rats as well in the study in juvenile rats treated with baloxavir marboxil. According to the applicant, the effects could be due to fasting of the animals before necropsy (16 h or more) and autoclavation of the animal feed both reducing the vitamin K levels in the rats. Furthermore, it is noted that in the repeat dose studies as well as in the investigational study, metal grid floors were put in the cages thus preventing access of the rats to the faeces and another potential source of vitamin K.

In investigational studies on the effect of vitamin K on PT and APTT, it appears that baloxavir marboxil in itself may have an effect on PT and APTT. Prolongation of PT and APTT are observed in rats at 200 mg/kg in the 2- and 4-week repeat dose study, which correlates with clinically relevant dose levels (200 mg/kg exposure margin = 1; 20 mg/kg (NOAEL): exposure margin = 0.5 (based on AUC_{24h})). The apparent vitamin K deficiency is not commonly observed in studies in rats, though the fasting period (16 h or more) and type of fodder does not seem out of the ordinary in order to explain the observed effects. Prolongation of PT and APTT was however not observed in monkeys at any dose level. A summary of a review of haemorrhagic events in humans based on post-marketing data was presented by the applicant, in which is it concluded that there is no association with treatment with baloxavir marboxil, which is further supported by the lack of direct findings on prolongation of PT or APTT in the clinical trials. Furthermore, it was pointed out that there are large differences in the required amount of vitamin K between rats and humans. Thus, vitamin K deficiency is not commonly observed in humans as vitamin K sources are more readily available through the diet and since smaller amounts are required than in rats. Taking the provided information into consideration as well as the fact that baloxavir marboxil is only intended as a single dose in humans whereas it was given as repeated dosing in rats for up to 4 weeks, it seems that the observed prolongation of PT and APTT in rats have limited clinical relevance. Although the dose-dependent effect of baloxavir on PT and APPT in rat appear to be of limited clinical relevance, clinical findings of spontaneous bleeding may not be separated from bleeding induced by influenza virus. The effect on PT and APTT in the rat has been adequately reflected in section 5.3 of the SmPC.

2.3.5. Ecotoxicity/environmental risk assessment

Summary of main study results

Substance (INN/Invented Name): (12aR)-12-[(11S)-7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepin11-yl]-7-hydroxy-3,4,12,12a-tetrahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazine-6,8-dione (baloxavir) **CAS-number:** 1985605-59-1					
PBT screening		**Result**			**Conclusion**
Bioaccumulation potential – log Kow		Log Dow = 2.0 at pH 7			Potential PBT NO
Phase I					
Calculation	**Value**	**Unit**			**Remarks**
$PEC_{surfacewater}$	0.0185	µg/L			>0.01 threshold Yes
Other concerns (e.g. chemical class)					None
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} =16200 (sewage sludge) K_{oc} = 44000 (sewage sludge) K_{oc} = 185000 (sandy loam) K_{oc} = 107000 (sandy clay loam) K_{oc} = 186000 (clay loam)			Terrestrial studies triggered
Ready Biodegradability Test	OECD 301	Not conducted			Considered not readily biodegradable
Aerobic Transformation in Aquatic Sediment systems	OECD 308	DT_{50} water = 1.45 and 5.15 days DT_{50} sediment = Could not be determined DT_{50} total system = Could not be determined			No decline rate in the sediment phase could be calculated.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/Species: *Raphidocelis subcapitata*	OECD 201	NOEC	92.0	µg/L	Growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	490	µg/L	Parental growth
Fish, Early Life Stage Toxicity Test/Species: *Pimephales promelas*	OECD 210	NOEC	180	µg/L	Survival
Activated Sludge, Respiration Test	OECD 209	NOEC	56000	µg/L	

Phase IIb Studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Units**	**Remarks**
Bioaccumulation	OECD 305				Not required
Aerobic Transformation in Soil (Four soils)	OECD 307				It was not possible to determine the rate of degradation in soil.
Soil Micro-organisms: Nitrogen Transformation Test	OECD 216	Effect	No effect at 21 × PEC_{SOIL}		PEC_{SOIL}= 0.03 mg/kg dw
Terrestrial Plants, Growth (Six species)	OECD 208	NOEC	111.11	mg/kg dw	Cabbage, carrot, lettuce, tomato, oat and onion tested NOEC for Lettuce and tomato growth
Earthworm, Acute Toxicity Test	OECD 207	LC_{50}	1000	mg/kg dw	
Collembola, Reproduction Test	OECD 232	NOEC	1000	mg/kg dw	
Sediment dwelling organism	OECD 218	NOEC	4950	mg/kg dw	Emergence; Corrected for 10% organic carbon

2.3.6. Discussion on non-clinical aspects

Pharmacology

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

Baloxavir was evaluated in a range of in vitro and in vivo infection models and the potency and dosing regimens was compared to already marketed neuramidine (NA) inhibitors primarily oseltamivir (Tamiflu). Baloxavir was shown to be more potent than other marketed products in vitro. In vivo studies showed that baloxavir marboxil provided adequate efficacy with treatment for only one day BID at lower doses than oseltamivir, whereas oseltamivir required 5 days treatment to show significant effect on viral shedding and/or survival. Baloxavir marboxil was effective against large range of influenza virus, including A, B, neuramidine resistant, avian etc.

In a disease model of delayed treatment, mice were inoculated with a lethal dose of virus (A/PR/8/34) and treated with baloxavir marboxil at 24, 48, 72 or 96 hours after. Here it was demonstrated that treatment with baloxavir marboxil up to initiation 72 hours after inoculation, provided full survival. Exposure to baloxavir was followed in some disease models. From a nonclinical point of view,

exposure-response relationship and the posology (single dose within 48 hours of onset of symptoms) in patients appear to be justified.

In vitro and in vivo proof of concept is considered well established.

As for safety pharmacology, baloxavir appear selective for the intended viral target, show high margin to cellular toxicity, low potential for interaction with cardiovascular targets (hERG, guinea pig papillary muscle) and showed no clinically relevant adverse effects in the in vivo CV safety study in monkey. No indication of impact on respiratory or CNS system was revealed in rat.

Pharmacokinetics

Pharmacokinetic studies were conducted in with mice, rats, rabbits, monkeys, and ferrets, which were also selected for toxicological assessment. PK assessment was performed after single oral administration as is intended clinically. Baloxavir marboxil was below the limit of quantification at early time points in most studies confirming rapid hydrolysis to baloxavir. Baloxavir displayed a linear PK profile with generally no evidence of accumulation in tissues. Baloxavir-glucuronide is the major metabolite in humans. A revised acceptable safety evaluation of the baloxavir-glucuronide metabolite was presented.

Toxicology

In general, baloxavir marboxil is considered of low toxic potential in toxicological relevant species in repeat-dose toxicity studies. Furthermore, it is not considered of genotoxic potential or to affect male and female fertility. Developmental findings in the EFD study in rabbits as well as the PPND study appears to be of limited clinical relevance.

In investigational studies on the effect of vitamin K on PT and APTT, it appears that baloxavir marboxil in itself may have an effect on PT and APTT. Prolongation of PT and APTT are observed in rats at 200 mg/kg in the 2- and 4-week repeat dose study, which correlates with clinically relevant dose levels (200 mg/kg: exposure margin = 1; 20 mg/kg (NOAEL): exposure margin= 0.5 (based on AUC_{24h})). The apparent vitamin K deficiency is not commonly observed in studies in rats, though the fasting period (16 h or more) and type of fodder does not seem out of the ordinary in order to explain the observed effects. Prolongation of PT and APTT was however not observed in monkeys at any dose level. A summary of a review of haemorrhagic events in humans based on post-marketing data was presented by the applicant, showing no association with treatment with baloxavir marboxil, which is further supported by the lack of direct findings on prolongation of PT or APTT in the clinical trials. Furthermore, there are large differences in the required amount of vitamin K between rats and humans supporting that vitamin K deficiency is not commonly observed in humans as vitamin K sources are more readily available through the diet and since smaller amounts are required than in rats. Baloxavir marboxil is only intended as a single dose in humans whereas it was given as repeated dosing in rats for up to 4 weeks. Taken together, it seems that the observed prolongation of PT and APTT in rats have limited clinical relevance. The effect on PT and APTT in the rat has been adequately reflected in section 5.3 of the SmPC.

2.3.7. Conclusion on the non-clinical aspects

A vast program of in vitro and in vivo pharmacology was conducted in disease models for baloxavir marboxil. Nonclinical proof of concept as an antiviral agent against influenza virus appear well-established. Safety pharmacology revealed no concerns on CNS, CV or respiratory safety.

Pharmacokinetics of baloxavir marboxil is well described.

The toxicological programme of baloxavir marboxil consisted of 2- and 4- week repeat dose studies in rats and monkeys. Furthermore, the genotoxic potential was investigated as well as studies on fertility and developmental toxicity. Considering the clinical administration of single dose only, the toxicological programme is considered sufficient to address the intended use of baloxavir marboxil.

Overall, from the nonclinical part of the dossier is considered satisfactory. There are no remaining non-clinical issues precluding granting of a Marketing authorisation.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. GCP non-compliance identified during site audits of Study T0832 (critical and major deviations) have been handled appropriately by excluding the vast majority of the patients from the sites with non-compliance.

The applicant 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

List of Completed Clinical Studies with Baloxavir Marboxil

Study Design	Study Number	Patient Population/ Country	Study Treatment (Dose, Formulation, Food Condition)	No. of Subjects/ Patients[a]
Clinical Pharmacology Studies				
Phase 1, single-ascending dose	1510T0811	Healthy adult subjects / Japan	baloxavir marboxil (suspension): 6, 20, 40, 60, 80 mg, single dose: 40 mg, single dose (between meal/fed [high-fat high-calorie meal]) placebo (suspension)	Total: 40 bxm: 30 6 mg: 6 20 mg: 6 40 mg: 6 60 mg: 6 80 mg: 6
Phase 1, open-label, non-randomized, crossover, DDI (midazolam) study	1519T0814	Healthy adult subjects / US	baloxavir marboxil (20 mg tablet): 40 mg, single dose CYP3A4 substrate (midazolam): 5 mg, single dose	Total: 12 (all 40 mg bxm)
Phase 1, open-label, non-randomized, crossover, DDI (itraconazole) study	1520T0815	Healthy adult subjects / US	baloxavir marboxil (20 mg tablet): 20 mg, single dose P-gp inhibitor (itraconazole): 200 mg QD multiple doses	Total: 12 (all 20 mg bxm)
Phase 1, open-label, randomized, crossover, DDI (oseltamivir) study	1606T0818	Healthy adult subjects / Japan	baloxavir marboxil (20 mg tablet): 40 mg, single dose Oseltamivir phosphate: 75 mg BID, multiple doses	Total: 18 (all 40 mg bxm)
Phase 1, open-label, non-randomized, crossover, DDI (probenecid) study	1612T081C	Healthy adult subjects / US	baloxavir marboxil (20 mg tablet): 80 mg, single dose UGT inhibitor (probenecid) : 500 mg BID, multiple doses	Total: 12 (all 80 mg bxm)
Phase 1, open-label, non-randomized, crossover, DDI (digoxin and rosuvastatin) study	1613T081D	Healthy adult subjects / US	baloxavir marboxil (20 mg tablet): 80 mg, single dose P-gp substrate (digoxin): 0.25 mg, single dose BCRP substrate (rosuvastatin): 10 mg, single dose	Total: 24 (all 80 mg bxm)

Study Design	Study Number	Patient Population/ Country	Study Treatment (Dose, Formulation, Food Condition)	No. of Subjects/ Patients[a]
Phase 1, randomized, 2-sequence, 2-period crossover, open-label bioequivalence study	1703T081G	Healthy male subjects / Japan	Single oral dose of baloxavir marboxil: 20 mg tablet or granules 2% Single administration repeated twice with 28-day dosing interval	Total: 28 bxm: 28 20 mg: 28 2% granules (1 g): 28
Mass Balance Study				
Phase 1, open-label study	1532T0817	Healthy adult subjects / UK	[^{14}C]baloxavir marboxil (suspension): 40 mg, single dose	Total: 6 (all 40 mg bxm)
Thorough QT/QTc Study				
Phase 1, open-label study	1527T0816	Healthy adult subjects / Japan	baloxavir marboxil (20 mg tablet): 40, 80 mg, single dose moxifloxacin: 400 mg, single dose placebo	Total: 64 bxm: 64 40 mg: 63 80 mg: 63
Clinical Pharmacology Study for Patients with Hepatic Impairment				
Phase 1, open-label, healthy patient matched, 2-part sequential study	1611T081B	Adult subjects with mild or moderate hepatic impairment and healthy demographically-matched control subjects / US	baloxavir marboxil (20 mg tablet): 40 mg, single dose	Total: 16 (all 40 mg bxm)
Biopharmaceutical Studies				
Phase 1, crossover BA and FE study	1512T0813	Healthy adult subjects / Japan	Relative bioavailability (BA) part baloxavir marboxil (suspension and 20 mg tablet): 20 mg, single dose (fasted) Food effect (FE) part baloxavir marboxil (20 mg tablet): 20 mg, single dose (fasted/before meal/fed [moderate fat meal])	Total: 29 (all 20 mg)

Study Design	Study Number	Patient Population/ Country	Study Treatment (Dose, Formulation, Food Condition)	No. of Subjects/ Patients[a]
Phase 1, crossover BE and FE study	1622T081F	Healthy adult subjects / Japan	Bioequivalence (BE) part baloxavir marboxil (10 mg tablet and 20 mg tablet): 20 mg, single dose (fasted) FE part baloxavir marboxil (20 mg tablet): 40 mg, single dose (fasted/fed [moderate fat meal]) FE-10 mg part baloxavir marboxil (10 mg tablet) : 10 mg, single dose (fasted/fed [moderate fat meal])	Total: 78 bxm: 78 10 mg: 14 20 mg: 50 40 mg: 14
Phase 2 and 3 Studies				
Phase 2, randomized, placebo-controlled double-blind study	1518T0821	Adult OwH patients (≥ 20 to ≤ 64 years) / Japan	Single dose of baloxavir marboxil (10, 20, 40 mg) or placebo	Total: 400 bxm: 300 10 mg: 100 20 mg: 100 40 mg: 100
Phase 3, open-label, non-controlled study	1618T0822	OwH pediatric patients (≥ 6 months to ≤ 11 years) / Japan	baloxavir marboxil: single dose of following: Weight ≥ 40 kg: 40 mg Weight ≥ 20 kg and < 40 kg: 20 mg Weight ≥ 10 kg and < 20 kg: 10 mg Weight ≥ 5 kg and < 10 kg: 5 mg	Total: 108 bxm: 107 5 mg: 2 10 mg: 31 20 mg: 66 40 mg: 8
Phase 3, randomized, placebo / active control, double-blind study	1601T0831	Adult and adolescent OwH patients (≥ 12 to ≤ 64 years) / Japan and US	baloxavir marboxil: single dose of following: Weight < 80 kg: 40 mg Weight ≥ 80 kg: 80 mg Placebo Oseltamivir: 75 mg BID for 5 days	Total: 1436 bxm: 610 40 mg: 467 80 mg: 143

Study Design	Study Number	Patient Population/ Country	Study Treatment (Dose, Formulation, Food Condition)	No. of Subjects/ Patients[a]
Phase 3, randomized, placebo / active control, double-blind study	1602T0832	Adult and adolescent patients who are at high risk for influenza complications / Japan, Taiwan, South Korea, Hong Kong, US, Australia, Europe, New Zealand, and South Africa	baloxavir marboxil: single dose: Weight < 80 kg: 40 mg Weight ≥ 80 kg: 80 mg Placebo Oseltamivir: 75 mg BID for 5 days	Total: 2182 bxm: 730 40 mg: 311 80 mg: 419
Phase 3, open-label, non-controlled study	1705T0833	OwH pediatric patients with influenza / Japan	Single oral dose of baloxavir marboxil: 1 mg/kg or 10 mg	Total: 33 bxm: 33 4 mg: 1 7 mg: 4 8 mg: 5 9 mg: 2 10 mg: 21
Phase 3, randomized, placebo-controlled, double-blind study	1719T0834	Subjects who were household members of influenza-infected index patients / Japan	Single dose of baloxavir marboxil: Age ≥ 12 years: Weight < 80 kg: 40 mg Weight ≥ 80 kg: 80 mg Age < 12 years: Weight < 10 kg: 1 mg/kg (2% granule), Weight 10 to < 20 kg: 10 mg (2% granule), Weight 20 to < 40 kg: 20 mg (tablet), or Weight ≥ 40 kg: 40 mg (tablet) Placebo	Total: 752 bxm: 374 10 mg: 19 20 mg: 48 40 mg: 290 80 mg: 17

[a] Total number of patients/subjects randomized and number of patients/subjects who received baloxavir marboxil (overall and by dose).

BA = bioavailability; BCRP = breast cancer resistance protein; BE = bioequivalence; BID = twice daily; bxm = baloxavir marboxil; DDI = drug-drug interaction; DSMB = data safety monitoring board; FE = food effect; OwH = otherwise healthy; P-gp = P-glycoprotein; QD = once daily; UGT = uridine diphosphate glucuronosyltransferase.

Annex 1.9.1 List of Completed Clinical Studies with Baloxavir Marboxil

2.4.2. Pharmacokinetics

Methods and dosing

Methods

Bioanalytical analysis

The bioanalytical method for the simultaneous determination of concentrations of baloxavir marboxil (bxm) and baloxavir in human plasma was validated where the lower limit of quantification (LLOQ) was set to 0.100 ng/mL for both baloxavir marboxil and baloxavir. Plasma samples were analysed after deproteinization by a liquid chromatography tandem mass spectrometry (LC/MS/MS) method.
The analytical methods were validated across the calibration range with respect to selectivity, recovery, accuracy, precision, and stability under a variety of conditions.
Concentrations of baloxavir in human nasal or throat swab samples collected in the global phase 3 study T0831 was determined using LC/MS/MS. Nasal or throat swab samples were analysed after deproteinization. The bioanalytical method was validated with the LLOQ of 0.0500 ng/mL.
Validated bioanalytical methods for the determination of oseltamivir/oseltamivir carboxylate, digoxin, midazolam, moxifloxacin, itraconazole, rosuvastatin, and probenecid were also established.

PK parameters

Biologic samples for PK determination of bxm/baloxavir were collected in both single and multiple dose studies and in both phase 1, 2, and 3 studies in healthy volunteers and patients. The measurements comprised standard PK parameters, and the results were evaluated in the individual studies as well as in population PK analyses.

Population PK and PKPD analyses.

PK data were analysed in a pop PK model. The population PK model was used to calculate Bayesian estimations of PK parameters in individual OwH and HR patients, to evaluate the effects of selected covariates, and to estimate the PK/PD responses in the populations. The final model was based on data from 10 phase 1 studies, one phase 2 study, and phase 3 studies in OwH and HR subjects, and a total of 11848 baloxavir plasma concentrations from 1827 subjects including adolescents aged ≥ 12 years were used for population pharmacokinetic analyses. The models are adequately described and validated.

The PK of baloxavir was well described using a three-compartment model with first-order elimination and absorption processes and a lag time. Significant covariates contained in the final model were gender, body weight, and race.

The population pharmacokinetic parameter estimates of the final model are shown in Table 1 .

Table 1 Population Pharmacokinetic Parameters for the Final Model

Parameter	Model Equation	Inter-individual Variability (CV%)
CL/F (L/hour)	$10.8 \times (\text{Body Weight}/67.7)^{0.362} \times 0.519^{\text{Asian}}$	41.1%
Vc/F (L)	$565 \times (\text{Body Weight}/67.7)^{0.833} \times 0.564^{\text{Asian}}$	62.7%
Q1/F (L/hour)	$12.4 \times (\text{Body Weight}/67.7)^{0.362}$	---
Q2/F (L/hour)	$1.43 \times (\text{Body Weight}/67.7)^{0.362}$	---
Vp1/F (L)	$141 \times (\text{Body Weight}/67.7)^{0.833}$	29.3%
Vp2/F (L)	$139 \times (\text{Body Weight}/67.7)^{0.833}$	35.4%
Ka (/hour)	$1.03 \times 0.682^{\text{Female}}$	123.7%
Lag Time hour)	0.345	---
Covariance between CL/F and Vc/F		0.209
Intra-individual variability		
Proportional residual error (CV%)		20.2%

Source: OwH+HR PopPK Report, Table 6.

Dosing regimen

In the clinical trials, a body weight-based dosing regimen was used. Patients weighing < 80 kg received 40 mg bxm as a single dose and patients weighing ≥ 80 kg received a single dose of 80 mg.

In the PEP study, the children enrolled received the following dose: weight <10 kg: 1 mg/kg, weight 10-<20 kg: 10 mg, weight 20-<40 kg: 20 mg, and weight ≥40 kg: 40 mg.

Absorption

Baloxavir marboxil is a prodrug and after oral administration, bxm is extensively converted to its active metabolite, baloxavir, predominantly by AADAC in the gastrointestinal lumen, intestinal epithelium, and liver. The plasma concentration of bxm was very low or below the limit of quantitation (< 0.100 ng/mL) at all time points.

Solubility of bxm is independent of pH in the range of 1 to 9. Therefore, a change in stomach pH is not expected to affect the absorption of bxm.

Distribution

The in vitro serum protein-binding ratios of baloxavir were 92.9% to 93.9%. In clinical studies, the apparent volume of distribution (Vz/F) was estimated to be 1180 L in non-Asians and 619 L (i.e. about 50% lower) in Japanese healthy subjects after single oral doses of 80 mg bxm.

Bioavailability

The absolute oral bioavailability of bxm/baloxavir has not been established.

The PK of baloxavir in healthy adults (n=12, 9 white and 3 African American) receiving 80 mg of bxm is seen in Table 2 . Time to achieve peak plasma concentration (Tmax) of baloxavir was reached 4 hours after administration, the elimination half-life was 79.1 hours, the geometric mean

(% geometric CV) of the C_{max} and $AUC_{0\text{-}inf}$ of baloxavir were 145 ng/mL (25.4%) and 6551 ng • hr/mL (22.5%), respectively.

Table 2 Pharmacokinetic Parameters of baloxavir following Single Oral Administration of Baloxavir Marboxil at 80 mg to Healthy Adults in the Fasted State

Parameter	Geometric Mean (% geometric coefficient of variation)
No. of subjects	12
C_{max} (ng/mL)	145 (25.4)
T_{max} [a] (hr)	4.00 (3.00, 5.00)
$AUC_{0\text{-}last}$ (ng • hr/mL)	6305 (21.2)
$AUC_{0\text{-}inf}$ (ng • hr/mL)	6551 (22.5)
$t_{1/2\_z}$ (hr)	79.1 (22.4)
MRT (hr)	82.5 (22.2)
CL/F (L/hr)	10.3 (22.5)
V_z/F (L)	1180 (20.8)

a: Median (minimum, maximum)
Source: Study 1612T081C, Table 11-3.

Bioequivalence

All the phase 3 clinical studies used two or four of the to-be-marketed 20 mg tablets to deliver the 40 mg or 80 mg dose. A biowaiver will be applied for a bioavailability and/or bioequivalence study between the to-be-marketed 20 mg film-coated tablet formulation and the to-be-marketed 40 mg film-coated tablet formulation (previously granted by the FDA).

Bioequivalence between the granules for paediatric use and the to-be-marketed 20 mg tablet was demonstrated in a BE study.

Influence of food

A food-effect study involving oral administration of one 20 mg bxm tablet (phase 1 and phase 2 clinical formulation) to healthy subjects under fasting conditions or taken with a moderate meal containing dairy (approximately 400 to 500 kcal, of which 150 kcal was from fat) indicated that food decreased the C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ 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. An in vivo study indicated that baloxavir is chelated by polyvalent cations and due to the risk of chelation, it is recommended that bxm should not be taken with polyvalent cation-containing laxatives or antacids, or oral supplements containing iron, zinc, selenium, calcium, or magnesium.

Elimination

The elimination half-life of baloxavir is long (79.1 hours). The apparent clearance of baloxavir differ substantially between Asians (5.6 L/h) and non-Asians (10.8 L7h) but the terminal half-life is only slightly lower in Non-Asians. This is explained by the larger Vd in the non-Asians. Bxm is thought to be hydrolyzed by AADAC, a serine esterase, in the small intestine and liver. The metabolite baloxavir is the active agent. Baloxavir is subject to biliary secretion and is primarily excreted via feces. Baloxavir is only sparsely excreted in the urine (3.3%).

Metabolites

In plasma, baloxavir was the main entity accounting for 82.2% of total radioactivity. Other metabolites were baloxavir glucuronide and baloxavir sulfoxide, accounting for 16.4% and 1.5% of total radioactivity in plasma, respectively. The PK and potential for DDIs of baloxavir glucuronide have not been reported.

Inter-conversion

After single oral dosing of baloxavir marboxil, no measurable levels of prodrug were detected, and only the baloxavir stereoisomer was found. Hence, baloxavir is not interconverted into any of its other stereoisomers in human.

Dose proportionality and time dependencies

The maximum plasma concentration (C_{max}) and area under the concentration-time curve from time 0 to infinity ($AUC_{0\text{-}inf}$) increased in an essentially dose-proportional manner in the clinical studies regardless of formulation, suggesting linear pharmacokinetics of baloxavir over the entire clinical dose range of bxm tested, i.e., at least up to 80 mg. This applied to both Asian and Non-Asian healthy volunteers.

Intra- and interindividual variability

Inter-individual variability was estimated on the absorption rate constant (Ka), the oral clearance (CL/F), the apparent central volume of distribution (Vc/F) and the apparent peripheral volume of distribution (Vp/F) in the final pop PK model. The interindividual variability in the selected PK parameters estimated in the final pop PK model varied between 29% and 124% (Table 1 above).

Pharmacokinetics in target population

Very similar exposures have been demonstrated when comparing the baloxavir exposure ($AUC_{0\text{-}inf}$, C_{max}, and C_{24}) in the OwH and HR populations, indicating that HR factors did not impact oral drug clearance or bioavailability of baloxavir in a relevant manner. From Table 3 it is noted that a non-Asian subject receiving 80 mg of bxm is likely to have the same exposure as an Asian subject receiving 40 mg of bxm. A non-Asian subject receiving 40 mg of bxm will have the lowest exposure (35-37 ng/mL in terms of C_{24}).

Table 3 Comparison of PK in OwH Patients (T0831) and HR (T0832) by Body Weight and Race (ITTI Patients with at least one PK parameter estimated)

Race	Dose (body	Population	No. of Subjects	C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (ng • hr/mL)	Modelled C_{24} (ng/mL)	Observed C_{24}
All Patients	40 mg (< 80 kg)	OwH T0831	368	92.2 (11.1–221)	5799 (909.5–13200)	51.3 (8.72–117)	56.0 (5.81–158)
		HR T0832	234	85.9 (12.2–382)	5265 (720.3–14690)	46.8 (7.87–123)	52.1 (5.77–231)
	80 mg (≥ 80 kg)	OwH T0831	78	113 (27.1–253)	7825 (2247–16340)	66.8 (21.4–155)	74.9 (17.5–209)
		HR T0832	144	94.2 (9.21–241)	6459 (890.8–16640)	57.2 (7.36–134)	62.9 (5.86–198)
Non-Asian	40 mg (< 80 kg)	OwH T0831	59	63.9 (11.1–133)	3648 (909.5–7609)	36.3 (8.72–85.9)	37.2 (7.35–81.4)
		HR T0832	96	60.6 (12.2–158)	3661 (720.3–8571)	34.5 (7.87–77.9)	35.9 (5.77–90.2)
	80 mg (≥ 80 kg)	OwH T0831	44	94.6 (27.1–196)	6345 (2247–15040)	57.9 (21.4–155)	62.9 (17.5–209)
		HR T0832	118	84.9 (9.21–240)	5737 (890.8–14810)	52.9 (7.36–134)	58.7 (5.86–198)
Asian	40 mg (< 80 kg)	OwH T0831	309	97.6 (20.1–221)	6210 (1399–13200)	54.2(15.8–117)	59.8 (5.81–158)
		HR T0832	138	104 (24.0–382)	6380 (2294–14690)	55.3 (20.1–123)	64.0 (25.4–231)
	80 mg (≥ 80 kg)	OwH T0831	34	136 (30.9–253)	9741 (4527–16340)	78.3 (25.4–120)	88.7 (39.3–142)
		HR T0832	26	137 (40.9–241)	9733 (4893–16640)	76.7 (32.1–115)	87.6 (33.8–126)

C_{max}, $AUC_{0\text{-}inf}$: Bayesian estimation based on the OwH population pharmacokinetic model.
Observed C_{24}: the observed plasma concentrations at 20 to 28 hours post-dose.
Arithmetic mean (minimum-maximum) are shown for all PK parameters.

PK in the PEP population

Bayesian-estimates of AUC_{0-inf}, C_{max}, C_{24}, C_{72}, C_{240} by age category and dose are summarized in Table 4 below.

In subjects ≥12 years, the mean C_{24} and AUC_{0-inf} in the 80 mg dose group was 37%–38% higher compared to subjects in the 40 mg dose group (Table 4 below), which is consistent with the exposure increase seen with the 80 mg dose in Asian patients compared with the 40 mg dose in the treatment studies (T0831 and T0832, Table 3). With the 40 mg dose, the individual PK parameters were comparable between subjects ≥12 years and <12 years of age, although the subjects <12 years receiving the 40 mg dose were limited (n=4).

Estimated plasma concentrations of baloxavir by age, dose, and race on day 1 to 15 after drug administration is shown in Table 5 below.

Table 4 Bayesian-Estimated Pharmacokinetic Parameters of Baloxavir by Dose and Age Groups in PEP Study T0834

Age (years)	Baloxavir Marboxil Dose	No. of Subjects	$AUC_{0\text{-}inf}$ (ng.hr/mL)	C_{max} (ng/mL)	C_{24} (ng/mL)	C_{72} (ng/mL)	C_{240} (ng/mL)
≥12 years	40 mg	284	6262 (2118–16050)	93.9 (33.9–229)	53.1 (25.1–95.5)	26.7 (9.34–52.1)	5.14 (0.583–19.8)
	80 mg	17	10180 (5527–14930)	125 (45.3–195)	75.3 (36.3–108)	42.1 (23.9–60.1)	10.1 (2.73–15.1)
	Overall	301	6483 (2118–16050)	95.6 (33.9–229)	54.3 (25.1–108)	27.6 (9.34–60.1)	5.42 (0.583–19.8)
<12 years	10 mg	18	3321 (2221–5788)	84.4 (63.9–126)	42.5 (30.2–59.4)	11.0 (6.61–23.5)	1.26 (0.638–4.31)
	20 mg	46	4482 (3102–5782)	97 (69.8–127)	54.8 (42.6–71.3)	16.3 (9.09–21.9)	2.14 (0.901–3.81)
	40 mg	4	7245 (6591–7931)	111 (85.7–124)	75.1 (62.9–83.1)	29.3 (26.2–32.4)	5.23 (4.08–6.26)
	Overall	68	4337 (2221–4278)	94.5 (63.9–127)	52.7 (30.2–83.1)	15.7 (6.61–32.4)	2.09 (0.638–6.26)

Mean (minimum–maximum) are presented.

Source: T0834 PEP PK Report: Tables 2(a), 2(c), 2(d); Tables 3(a), 3(c), 3(d); Tables 4(a), 4(c), 4(d); Tables 6(a), 6(c), 6(d); PEP PK Bridging Report: Tables 2(a), 2(b).

Table 5 Predicted Plasma S-033447 Concentrations for Asian Adult and Paediatric Subjects and Non-Asian Adult Subjects based on the population Pharmacokinetics Models for Adults and Paediatrics

		Asian pediatrics			Asian adults		Non-Asian adults	
Dose (mg)		10	20		40	80	40	80
Body weight (kg)		10	20	30	60	90	60	90
Day	Time (hr)	Predicted plasma S-033447 concentration (ng/mL)						
0	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	24	69.0	76.0	53.0	53.4	82.4	33.7	52.3
2	48	33.2	40.3	29.7	37.1	59.2	22.0	35.9
3	72	19.1	24.2	18.3	27.2	45.4	15.0	25.9
4	96	12.5	16.1	12.4	20.4	35.4	10.4	19.0
5	120	8.83	11.6	8.98	15.6	28.0	7.38	14.1
6	144	6.46	8.73	6.83	12.1	22.4	5.33	10.6
7	168	4.81	6.74	5.35	9.61	18.2	3.92	8.12
8	192	3.60	5.28	4.27	7.71	15.0	2.93	6.27
9	216	2.70	4.16	3.44	6.26	12.4	2.22	4.90
10	240	2.03	3.30	2.79	5.13	10.4	1.71	3.87
11	264	1.53	2.61	2.26	4.24	8.76	1.33	3.09
12	288	1.15	2.07	1.84	3.52	7.43	1.05	2.49
13	312	0.866	1.64	1.50	2.94	6.34	0.830	2.02
14	336	0.652	1.31	1.22	2.46	5.43	0.662	1.65
15	360	0.490	1.04	0.996	2.06	4.66	0.530	1.36

Special populations

When comparing C_{max}, $AUC_{0\text{-}inf}$ and C_{24} across the different phase 1 studies in healthy Japanese and American adults, these parameters were about 45% to 50% lower in non-Japanese subjects compared

to Japanese subjects, and race (Asian vs. non-Asian) and body weight were significant covariates in the population pharmacokinetic analysis. The body weight-based dosing used in the phase 3 OwH (T0831) and HR (T0832) studies reduced the overall differences in drug exposure between Asian and non-Asian patients to about 30%.

No dose adjustment is necessary due to gender or age in adolescents >12 years, in patients with mild to moderate hepatic impairment, or in patients with renal impairment.

Pharmacokinetic interaction studies

In vitro

Baloxavir marboxil is a substrate for AADAC, UGT1A3 and CYP3A4. Furthermore, baloxavir marboxil and baloxavir are P-gp substrates but not substrates of BCRP.

CYP inhibition:

- Baloxavir marboxil inhibited CYP2B6, CYP2C8 and CYP3A4 (IC_{50} 23.2 µmol/L for midazolam as substrate).
- Baloxavir inhibited CYP2B6 and CYP3A4 (IC_{50} 43.2 µmol/L for midazolam as substrate; this compares with Cmax after a 40 mg dose in healthy Japanese adults of 0.25 µmol/L) in a concentration-dependent manner.
- Time-dependent inhibition by baloxavir marboxil or baloxavir was not observed.

CYP induction:

- Baloxavir marboxil did not demonstrate potential to induce CYP1A2, CYP2B6 and CYP3A4.
- Baloxavir marginally increased the mRNA levels of CYP1A2, CYP2B6 and CYP3A4 but no concomitant increase in CYP enzyme activity was seen.

Transporter inhibition:

Baloxavir marboxil was found to be an inhibitor of P-gp but did not inhibit BCRP.
Baloxavir inhibited transport mediated by P-gp, BCRP, OATP1B1, OCT1, MATE1 and MATE2-K.
Baloxavir did not inhibit transport mediated by OATP1B3, OAT1, OAT3, OCT2 or BSEP.

In vivo

The applicant conducted 5 drug-drug interaction studies with results as summarised in the figures.

Figure 3 Summary of the Effect of Baloxavir Marboxil/Baloxavir on the Pharmacokinetics of Other Drugs

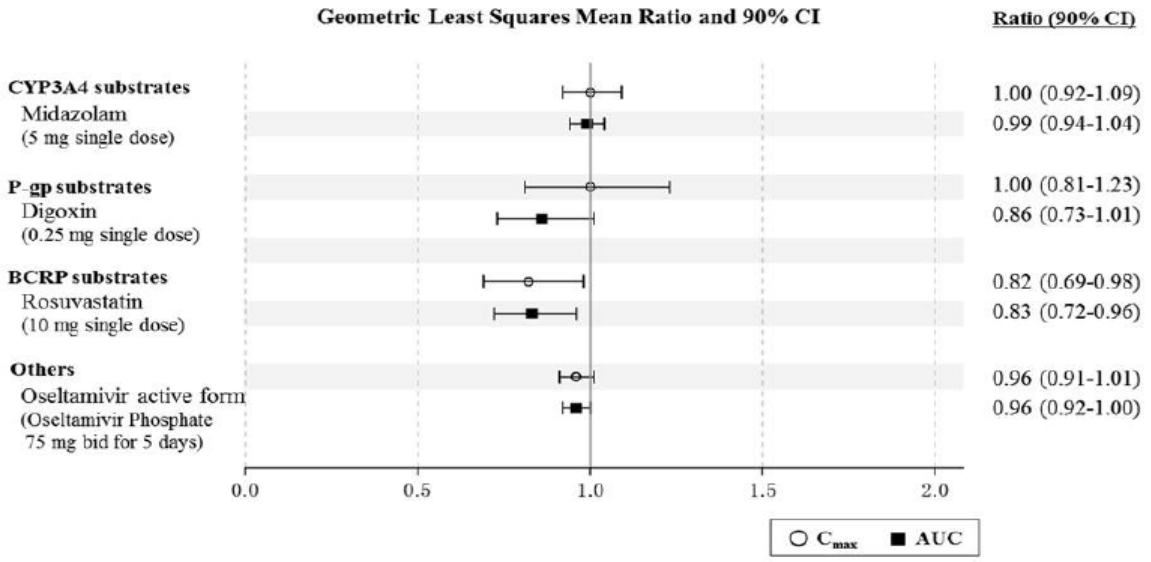
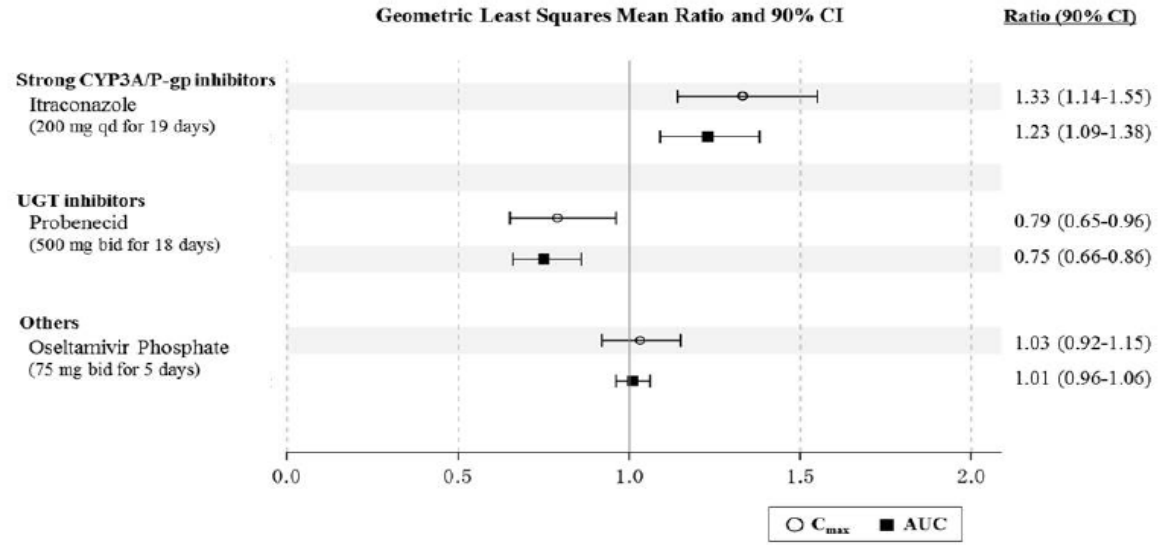


Figure 4 Summary of the Effect of Other Drugs on the Pharmacokinetics of Baloxavir



2.4.3. Pharmacodynamics

Mechanism of action

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.

Primary and Secondary pharmacology

Virus titre was used as a pharmacodynamic endpoint and, together with the clinical endpoint time to alleviation of symptoms (TTAS), as a measure of the relationship between baloxavir plasma concentration and effect.

Relationship between plasma concentration and effect

Exposure-response relationship has been examined in the phase 2 (T0821) and phase 3 studies (T0831, T0832, and T0834). Virus titer was examined separately in all 4 studies.

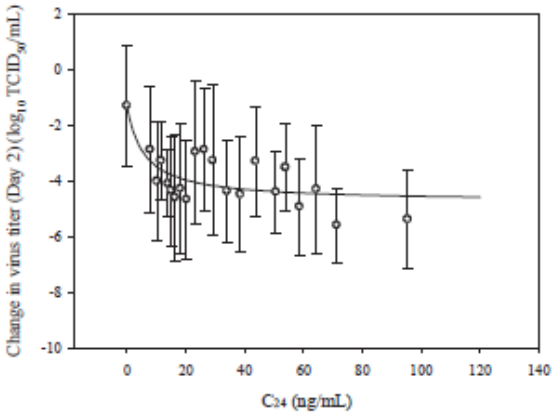
PK-virus titer analysis

Dose finding study (T0821), OwH Japanese subjects

The relationship between the C_{24} of S-033447 and the change from baseline in the influenza virus titer on Day 2 (binned data) is provided in Figure 5**.** There was a correlation between the C_{24} of baloxavir and the change from baseline in the influenza virus titer on Day 2. An Emax model showed that a maximum anti-virus effect was almost reached for patients with the C_{24} greater than 20 ng/mL.

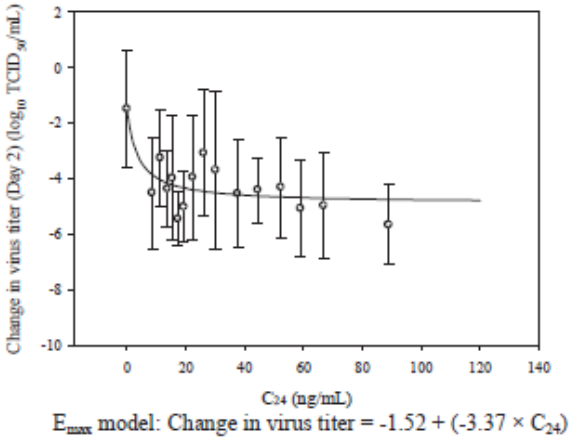
Figure 5 Relationship between C_{24} and Change from Baseline in Influenza Virus Titer on Day 2 (Binned Data)

Overall virus types



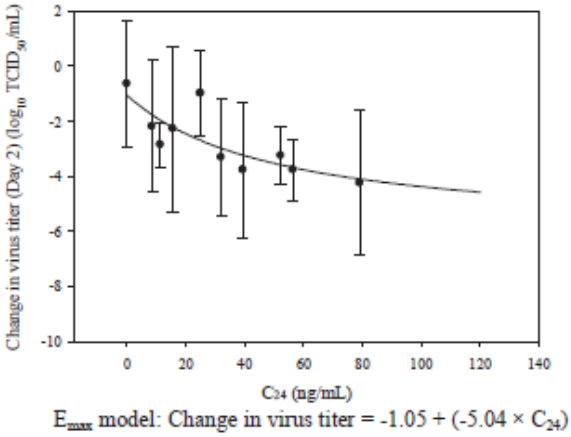
E_{max} model: Change in virus titer = -1.33 + (-3.41 × C_{24}) / (5.88 + C_{24})

Virus type A



E_{max} model: Change in virus titer = -1.52 + (-3.37 × C_{24}) / (3.82 + C_{24})

Virus type B



E_{max} model: Change in virus titer = -1.05 + (-5.04 × C_{24}) / (52.0 + C_{24})

Source: Table 9 and Figure 18 in the PK report in Appendix 16.1.9

Phase 3 OwH and HR studies

Change in virus titer from baseline to day 2 was examined in the two phase 3 studies (T0831 and T0832) stratified by virus type. In OwH subjects, there was a numerically larger change in virus titer in subjects treated with bxm than placebo. In the bxm treated group, the change in virus titer was similar in subjects with the lowest baloxavir plasma concentration (<20 ng/ml) and highest baloxavir plasma concentration (≥60 ng/ml) indicating no exposure-response relationship.

In HR subjects, there was also a numerically larger change in virus titer in subjects treated with bxm than placebo. In the bxm treated group there was a tendency towards a larger change in virus titer with higher baloxavir plasma concentration indicative of a positive exposure-response relationship without reaching a plateau.

PK-efficacy analysis

Time to alleviation of symptoms (TTAS)

Study T0821, T0831, T0832 combined.

Graphical analyses were conducted to investigate any link between a patient's baloxavir exposure and TTAS.

The patient population for this graphical analysis were the patients from the placebo arms of the phase 2 study T0821 and the phase 3 studies T0831 and T0832, as well as the baloxavir marboxil-treated patients from the same studies that were included in the population PK analysis.

Based on the individual estimated AUC_{inf} values, patients in baloxavir marboxil arms were classified into two exposure categories (low and high), defined by the median of the estimated AUC_{inf} distribution.

Survival analysis with Kaplan Meier estimation and log-rank tests were then used to compare the TTAS over the two exposure categories and the placebo group. For all comparisons, a p value <0.05 was considered statistically significant.

The distribution of the predicted AUCinf across the three studies is given in Table 6, showing a tendency of lower exposure in the phase 2 0821 study, which is as expected because lower doses of bxm (10 mg and 20 mg) were included in this phase 2 dose-finding study compared with the phase 3 studies that used either 40 mg or 80 mg depending on the patient's body weight.

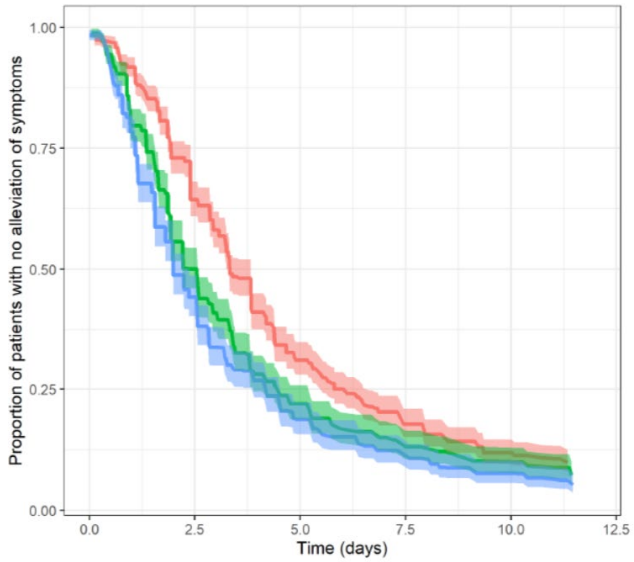
Table 6 Observed distribution of Baloxavir exposure (from computed AUC_{0_INF} (µg.hr/mL)) across studies T0821, T0831 and T0832

Study	N	AUC_{0_Inf} (µg.hr/mL)	
		Mean(SD)	Median [Min- Max]
T0821	299	4.13 (2.32)	3.57 [0.874 – 12.6]
T0831	429	6.16 (2.59)	5.89 [0.911 -16.0]
T0832	364	5.81 (2.83)	5.26 [0.722 -16.7]

Bxm-treated patients in the database were split into two groups of exposure: those with AUC0_inf included in the minimum to median range of AUC0_inf ([0.722 – 5.13) µg.hr/mL, defining the low exposure group) and those with AUC0_inf included in the median to the maximum range of AUC0_inf ([5.13 -16.7] µg.hr/mL, defining the high exposure group).

Figure 6 illustrates the observed TTAS Kaplan Meier curves in the placebo group and in the baloxavir low and high exposure groups. Figure 7 also illustrates the observed TTAS Kaplan Meier curves but only for patients with a composite symptom score at baseline ≥ 13, the observed median composite symptom score in the database. The TTAS Kaplan Meier curves for patients less severely affected, defined as patients with a composite symptom score at baseline lower than 13, is shown in the **Appendix 1** Figure 8 below.

Figure 6 Observed TTAS Kaplan Meier Curves per exposure levels in studies in al patens from studies T0821, T0831 and T0832



Note: Observed TTAS Kaplan Meier curves and corresponding 95% CI are represented in red for the Placebo group, in green for the low baloxavir exposure group (AUC_{inf} in [0.722 – 5.13) µg.hr/mL) and blue for the high baloxavir exposure group (AUC_{inf} in [5.13 -16.7] µg.hr/mL).

Figure 7 Observed TTAS Kaplan Meier Curves per exposure levels in studies in patens from studies T0821, T0831 and T0832 with composite symptom score at baseline ≥ 13.

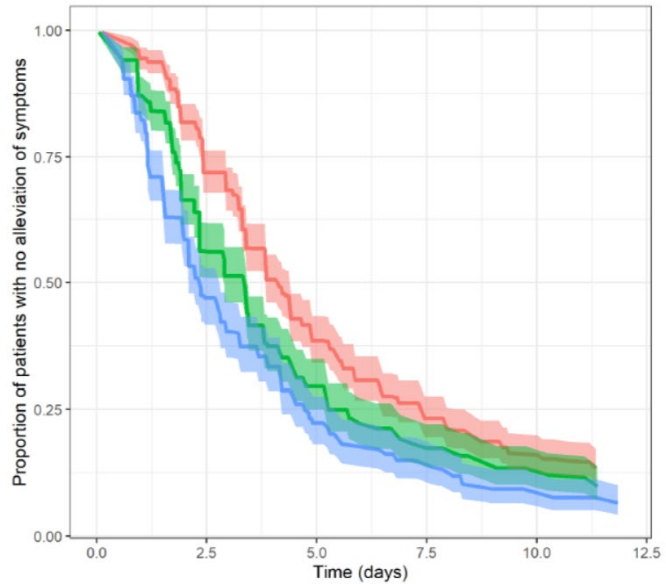
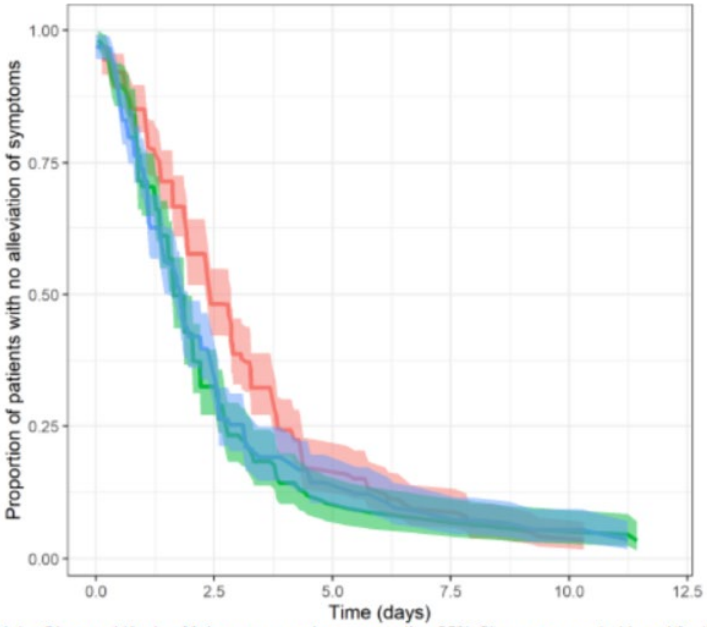


Figure 8

Appendix 1 Observed TTAS Kaplan Meier Curves per exposure levels in patients from studies T0821, T0831 and T0832 with a composite symptom score at baseline <13



Note: Observed Kaplan Meier curves and corresponding 95% CI are represented in red for the Placebo group, in green for the low baloxavir exposure group (AUC_{inf} in [0.722 – 5.13) µg.hr/mL) and blue for the high baloxavir exposure group (AUC_{inf} in [5.13 -16.7] µg.hr/mL).

Table 7 reports log-rank tests used to compare these Kaplan Meier curves.

Table 7 Comparison of Kaplan-Meier Curves per Exposure category and per Composite Symptom Score at Baseline

Case	Group Comparison	P-value
All patients	Overall	P<0.0001
	Placebo versus Low exposure	P<0.0001
	Low exposure versus High exposure	P=0.03
Patients with TSS0 ≥13	Overall	P<0.0001
	Placebo versus Low exposure	P<0.001
	Low exposure versus High exposure	P<0.01
Patients with TSS0 <13	Overall	P<0.01
	Placebo versus Low exposure	P<0.01
	Low exposure versus High exposure	P=0.7 NS

Note: The Kaplan-Meier method with a log-rank test was applied to compare the survival curves. For all comparisons, a p value<0.05 was considered statistically significant.

Alleviation of symptoms was more pronounced in patients with high baloxavir exposure in terms of $AUC_{0\text{-}inf}$ compared with low exposure especially in patients with a high symptom score.

Bridging between PEP Japanese subjects and non-Asians

The PEP study was designed to evaluate if a single dose of baloxavir (40 mg or 80 mg in adults) would decrease the risk of getting influenza among subjects living together with household members suffering from influenza. Based on population PK models for adults/adolescents and children, it was predicted that the same dosage regimen as used for treatment could maintain the plasma baloxavir concentrations for about 10 days.

As study T0834 was conducted in Japan, an exposure matching approach is used to bridge the T0834 PEP data obtained in Japanese subjects to non-Asian subjects ≥12 years of age. This bridging approach consists of 3 steps:

1. Confirm the expectation that baloxavir exposures observed in Japanese subjects in the PEP study are similar to those in Asian patients in the OwH and HR treatment studies;
2. Assess the relationship between baloxavir concentration and key PEP clinical endpoints for all subjects in study T0834;
3. Compare baloxavir exposures in PEP Japanese subjects to those of non-Asian patients ≥12 years of age in the OwH and HR treatment studies, with the aim of assessing whether prophylactic efficacy can be bridged to non-Asian patients, who are known to have lower exposures to baloxavir than Asian patients.

The study demonstrated (1) a similar exposure-response relationship between paediatric Japanese subjects (<12 years of age) and Japanese subjects ≥12 years of age, and (2) a similar baloxavir exposure between paediatric Japanese subjects and non-Asian OwH and HR subjects ≥12 years of age. Therefore, the Applicant concludes that an exposure-response difference between Asian subjects ≥12 years of age and non-Asian subjects ≥12 years of age would not be expected, even though adult Asian patients tend to have slightly higher baloxavir exposure than non-Asian adults.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetics of bxm/baloxavir has been studied in healthy subjects, in special populations, and in patients with influenza being either at high risk of influenza complications (HR population) or otherwise healthy (OwH population). Data from both Asian and non-Asian subjects were obtained. The PK data were analysed in individual studies and were used to build a population PK model based on data from the phase 1, 2, and 3 studies. Individual Bayesian post-hoc baloxavir PK parameters were derived from the population PK model. The model is considered valid and suitable for the intended purposes.

The dosing regimen in the clinical studies was based on body weight since it was demonstrated early in the development programme that weight and race were predictors of exposure and that the average overall exposure was higher in Asians than in non-Asians. This difference in exposure is most likely a result of differences in absolute bioavailability, which do not seem to be caused by ethnicity related genetic polymorphism in the hydrolysing enzyme (AADAC). The weight-based dosing was introduced to reduce the differences in exposure. According to the weight-based dosing regimen, subjects ≥ 80kg was to receive a single dose of 80 mg bxm and subjects <80 kg a single dose of 40 mg bxm. The posology in children was also a single dose according to weight: <10 kg: 1 mg/kg, weight 10-<20 kg: 10 mg, weight 20-<40 kg: 20 mg, and weight ≥40 kg: 40 mg.
With regard to age, the available data from 1602T0832 suggest that exposures are broadly comparable between subjects with influenza who are <65 years, 65-74 or 75+ years. 47 patients aged 75+ years received baloxavir, including one 85-year-old Asian patient.

The PK of baloxavir was best described using a three-compartment model with first-order elimination and absorption processes and a lag time. After introducing a weight-adjusted dosing, the overall difference in exposure was reduced from 45-50% to around 30%. Bxm has been administered to four adult patients weighing < 40 kg and their estimated AUC values were within the range seen in the T0831 OwH phase 3 study.

Baloxavir human serum protein-binding ranged from 92.9% to 93.9% *in vitro*. The unbound fraction was apparently similar across species. Based on the observed data in the hepatic impairment study and the applicant's calculations, an important effect of hepatic or renal impairment on the free fraction of baloxavir and accordingly efficacy is unlikely.

Data suggest that baloxavir is subject to biliary secretion and is primarily excreted via faeces. Baloxavir is only sparsely excreted in the urine (3.3%). The half-life of baloxavir is estimated to be 79.1 hours. No dose adjustment would be needed for patients with mild or moderate hepatic impairment. The safety and efficacy of Xofluza has not been established in patients with severe hepatic impairment.

In plasma, baloxavir was the main entity accounting for 82.2% of total radioactivity. Other metabolites were baloxavir glucuronide and baloxavir sulfoxide, accounting for 16.4% and 1.5% of total radioactivity in plasma, respectively.

In the large phase II/III studies, the effect of food was minimal and since the efficacy was not affected by concomitant food intake, the product may be taken with or without food.

The *in vitro*-based steady-state DDI assessments as well as the lack of interaction with rosuvastatin support that baloxavir is not a relevant *in vivo* inhibitor of OATP1B1, OCT1, MATE-1 and MATE2-K.

The primary exposure-response endpoint was time to alleviation of symptoms (TTAS) and virus titre was used as a PD endpoint.

In the dose finding study (T0821), the primary endpoint, time to alleviation of symptoms (TTAS), was numerically lower but not statistically lower in patients treated with bxm compared with placebo. However, a decrease in virus titre was observed.

The combined analysis of study T0821, T0831, and T0832 showed that TTAS were lower for subjects with high baloxavir exposure in terms of $AUC_{0\text{-}inf}$ compared with low exposure, although the difference between the two exposure groups was small. In patients with symptom score ≥ 13, the difference in TTAS was larger between the exposure groups than in patients with symptom score <13.

In the PEP population, no differences in plasma concentrations were observed between those who met the primary (influenza-infected with fever AND at least one respiratory symptom) or secondary endpoints (influenza-infected with fever OR at least one respiratory symptom) and those who did not. Therefore, no exposure-response relationship was observed in the PEP population.

The dedicated QTc study did not show prolongation of the QTc.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology programme conducted was comprehensive and adequate in terms of number of enrolled subjects and type of studies performed. The overall conclusion is that the proposed dosing regimen for Asian and non-Asian adolescents and adults is considered appropriate for both the treatment and the PEP indications.

2.5. Clinical efficacy

Baloxavir marboxil is proposed for treatment of influenza infection and for post-exposure prophylaxis. 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 separately.

2.5.1. Clinical efficacy in the treatment indication

The treatment indication sought for baloxavir marboxil is:

- treatment of influenza in patients aged 12 and above, including patients at high risk of developing influenza-related complications

A total of 18 clinical studies of baloxavir marboxil have been conducted, including:

- 1 randomised, double-blind, placebo controlled, pivotal, Phase 2 study on the treatment of diagnosed influenza in otherwise healthy subjects (T0821).

- 2 multicentre, randomised, double-blind, placebo- and comparator controlled, pivotal, Phase 3 studies on the treatment of diagnosed influenza in otherwise healthy subjects (T0831) and in patients at high-risk of developing complications (T0832).

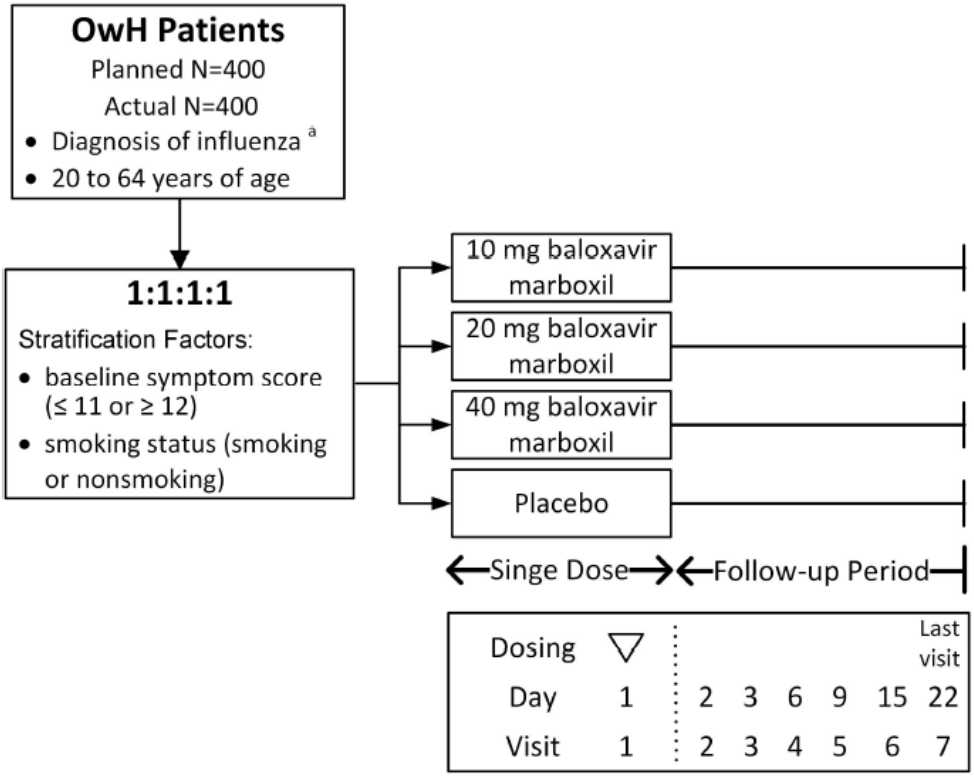
In total, 1442 subjects received the proposed 40-80 mg dose (dependent on weight below or above 80 kgs) in the dosage form intended for commercial use as a treatment of influenza infection.

2.5.1.1. Dose response study

One dose-response study was conducted in Japan, study T0821, in otherwise healthy (OwH) patients.

An overview of the study design is provided in the figure below. Adult patients (20 to 64 years of age) were randomly assigned in a ratio of 1:1:1:1 to receive 10, 20, or 40 mg of baloxavir marboxil, or placebo. The study planned to randomize 400 patients in order to detect a significant difference between at least one dose group and the placebo group. The actual number of patients randomized was 400 patients.

Figure 9 Overview of OwH Study T0821 Design



OwH = otherwise healthy.

[a] Influenza diagnosed per protocol i.e. positive rapid influenza diagnostic test for influenza with nasal or throat swabs, fever (axillary temperature ≥ 38°C), at least one general symptom (headache, feverishness or chills, muscle or joint pain, and fatigue) with a severity of moderate or greater, and at least one respiratory symptom (cough, sore throat, and nasal congestion) with a severity of moderate or greater.

If influenza symptoms were so severe that the patient needed rescue therapy between Visits 1 and 7, the use of acetaminophen at a dose of 1500 mg/day or less was permitted only for the relief of fever or pain. The use of antiviral, antimicrobial, antifungal, antipyretic/analgesic (except provided acetaminophen), antitussive/expectorant, antihistamine, corticosteroid, immunosuppressant, herbal (indicated for influenza virus infection), other over-the-counter medications with equivalent efficacy, and certain other drugs was prohibited from Visit 1 until Visit 7 or early termination.

2.5.1.2. Main studies

The efficacy of treatment of influenza was evaluated in two pivotal studies conducted in an otherwise healthy (OwH) population, study T0831, and in a high risk (HR) population, study T0832.

A Phase 3, Multicenter, Randomized, Double-blind Study of a Single Dose of S-033188 (Baloxavir Marboxil) Compared with Placebo or Oseltamivir 75 mg Twice Daily for 5 Days in Otherwise Healthy Patients with influenza (CAPSTONE-1)(Study T0831)

A Phase 3, Multicenter, Randomized, Double-blind Study of a Single Dose of S-033188 Compared with Placebo or Oseltamivir 75 mg Twice Daily for 5 Days in Patients with Influenza at High Risk of Influenza complications (CAPSTONE-2)(Study T0832)

Methods

Study Participants

The patient in- and exclusion criteria are described below.

Inclusion:

In both the **OwH-study and the HR-study**, the patients were included if they were able to understand the study and comply with all study procedures, were male or female patients ≥12 years, and had a diagnosis of influenza virus infection confirmed by all of the following:

a. Fever ≥ 38ºC (axillary) in the predose examinations or > 4 hours after dosing of antipyretics if they were taken

b. At least 1 of the following general systemic symptoms associated with influenza were present with a severity of moderate or greater

- Headache
- Feverishness or chills
- Muscle or joint pain
- Fatigue

c. At least 1 of the following respiratory symptoms associated with influenza were present with a severity of moderate or greater

- Cough
- Sore throat
- Nasal congestion

The time interval between the onset of symptoms and the predose examinations (Screening) was 48 hours or less. The onset of symptoms was defined as either:

a. Time of the first increase in body temperature (an increase of at least 1ºC from normal body temperature)

b. Time when the patient experienced at least 1 general or respiratory symptom

Women of childbearing potential (WOCBP) who agreed to use a highly effective method of contraception for 3 months after the first dosing of study drug.

For the **OwH-population**, it was explicit that the patients did not fulfil any high-risk criteria (including age ≥ 65 years, while is for the HR-population was a requirement to fulfil at least one high-risk criteria. The employed high-risk criteria are stated below. There criteria are adopted, although somewhat modified, from the Centre for Disease Control (CDC) high-risk criteria.

a. Asthma or chronic lung disease (such as chronic obstructive pulmonary disease or cystic fibrosis)

b. Endocrine disorders (including diabetes mellitus)

c. Residents of long-term care facilities (e.g., nursing homes)

d. Compromised immune system (including patients receiving corticosteroids not exceeding 20 mg of prednisolone or equivalent, and patients being treated for human immunodeficiency virus [HIV] infection with a CD4 count > 350 cells/mm3 within the last 6 months)

e. Neurological and neurodevelopmental disorders (including disorders of the brain, spinal cord, peripheral nerve, and muscle, eg, cerebral palsy, epilepsy [seizure disorders], stroke, muscular dystrophy, or spinal cord injury)

f. Heart disease (such as congenital heart disease, congestive heart failure, or coronary artery disease), excluding hypertension without any other heart-related symptoms

g. Adults ≥ 65 years of age

h. American Indians and Alaskan Natives

i. Blood disorders (such as sickle cell disease)

j. Metabolic disorders (such as inherited metabolic disorders and mitochondrial disorders)

k. Morbid obesity (BMI ≥ 40 kg/m2)

l. Women who were within 2 weeks postpartum and were not breastfeeding

Exclusion:

A subpopulation of patients with complicated influenza was excluded, i.e. patients who required inpatient treatment were excluded.

1. Patients who had a severe influenza virus infection requiring inpatient treatment

2. Patients with known allergy to oseltamivir

3. Patients who were unable to swallow tablets or capsules

4. Patients who previously received baloxavir marboxil

5. Patients who weighed < 40 kg

6. Patients who were exposed to an investigational drug within 30 days prior to the predose examinations

7. Women who were pregnant, breastfeeding, or who had a positive pregnancy test in the predose examinations. The following female patients who had documentation of either a or b below did not need to undergo a pregnancy test in the predose examinations:

    a. Postmenopausal (defined as cessation of regular menstrual periods for 2 years or more and confirmed by a follicle-stimulating hormone test) women

    b. Women who were surgically sterile by hysterectomy, bilateral oophorectomy, or tubal ligation

8. Patients with concurrent infections at the predose examinations requiring systemic antimicrobial therapy

9. Patients with liver disease associated with hepatic impairment

10. Patients with cancer within the last 5 years (unless nonmelanoma skin cancer)

11. Patients with untreated HIV infection or treated HIV infection with a CD4 count below 350 cells/mm3 in the last 6 months

12. Patients with immunosuppression following organ or bone marrow transplants

13. Patients exceeding 20 mg of prednisolone or equivalent dose of chronic systemic corticosteroids

14. Patients who received peramivir, laninamivir, oseltamivir, zanamivir, rimantadine, umifenovir, or amantadine within 30 days prior to the predose examinations

15. Patients who received an investigational monoclonal antibody for a viral disease in the last year

16. Patients who had a creatinine clearance value ≤ 60 mL/min (≤ 30 mL/min in Japan)

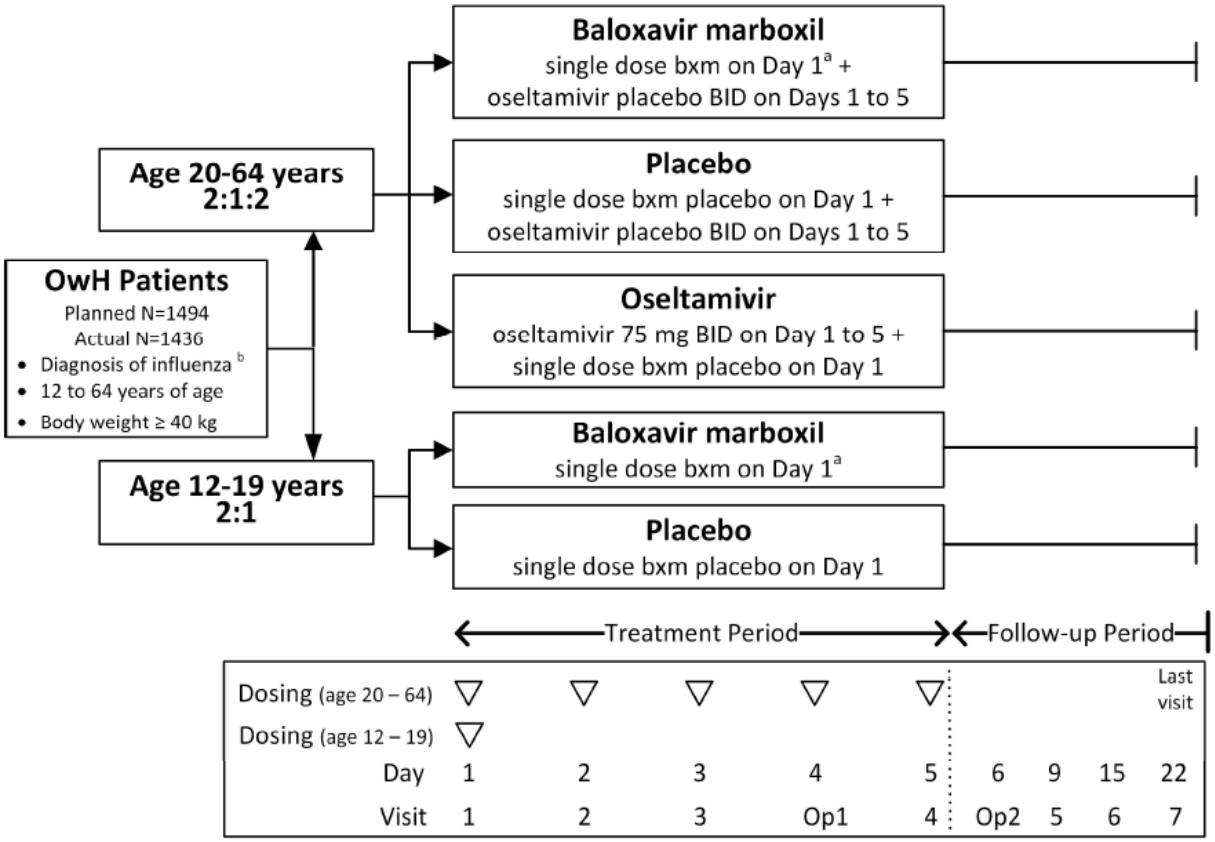
Treatments

OwH

Adult patients (20 to 64 years of age) were randomized in a 2:1:2 ratio to receive baloxavir marboxil (single dose on Day 1), placebo, or oseltamivir (75 mg twice daily [BID] for 5 days). Adolescent patients (12 to 19 years of age) were randomized in a 2:1 ratio to receive either baloxavir marboxil or placebo. Baloxavir marboxil dosing was based on the patient's body weight at screening: patients who weighed 40 to < 80 kg received 40 mg and patients who weighed ≥ 80 kg received 80 mg. Oseltamivir was not administered to patients <20 years of age due to a labelling restriction on its use in OwH adolescents in Japan at the time of the study (the restriction was lifted in August 2018 after the study was complete). In each age group, patients were also stratified by the following three factors: region (Japan/Asia or Rest of the World), body weight (< 80 kg or ≥ 80 kg), and composite influenza symptom score at baseline (≤ 11 or ≥ 12). As rescue therapy between Visits 1 and 7, the use of acetaminophen at a dose of 3000 mg/day or less was permitted only for the relief of fever or pain.

The study in otherwise healthy subjects is depicted below.

Figure 10 Overview of OwH Study T0831 Design



BID = twice daily; bxm = baloxavir marboxil; Op = optional; OwH = otherwise healthy.

Stratification factors: baseline symptom score (≤ 11 or ≥ 12), region (Japan or US), and body weight (< 80 kg or ≥ 80 kg).

[a] Baloxavir marboxil dose dependent on body weight at baseline: 40 mg for patients 40 to < 80 kg; 80 mg for patients ≥ 80 kg.

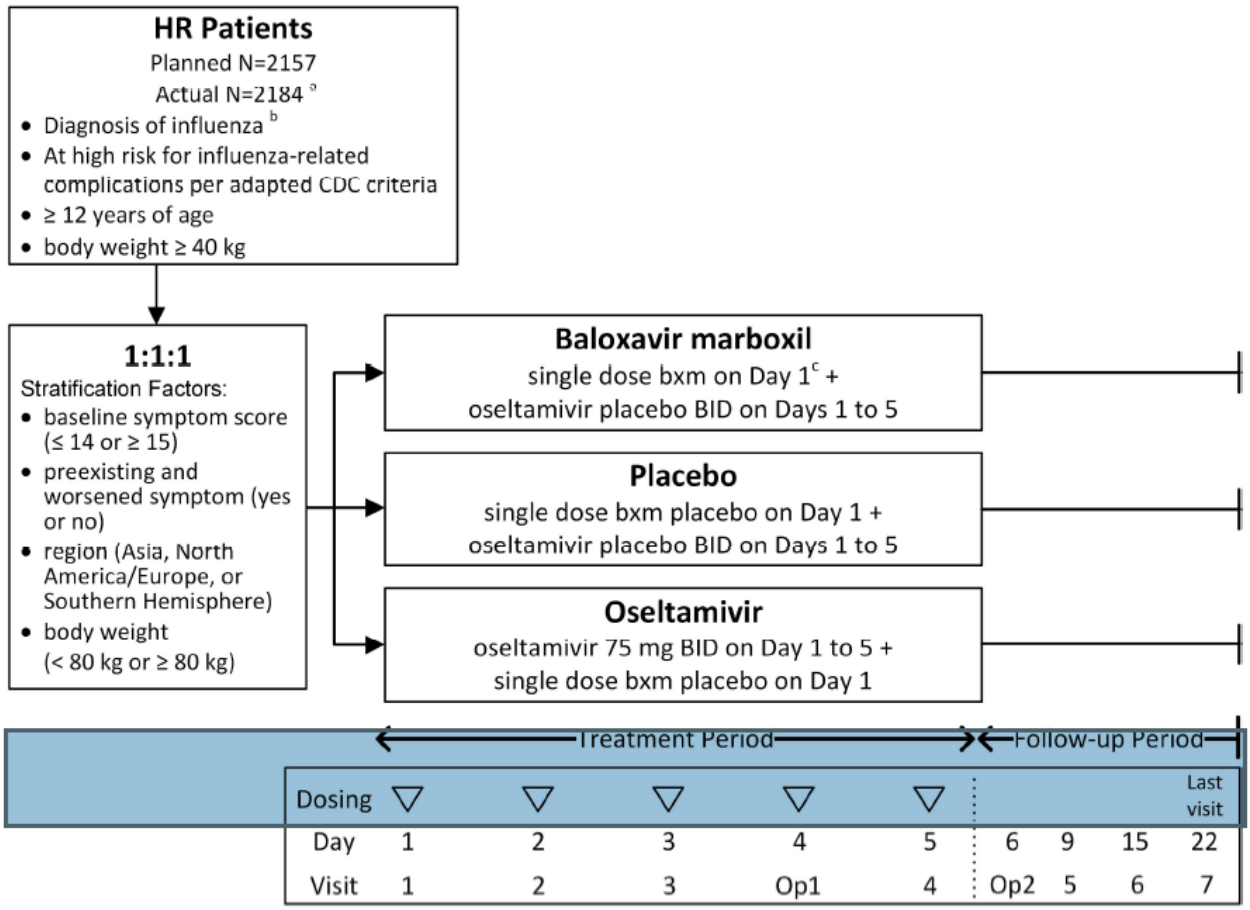
[b] Influenza diagnosed per protocol i.e. fever (axillary temperature ≥ 38°C), at least one general symptom (headache, feverishness or chills, muscle or joint pain, and fatigue) with a severity of moderate or greater, and at least one respiratory symptom (cough, sore throat, and nasal congestion) with a severity of moderate or greater.

HR

Eligible patients were randomized in a 1:1:1 ratio to receive a single oral dose of baloxavir marboxil, repeated doses of oseltamivir (75 mg BID for 5 days), or placebo. Baloxavir marboxil dosing was based on the patient's body weight at screening: patients who weighed 40 to < 80 kg received 40 mg and patients who weighed ≥ 80 kg received 80 mg. Patients were also stratified by the following four factors: baseline symptom score (≤ 14 or ≥ 15), pre-existing and worsened symptoms (yes or no), region (Asia, North America/Europe, or Southern Hemisphere), and body weight (< 80 kg or ≥ 80 kg). As rescue therapy between Visits 1 and 7, the use of acetaminophen at a dose of 3000 mg/day or less was permitted only for the relief of fever or pain.

The study in high-risk subjects is depicted below.

Figure 11 Overview of HR Study T0832 Design



BID = twice daily; bxm = baloxavir marboxil; CDC = Centers for Disease Control and Prevention; HR = high risk; Op = optional.

[a] The actual number of patients randomized was 2184 patients, including 2 patients who were randomized twice in error. Thus, a total of 2182 unique patients were randomized to treatment (Table 1).

[b] Influenza diagnosed per protocol i.e. fever (axillary temperature ≥ 38°C), at least one general symptom (headache, feverishness or chills, muscle or joint pain, and fatigue) with a severity of moderate or greater, and at least one respiratory symptom (cough, sore throat, and nasal congestion) with a severity of moderate or greater.

[c] Baloxavir marboxil dose dependent on body weight at baseline: 40 mg for patients 40 to < 80 kg; 80 mg for patients ≥ 80 kg.

Objectives

The study objectives of the studies T0831 and T0832 were to evaluate the efficacy of a single, oral dose of baloxavir marboxil compared with placebo and oseltamivir by measuring the time to alleviation or improvement of symptoms in otherwise healthy patients (T0831) and patients, who were assessed as having a higher risk of developing influenza-related complications (T0832).

The studies aimed at showing superiority of baloxavir marboxil as compared to placebo and subsequently to show non-inferiority to oseltamivir.

Outcomes/endpoints

Primary endpoint

The primary efficacy endpoint in both the OwH and HR populations was time to recovery from the influenza infection. In the OwH population, the recovery was evaluated as time to alleviation of symptoms, TTAS, while it in the HR population was evaluated as time to improvement of symptoms, TTIS. The TTIS is a modification of the TTAS to encompass that some patients had 'influenza-like symptoms' at baseline, e.g. COPD patients with cough and fatigue.

Alleviation of symptoms, TTAS, was defined as the time when all 7 influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) had been assessed by the patient as 0 (none) or 1 (mild) for a duration of at least 21.5 hours (24 hours minus 10%).

Improvement of symptoms, TTIS, was defined as follows:

- Alleviation of new symptoms that were not present before the onset of influenza: the symptom score must have been assessed by the patient as 0 (none) or 1 (mild) on the 4-point scale
- Improvement of pre-existing symptoms that were judged by the patient to have been worsened by influenza: the symptom score must have improved by at least 1 point from baseline severity.
- Maintenance of pre-existing symptoms that were judged by the patient to have NOT been worsened by influenza: the symptom score must have at least stayed the same as at baseline.

Assessments both in OwH and the HR group were made by the patients in an eDiary pre-dose on Day 1, twice daily (morning and evening) until Day 9, and once daily (evening) from Days 10 to 14.

Secondary endpoints

The Applicant included several secondary endpoints, please refer to the tables below (first OwH, then HR). The secondary endpoints were not prioritised and the analyses of the secondary endpoints did not include correction for multiplicity.

Secondary endpoints in the OwH population

Table 8 OwH Studies T0831 and T0821: Definitions of Key Secondary Efficacy Endpoints

	Definition
Secondary Clinical Endpoints	
Time to alleviation of the 4 systemic symptoms (hours) [a]	The time between the initiation of the study treatment and the alleviation of the 4 systemic symptoms (headache, feverishness or chills, muscle or joint pain, and fatigue). [b]
Time to alleviation of the 3 respiratory symptoms (hours) [a]	The time between the initiation of the study treatment and the alleviation of the 3 respiratory symptoms (cough, sore throat, and nasal congestion). [b]
Time to alleviation of individual influenza symptoms (hours)	The time between the initiation of the study treatment and the alleviation of the individual symptom. [b]
Time to resolution of fever (hours)	The time between the initiation of the study treatment and the resolution of fever. The resolution of fever was defined as the time when the patient's self-measured axillary temperature became less than 37°C and was maintained at <37°C for at least 12 hours.
Proportion of patients whose symptoms had been alleviated at each time point (%) [c]	Percentage of patients whose symptoms had been alleviated at 12, 24, 36, and 48 hours post-dose and every 24 hours thereafter until 216 hours (9 days) post dose. [b]
Secondary Virology Endpoints	
Time to cessation of viral shedding by virus titer (hours) [a]	The time between the initiation of the study treatment and first time when the virus titer was below the limit of detection.
Time to cessation of viral shedding by virus RNA by RT-PCR (hours) [c]	The time between the initiation of the study treatment and first time when virus RNA by RT-PCR was below the limit of detection.
Proportion of patients with positive influenza virus titer at each time point (%)	Percentage of patients whose influenza virus titer was not less than the LLOQ among those assessed for influenza virus titer. Measured on Days 2, 3, 4, 5, 6, and 9 (T0831) or Days 2, 3, 6 and 9 (T0821).
Change from baseline in virus titer at each time point ($log_{10}TCID_{50}$/mL)	Change from baseline in influenza virus titer among those assessed for virus titer. Measured on Days 2, 3, 4, 5, 6, and 9 (T0831) and Days 2, 3, 6 and 9 (T0821). Baseline was defined as the value obtained pre-dose on Day 1.

LLOQ = lower limit of quantification; RT-PCR = reverse transcription polymerase chain reaction; $TCID_{50}$ = 50% tissue culture infective dose.

[a] Not an endpoint in Phase 2 Study T0821; however, a post hoc analysis of the data was conducted and the results are presented in OwH+HR Section 3.1.2.3 of this SCE.

[b] The alleviation of a symptom was defined as the time when the symptom was assessed as 0 (none) or 1 (mild) for at least 21.5 hours (24 hours – 10%).

[c] Not an endpoint in Phase 2 Study T0821.

Secondary endpoints in the HR population

Table 9 HR Study T0832: Definitions of Key Secondary Efficacy Endpoints

	Definition
Secondary Clinical Endpoints	
Time to alleviation of symptoms (hours)	The time between the initiation of study treatment and the alleviation of all 7 influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue).[a]
Time to improvement in the 4 systemic symptoms (hours)	The time between the initiation of the study treatment and the improvement of the 4 systemic symptoms (headache, feverishness or chills, muscle or joint pain, and fatigue).[b]
Time to improvement in the 3 respiratory symptoms (hours)	The time between the initiation of the study treatment and the improvement of the 3 respiratory symptoms (cough, sore throat, and nasal congestion).[b]
Time to improvement of individual influenza symptoms (hours)	The time between the initiation of the study treatment and the improvement of the individual symptom.[b]
Time to resolution of fever (hours)	The time between the initiation of the study treatment and the resolution of fever. The resolution of fever was defined as the time when the patient's self-measured axillary temperature became less than 37°C and was maintained at < 37°C for at least 12 hours.
Proportion of patients whose symptoms had improved at each time point (%)	The percentage of patients whose symptoms had improved at 12, 24, 36, and 48 hours post-dose and every 24 hours thereafter until 216 hours (9 days) post dose.[b]
Requirement for systemic antibiotics for infections secondary to influenza infection (%)	The percentage of patients who took antibiotics for any of the predefined complications (sinusitis, otitis media, bronchitis, and pneumonia).
Incidence of influenza-related complications (%)	The percentage of patients who experienced each influenza-related complication. Influenza-related complications were death, hospitalization, sinusitis, otitis media, bronchitis, and radiologically-confirmed pneumonia that occurred or developed after the initiation of study treatment. Sinusitis, otitis media, bronchitis, and pneumonia were defined according to the following pre-defined diagnostic criteria: • Sinusitis: a purulent nasal discharge; facial pain, pressure sensation, or sensation of fullness; and nasal obstruction, congestion or stuffiness. • Otitis media: pain or fullness in one or more ears; and tympanic membrane bulging or fullness on otoscopy. • Bronchitis: a productive cough that got worse after Day 1. • Pneumonia: confirmed by chest X ray.

Secondary Virology Endpoints	
Time to cessation of viral shedding by virus titer (hours)	The time between the initiation of the study treatment and first time when the virus titer was below the limit of detection.
Time to cessation of viral shedding by RT-PCR (hours)	The time between the initiation of the study treatment and first time when the virus RNA by RT-PCR was below the limit of detection. For the patients with multiple virus types, this endpoint is 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 of detection for all virus types.
Proportion of patients with positive influenza virus titer at each time point (%)	Percentage of patients whose influenza virus titer was not less than the LLOQ among those assessed for influenza virus titer on Days 2, 3, 4, 5, 6, and 9.
Change from baseline in virus titer at each time point ($log_{10}TCID_{50}$/mL)	Change from baseline in influenza virus titer on Days 2, 3, 4, 5, 6, and 9. Baseline was defined as the last value obtained before Visit 1 (predose).

LLOQ = lower limit of quantification; RT-PCR = reverse transcription polymerase chain reaction; $TCID_{50}$ = 50% tissue culture infective dose.

[a] The alleviation of symptoms was defined as the time when all symptoms had been assessed by the patient as 0 (none) or 1 (mild) in the patient eDiary, for a duration of at least 21.5 hours.

[b] The improvement of influenza symptoms was defined as the time when the relevant symptom(s) had been alleviated, maintained, or improved for a duration of at least 21.5 hours.

Other endpoints

The OwH studies and the HR-study had two other endpoints in common, namely drug susceptibility at baseline and treatment-emergent amino acid substitutions in the PA, PB1, and PB2 genes.

Drug susceptibility at baseline

Virus in nasopharyngeal/pharyngeal swabs collected at baseline was propagated in cell cultures to obtain sufficient quantity for phenotypic analysis. Drug susceptibility was evaluated as follows:

- For baloxavir, the 50% effective concentration (EC50) was determined by plaque assay (OwH Phase 2 Study T0821) or Virospot assay (Phase 3 studies T0831 [OwH] and T0832 [HR]) and compared with that of the reference strains (A/Victoria/361/2011 for type A virus and B/Wisconsin/1/2010 for type B virus). The EC50 was defined as the baloxavir concentration required to decrease the number of plaques or immunostained spots formed by viral infection in cell cultures by 50%.
- For oseltamivir acid, the 50% inhibitory concentration (IC50) was determined by NA-star® assay and compared with that of the reference strains (A/Puerto Rico/8/34 for type A virus and B/Lee/40 for type B virus). The IC50 was defined as the oseltamivir acid concentration required to inhibit neuraminidase activity by 50%.

Treatment-emergent amino acid substitutions

To investigate treatment-emergent amino acid substitution in the PA gene after dosing with baloxavir marboxil in the OwH and HR studies, genotypic testing was performed directly on viral RNA isolated from patients who had paired nasopharyngeal/ pharyngeal swab samples at baseline (pre-dose Day 1) and after dosing (last time point based on positive RT-PCR result). No intermediate virus propagation

step was performed in order to avoid introduction of new mutations. In the Phase 3 studies, viral RNA was also isolated for genotypic testing from patients who received placebo. Treatment-emergent amino acid substitution was defined as an amino acid change occurring in the period between baseline (pre-dose Day 1) and the last time point with a positive RT-PCR result.

In the OwH studies only, extensive sequencing of the PB1 and PB2 genes was performed on samples from selected baloxavir marboxil-treated patients:

- T0831 - patients identified as non-responders (based on the criteria in Table 3) who did not exhibit a treatment-emergent change at position 38 in the PA gene.
- T0821 - patients infected with A/H1N1pdm virus who showed evidence of virus titer rebound after Day 6. Patients were identified on a case-by-case basis.

Randomisation/ Blinding (masking)

Please refer to the description of the studies; randomisation and blinding are addressed in the 'Treatment' section

Statistical methods

Intention to treat population

Efficacy was evaluated with the intention-to-treat infected analysis set, ITTI, consisting of randomised, treated patients with confirmed influenza (tested positive on the RT-PCR). Patients not treated or tested negative were excluded from the ITTI analysis set.

The RT-PCR test is taken at visit 1 or before and therefore excluding patients based on the result of the test should not be biased. From the point of view that baloxavir marboxil is only effective against illnesses caused by influenza virus and influenza is assessed pre-treatment it is plausible to perform the analysis on the ITTI to be able to estimate the treatment effect.

Per-protocol population

The Per-protocol Set (PPS) population consisted of randomized patients who were included in the ITTI population and did not meet any of the following conditions:

- Ineligible subjects
- Patients with noncompliance of treatment defined as the patients whose treatment compliance rate was less than 60%.
- Patients with inadequate follow-up defined as the patients had no symptom data after the initial treatment.
- Patients who had taken any prohibited medications
- Patients with incorrect treatment allocation
- Patients with important protocol deviations (TO832 only)

Statistical tests

The analyses for the primary endpoint are controlled at a 5% significance level by hierarchical testing of the primary (baloxavir marboxil vs placebo) and secondary analysis (baloxavir marboxil vs oseltamivir) which is endorsed. Secondary endpoints are not controlled for multiplicity.

Primary endpoint

The primary endpoint was analysed using a stratified Peto-Prentice generalised Wilcoxon model stratified by baseline composite symptom score, region and pre-existing and worsened symptom (T0832 only). Patients' not experiencing alleviation/ improvement of symptoms were censored at last observed timepoint. Patients are expected to become alleviated/improved from symptoms during the trial in all treatment groups (possible difference in treatment will diminish towards the end of the trial). The applicant estimated treatment differences by subtracting the group medians and not by estimating differences in medians which for skewed distributions can result in very different results.

Sensitivity analysis of the primary endpoint was analysed using the stratified Peto-Prentice's generalized Wilcoxon test with baseline composite symptom score, region and Pre-existing and worsened symptom as the stratification factors (for T0832 only) looking into assumptions on analysis set (PP analysis set), censoring based on trial discontinuation (time of and reason for withdrawal) and primary endpoint definition (excluding cough). In addition, the robustness of analysis method was evaluated using a stratified logrank test.

Changes to the statistical analysis plan

The statistical analyses plans for trial T0831 and T0832 were both finalised before unblinding and there were no changes to the pre-specified analyses.

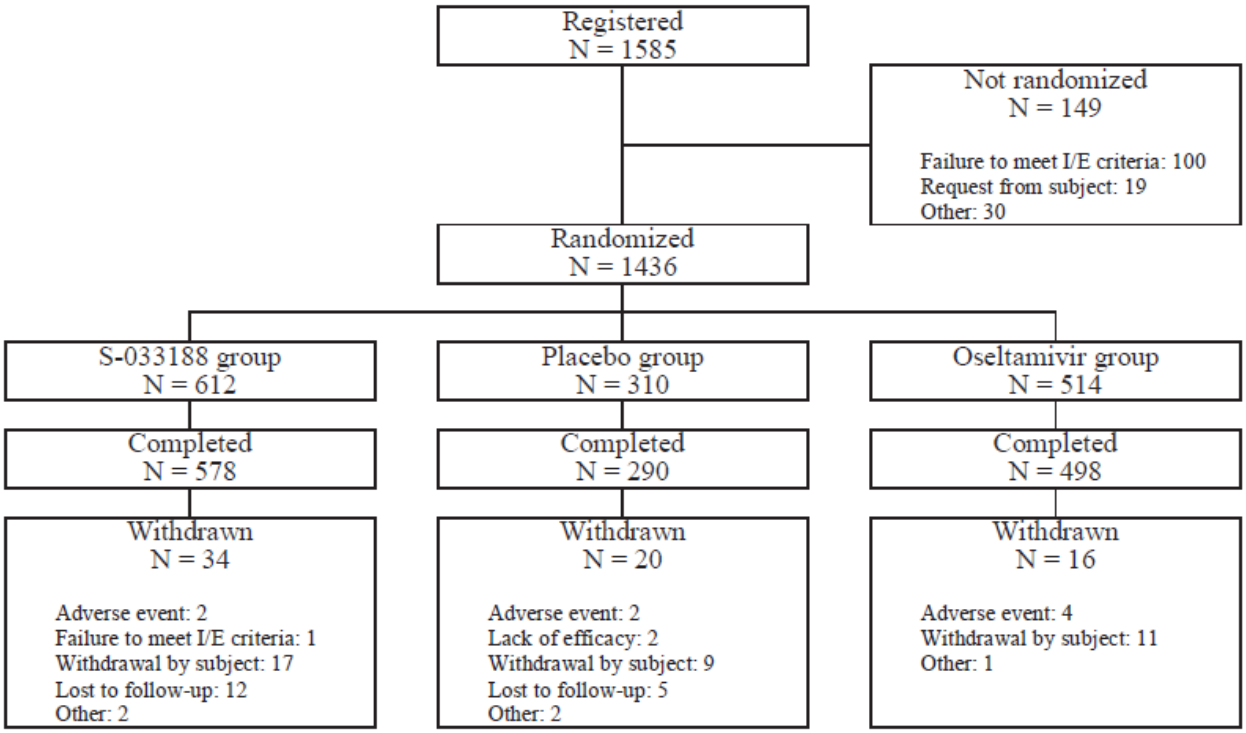
Results

Participant flow

The participants' flow in the OwH population:

A total of 1436 patients were randomized to treatment in Phase 3 OwH Study T0831. Among the 70 randomized patients who did not complete the study, the most common reason for non-completion in all treatment groups was withdrawal of consent (37 patients). Of the 1436 patients randomized, 4 patients received no study drug.

Figure 12 Patient Disposition

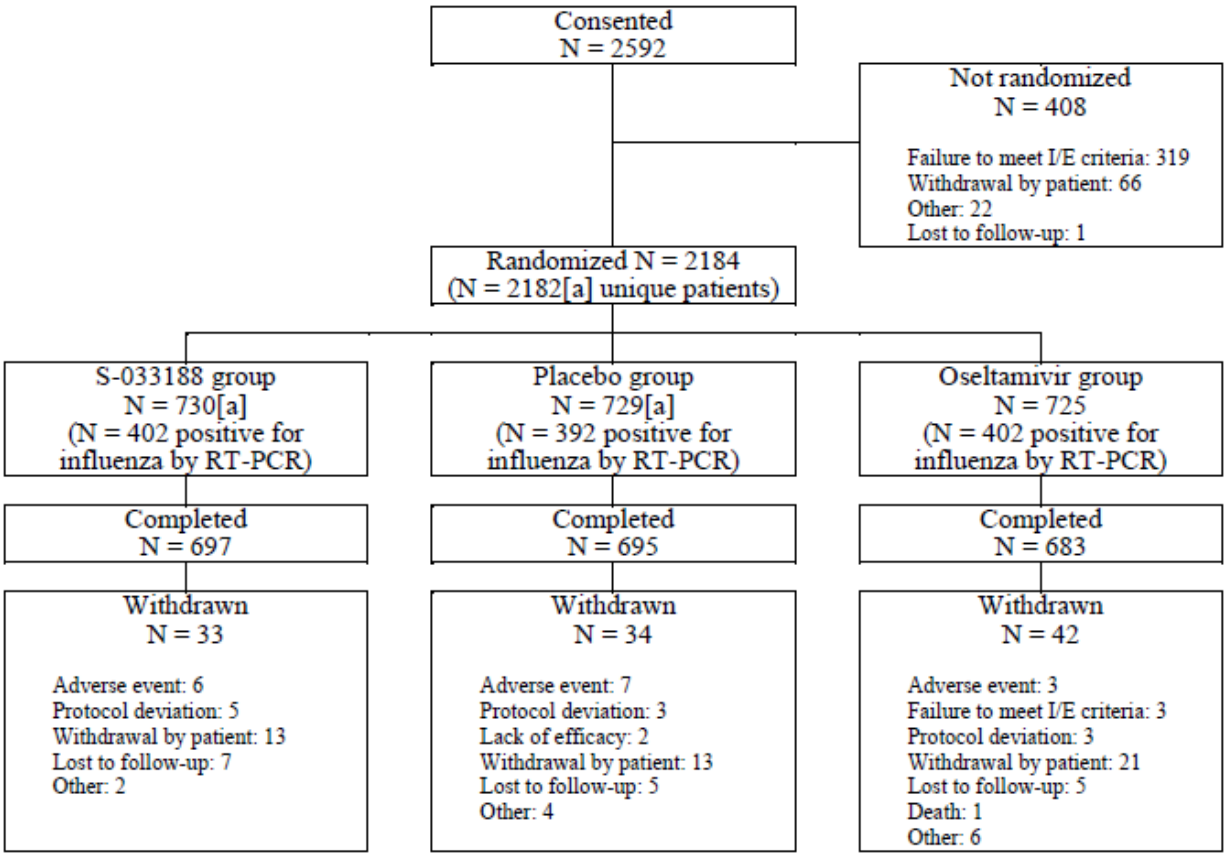


Patient registered doubly was counted only once.
Source: Table 14.1.1

The participants' flow in the HR population:

A total of 2184 patients were randomized to treatment in Study T0832, 2075 patients completed the study. A total of 6 patients received no study drug. Among the 109 randomized patients who did not complete the study, the most common reason for non-completion in all treatment groups was withdrawal of consent (47 patients).

Figure 13 Patient Disposition (All Randomized Patients)



ID – identification ; RT-PCR=reverse transcriptase-polymerase chain reaction

[a] Two patients were each assigned 2 patient IDs with re-assigned ID before dosing; therefore, there were a total of 2182 unique patients (729 patients in the baloxavir marboxil group, 725 patients in the oseltamivir group, and 728 patients in the placebo group)

Baseline data

Demographic data for the otherwise healthy and high-risk populations are summarised together below (note that patients included in the phase II T0821, OwH, are included).

Table 10 Comparison of Demographic and Baseline Characteristics in OwH (Pooled Studies T0821 and T0831) and HR (Study T0832) Patient Populations (ITTI Populations)

	OwH Patients (Pooled OwH Studies T0821 and T0831)		HR Patients (Study T0832)		
	Bxm N = 754	Placebo N = 331	Bxm N = 388	Placebo N = 386	Oseltamivir N = 389
Median age (years)	35.0	34.0	55.0	53.0	53.0
Male, n (%)	416 (55.2%)	181 (54.7%)	193 (49.7%)	180 (46.6%)	191 (49.1%)
Body weight ≥80 kg at BL, n (%)	114 (15.1%)	47 (14.2%)	149 (38.4 %)	154 (39.9%)	156 (40.1%)
Medical history, n (%)	212 (28.1%)	119 (36.0%)	379 (97.7%)	381 (98.7%)	382 (98.2%)
Race, n (%)					
Asian	646 (85.7%)	278 (84.0%)	167 (43.0%)	157 (40.7%)	163 (41.9%)
White	85 (11.3%)	40 (12.1%)	178 (45.9%)	194 (50.3%)	188 (48.3%)
Black or African American	18 (2.4%)	11 (3.3%)	39 (10.1%)	30 (7.8%)	29 (7.5%)
Median composite symptom scores at BL	13.0	13.0	15.0	15.0	14.0
Influenza virus subtype, n (%) [a]					
A/H1N1pdm	205 (27.2%)	76 (23.0%)	28 (7.2%)	17 (4.4%)	35 (9.0%)
A/H3	423 (56.1%)	202 (61.0%)	182 (46.9%)	185 (47.9%)	190 (48.8%)
B	106 (14.1%)	43 (13.0%)	167 (43.0%)	168 (43.5%)	149 (38.3%)
Mixed infection	10 (1.3%)	5 (1.5%)	4 (1.0%)	5 (1.3%)	5 (1.3%)
Other	10 (1.3%)	5 (1.5%)	7 (1.8%)	11 (2.8%)	10 (2.6%)

BL = baseline; Bxm = baloxavir marboxil; HR = high risk; OwH = otherwise healthy.
a Based on RT-PCR.

Numbers analysed

Patients included in the OwH population and HR population are tabulated below.

OwH

Table 11 Efficacy Analysis Populations (All Randomized Patients)

	S-033188 N = 612 n (%)	Placebo N = 310 n (%)	P value [a]
Patients included in ITTI	456 (74.5)	231 (74.5)	1.0000
Patients excluded from ITTI	156 (25.5)	79 (25.5)	
Reason for exclusion			
- Without diagnosis of influenza by RT-PCR	154	78	
- Patients who received no study drug	2	1	
Patients included in PPS	421 (68.8)	210 (67.7)	0.7644
Patients excluded from PPS	191 (31.2)	100 (32.3)	
Reason for exclusion			
- Without diagnosis of influenza by RT-PCR	154	78	
- Patients who received no study drug	2	1	
- Ineligible	17	9	
- Non-compliance of treatment	7	5	
- Inadequate follow-up	1	2	
- Prohibited medication	37	23	

HR

Table 12 Efficacy Analysis Populations (All Randomized Patients)

	S-033188 N = 730 n (%)	Placebo N = 729 n (%)	Oseltamivir N = 725 n (%)	P-value [a] S-033188 vs Placebo	P-value [a] S-033188 vs Oseltamivir
Patients included in ITTI population	388 (53.2)	386 (52.9)	389 (53.7)	0.9582	0.8747
Patients excluded from ITTI population	342 (46.8)	343 (47.1)	336 (46.3)		
Reason for exclusion[b]					
- Patients at sites with GCP noncompliance[c]	41[d]	32[e]	34[f]		
- Without diagnosis of influenza by RT-PCR	328	337	323		
- Patients who received no study drug	2	1	3		
Patients included in PPS population	335 (45.9)	333 (45.7)	332 (45.8)	0.9581	1.0000
Patients excluded from PPS population	395 (54.1)	396 (54.3)	393 (54.2)		
Reason for exclusion[b]					
- Patients at sites with GCP noncompliance[c]	41[d]	32[e]	34[f]		
- Without diagnosis of influenza by RT-PCR	328	337	323		
- Patients who received no study drug	2	1	3		
- Ineligible	27	16	24		
- Noncompliance of treatment	33	32	48		
- Inadequate follow-up	8	4	3		
- Prohibited medication	58	52	57		
- Incorrect treatment allocation	3	1	5		

GCP=Good Clinical Practice; ITTI=Intention-to-Treat infected; PPC=Per-protocol Set; RT-PCR=reverse transcription polymerase chain reaction
[a] Fisher`s exact test.

[b] Patients could have met >1 of the exclusion criteria and therefore may be counted in > 1 category.
[c] 6 Sites
[d] Includes 14 patients who were confirmed positive for influenza infection by RT-PCR and 27 patients who were not confirmed for influenza infection by RT-PCR
[e] Includes 6 patients who were confirmed positive for influenza infection by RT-PCR and 26 patients who were not confirmed positive for influenza infection by RT-PCR
[f] Includes 12 patients who were confirmed positive for influenza infection by RT-PCR and 22 patients who were

According to section 9.8.1 of the CSR, based on results of site audits, critical and major deviations (GCP noncompliance) were found at three sites and the Sponsor decided to close these sites. However, submitted data indicate that the ITTI population eliminated patients enrolled at 7 sites. Patients from all these sites were included in the safety population.
As a result, the data indicate that 107 patients (32-41 per group) were eliminated from the ITTI population due to enrolment at GCP noncompliant sites and this number included 32 (6-14 per group) with influenza confirmed by RT-PCR, i.e., who would otherwise have been eligible for the ITTI population.

Outcomes and estimation

As mentioned in the methods section, the Applicant estimated treatment differences by subtracting the group medians and not by estimating differences in medians which for skewed distributions can result in very different results. Therefore, the Applicant was asked to provide estimates of the treatment differences by applying an estimation method that is concordant with to the primary analysis method e.g. Brookmeyer CI.

Nevertheless, in the evaluation of primary and secondary endpoints below, emphasis is put on whether the recorded times to recovery in the baloxavir marboxil group are all in all shorter than in the placebo and oseltamivir groups.

OwH

Primary endpoint

The primary endpoint was time to alleviation, TTAS. The baloxavir marboxil group is compared first with placebo, subsequently with oseltamivir. The results are given below.

Comparison with placebo:

The time to alleviation, TTAS, was significantly shorter in the baloxavir marboxil group than in the placebo group. This result was reflected by a median time (95% CI) to alleviation in the baloxavir marboxil of 54 hours (50-59 h) as compared to 80 hours (73-87 h) in the placebo group.

The treatment with baloxavir marboxil appeared specifically to influence the period between day 1 and 5 after treatment initiation. I.e. more patients obtained alleviation of symptoms during day 1-5 in the baloxavir marboxil group than in the placebo group. By day 5 (120 hours), an equal proportion of patients in the baloxavir marboxil and the placebo group had recovered (above 80% in each group).

Table 13 OwH Study T0831: Overview of Key Efficacy Results – Time of Event Endpoints (ITTI Population)

Endpoint	Median [95% CI] (Hours)		Median Difference vs. Placebo (Hours) [a]	P-value [b]
	Bxm (All Patients) (N = 456)	Placebo (N = 231)		
Primary Endpoint				
Time to alleviation of symptoms	(n=455) 53.7 [49.5, 58.5]	(n=230) 80.2 [72.6, 87.1]	-26.5 [-35.8, -17.8]	< 0.0001

Table 14 OwH Study T0831: Proportion of Patients Whose Symptoms Had Alleviated at Each Time Point (ITTI Population)

Time Point	n Bxm/ Placebo	Bxm (N = 456) No. (%)	Placebo (N = 231) No. (%)	P-value [a] (vs. Placebo)
12 hours	373/197	36 (9.7%)	16 (8.1%)	0.5973
24 hours	445/218	103 (23.1%)	28 (12.8%)	0.0010
36 hours	361/195	153 (42.4%)	45 (23.1%)	<0.0001
48 hours	444/220	225 (50.7%)	58 (26.4%)	<0.0001
72 hours	431/216	297 (68.9%)	107 (49.5%)	<0.0001
96 hours	429/216	337 (78.6%)	151 (69.9%)	0.0115
120 hours	415/212	355 (85.5%)	173 (81.6%)	0.1298
144 hours	404/199	360 (89.1%)	170 (85.4%)	0.1170
168 hours	403/197	369 (91.6%)	174 (88.3%)	0.0757
192 hours	406/197	369 (90.9%)	180 (91.4%)	0.9453
216 hours	224/111	204 (91.1%)	102 (91.9%)	0.8657

Bxm = baloxavir marboxil.

Percentages are based on n.

[a] P value by Mantel-Haenszel test. Stratification factors: composite symptom scores at baseline and region.

Source: Table 11-29 OwH T0831 CSR.

Comparison with oseltamivir:

Time to alleviation of symptoms was comparable in the baloxavir marboxil and the oseltamivir groups.

Table 15. OwH Study T0831: Overview of Key Efficacy Results – Time to Event Endpoints (ITTI Population, Patents 20 to 64 Years of Age)

Endpoint	Median [95% CI] (Hours)		Median Difference vs. Oseltamivir (Hours) [a]	P-value [b]
	Bxm (N = 376)	Oseltamivir (N = 377)		
Primary Endpoint				
Time to alleviation of symptoms	(n=375) 53.5 [48.0, 58.5]	(n=377) 53.8 [50.2, 56.4]	-0.3 [-6.6, 6.6]	0.7560
Secondary Clinical Endpoints				
Time to alleviation of the 4 systemic symptoms [c]	(n=375) 36.7 [32.0, 40.1]	(n=377) 37.4 [31.5, 42.4]	-0.7	0.4194
Time to alleviation of the 3 respiratory symptoms [d]	(n=375) 46.0 [42.7, 52.0]	(n=377) 44.6 [40.6, 49.5]	1.3	0.4856
Time to alleviation of individual symptoms:				
Cough	(n=250) 38.2 [30.3, 43.4]	(n=262) 31.4 [28.6, 36.8]	6.8	0.6623
Sore throat	(n=211) 32.1 [27.6, 39.8]	(n=198) 30.4 [25.0, 43.9]	1.8	0.8184
Headache	(n=246) 26.9 [24.5, 30.8]	(n=239) 25.6 [21.9, 30.4]	1.3	0.9989
Nasal congestion	(n=217) 33.0 [30.5, 40.4]	(n=230) 31.3 [26.8, 39.8]	1.7	0.3706
Feverishness or chills	(n=337) 21.0 [20.0, 22.0]	(n=341) 21.2 [20.3, 22.0]	-0.1	0.9973

Table 16 OwH Study T0831: Proportion of Patients Whose Symptoms Had Alleviated at Each Time Point (ITTI Population, Patients 20 to 64 Years of Age)

Time Point	n Bxm/ Oseltamivir	Bxm (N = 376) No. (%)	Oseltamivir (N = 377) No. (%)	P-value [a] (vs. Oseltamivir)
12 hours	310/309	27 (8.7%)	15 (4.9%)	0.0458
24 hours	366/365	78 (21.3%)	83 (22.7%)	0.7565
36 hours	299/297	123 (41.1%)	115 (38.7%)	0.3297
48 hours	365/360	186 (51.0%)	196 (54.4%)	0.4442
72 hours	351/359	248 (70.7%)	262 (73.0%)	0.6029
96 hours	351/359	280 (79.8%)	289 (80.5%)	0.9881
120 hours	339/345	292 (86.1%)	300 (87.0%)	0.9257
144 hours	334/334	298 (89.2%)	305 (91.3%)	0.5317
168 hours	336/334	307 (91.4%)	315 (94.3%)	0.2144
192 hours	338/331	307 (90.8%)	316 (95.5%)	0.0413
216 hours	187/188	170 (90.9%)	181 (96.3%)	0.0409

Bxm = baloxavir marboxil.

Percentages are based on n.

[a] P value by Mantel-Haenszel test. Stratification factors: composite symptom scores at baseline and region.

Source: Table 11-29 OwH T0831 CSR.

Secondary endpoints

Secondary clinical endpoints included time to alleviation of 4 systemic symptoms (Headache, feverishness or chills, muscle or joint pain, and fatigue), of 3 respiratory symptoms (Cough, sore throat and nasal congestion), or of individual symptoms (feverishness or chills, muscle or joint pain, fatigue, cough, sore throat, headache, nasal congestion).

All secondary endpoints are considered exploratory as the Applicant did not prioritise these endpoints and as no corrections for multiplicity have been made. The secondary endpoints of the OwH-study are summarised in the table below and presented in detail in the sections below.

Table 17 OwH Study T0831: Overview of Key Efficacy Results – Time to Event Endpoints (ITTI Population)

Endpoint	Median [95% CI] (Hours)			
	Bxm (All Patients) (N = 456)	Placebo (N = 231)	Median Difference vs. Placebo (Hours) [a]	P-value [b]
Secondary Clinical Endpoints				
Time to alleviation of the 4 systemic symptoms [c]	(n=455) 33.8 [31.0, 38.3]	(n=230) 53.5 [45.9, 57.3]	-19.8	<0.0001
Time to alleviation of the 3 respiratory symptoms [d]	(n=455) 46.0 [43.4, 50.6]	(n=230) 69.1 [63.9, 78.1]	-23.1	<0.0001
Time to alleviation of individual symptoms:				
Headache	(n=296) 26.1 [22.9, 29.8]	(n=153) 37.9 [25.8, 42.2]	-11.8	0.0297
Feverishness or chills	(n=408) 20.9 [20.0, 21.9]	(n=214) 25.8 [21.7, 31.5]	-4.9	0.0003
Muscle or joint pain	(n=353) 23.2 [21.4, 26.3]	(n=169) 31.3 [25.5, 39.2]	-8.1	0.0094
Fatigue	(n=361) 25.3 [22.0, 29.2]	(n=188) 40.5 [31.2, 46.8]	-15.3	0.0007
Cough	(n=308) 38.3 [30.3, 43.5]	(n=171) 61.4 [44.8, 69.5]	-23.1	0.0001
Secondary Clinical Endpoints cont.				
Time to alleviation of individual symptoms cont.:				
Nasal congestion	(n=277) 31.8 [29.9, 38.7]	(n=153) 52.5 [41.5, 62.7]	-20.7	0.0027
Sore throat	(n=249) 31.5 [27.3, 39.2]	(n=119) 40.5 [31.8, 48.3]	-9.0	0.0298
Time to resolution of fever	(n=448) 24.5 [22.6, 26.6]	(n=230) 42.0 [37.4, 44.6]	-17.5 [-21.1, -11.9]	<0.0001

Bxm = baloxavir marboxil; CI = confidence interval; ITTI = Intention-to-Treat Infected; RT-PCR = reverse transcriptase-polymerase chain reaction.

a 95% CIs for the median difference are provided where available. Bootstrap estimates.

b P-values based on the stratified generalized Wilcoxon test. Stratification factors: composite symptom scores at baseline and region.

c Headache, feverishness or chills, muscle or joint pain, and fatigue.

d Cough, sore throat and nasal congestion.

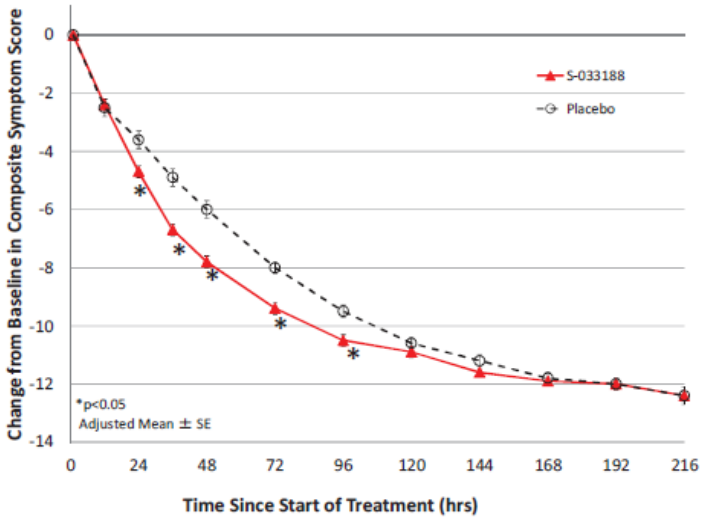
Additional presentation of secondary endpoints and subgroup analyses:

Ancillary analyses

In the patients infected with the predominant type A/H3 virus, the analysis of median TTAS was similar to that for the total ITTI population, with a significant difference for baloxavir vs. placebo. In the very small numbers with type A/H1N1pdm virus, the median TTAS was shorter in the baloxavir group. However, in the small numbers of patients infected with type B virus, the median TTAS was longer in the baloxavir vs. placebo group.

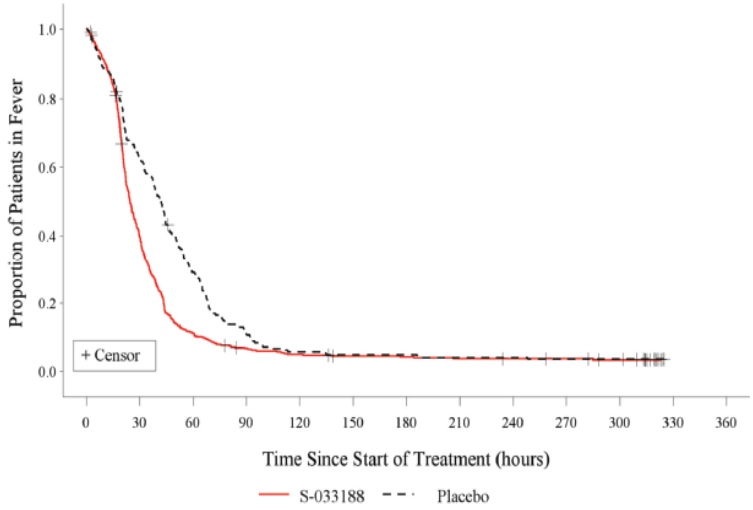
The median time to alleviation of the 4 systemic symptoms was 33.8 h with baloxavir vs. 53.5 h for placebo and 37.4 h for oseltamivir. The median time to alleviation of the 3 respiratory symptoms was 46 h with baloxavir vs. 69.1 h for placebo and 44.6 h for oseltamivir. The least squares mean change from baseline in the composite symptom score was greater with baloxavir vs. placebo from 24-96 h post-dose but there was no obvious difference vs. oseltamivir.

Figure 14 Change from Baseline in Composite Symptom Score (ITTI Population)



The time to resolution of fever was faster with baloxavir vs. placebo but not vs. oseltamivir.

Figure 15 Kaplan-Meier Curve: Time to Resolution of Fever (ITTI Population)



The median time to return to pre-influenza status was 129.2 h for baloxavir vs. 168.8 h for placebo, which was not statistically significant (p=0.0563). There was no difference vs. oseltamivir.

In the ITTI population, 16/456 baloxavir (3.5%) and 10/231 placebo patients (4.3%) experienced influenza-related complications. For the comparison with oseltamivir, the rates were 4.0% vs. 2.4%. The most frequent event was bronchitis (2.0% vs. 3.5% placebo and 1.6% oseltamivir).

Baloxavir gave statistically significant reductions in TTAS vs. placebo:

- In the subgroups with baseline composite symptom scores ≤ 11 (19.1 h; p=0.0078) and ≥ 12 27.0 h; p=<0.0001).
- Regardless of region; actual differences in median TTAS were 31.3 h in Japan/Asia and 30.6 h in N. America.

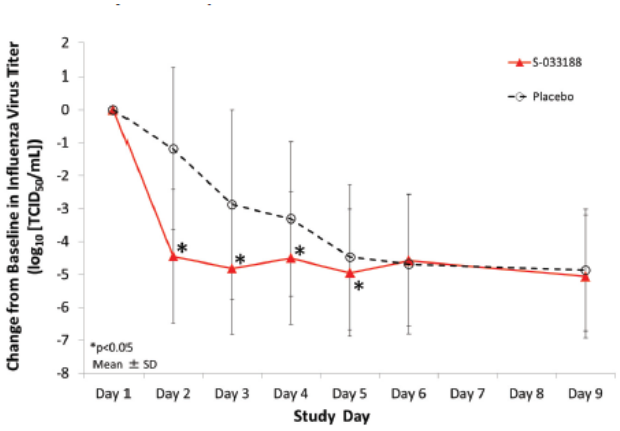
- Regardless of body weight/dose category; actual differences in median TTAS of 28.0 h in those < 80 kg and 18.7 h in those 80+ kg.
- Regardless of the timing of dosing in regard to food; actual differences in medians fell within the range 26.7 h and 29.1 h.
- Regardless of the time elapsed from onset of symptomatic influenza to start of treatment. However, the difference in median TTAS was 32.8 h when treatment started within 24 h compared to only 13.2 h when treatment started between 24 and 48 h.
- In adolescents and adults; the actual difference in median TTAS was greater in the adolescents vs. adults (38.6 h vs. 25.6 h).

For all the above, there were no important differences between baloxavir and oseltamivir.

The proportions with positive influenza virus titres (log_{10} $TCID_{50}$/mL) were statistically significantly lower in the baloxavir vs. placebo group from Days 2 through 5. In parallel with this finding, statistically significant differences in proportions with positive influenza virus titres (log_{10} $TCID_{50}$/mL) favouring baloxavir vs. oseltamivir occurred on Days 2, 3 and 5. Similar results vs. placebo and vs. oseltamivir were obtained in the predominant sub-group infected with type A/H3 virus. In patients infected with type B virus, the proportions with positive titres were lower in the baloxavir vs. placebo group but the differences from Days 2 through 5 were not statistically significant.

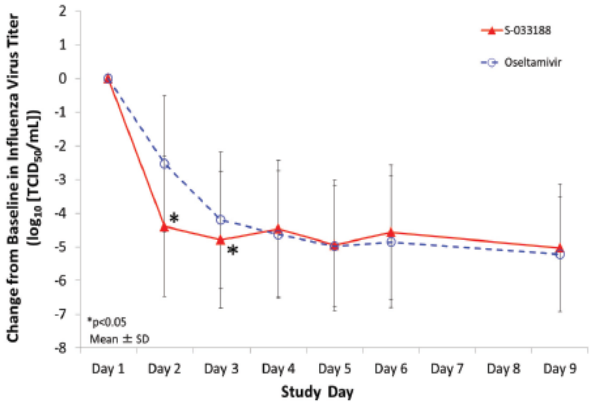
The virus titre was reduced more rapidly in the baloxavir group vs. the placebo group and the mean change from baseline was significantly greater in the baloxavir group from Days 2 through 5.

Figure 16 Change from Baseline in Influenza Virus Titer (ITTI Population)



Compared with the oseltamivir group, the reduction in titre was more rapid with baloxavir with significant differences on Days 2 and 3.

Figure 17 Change from Baseline in Influenza Virus Titer (≥ 20 Years of Age Stratum, ITTI Population)



Results in the sub-group with type A/H3 virus were similar to those in the ITT population. In the subgroup with type B virus, the mean change from baseline in titre was greater for baloxavir vs. placebo and vs. oseltamivir on Days 2 and 3 but not after that.

The median time to cessation of viral shedding determined by virus titre was 24 h for baloxavir vs. 96 h for placebo (p=<0.0001) and 72 h for oseltamivir (p=<0.0001). The same overall pattern was seen for those with type A/H3 virus. In the patients infected with type B virus or with A/H1N1pdm virus, there was a significant difference in time to cessation of shedding for baloxavir vs. placebo and a numerical difference vs. oseltamivir.

Based on the RT-PCR (log_{10} virus particles/mL), there were high rates and little difference between baloxavir vs. placebo groups for the proportions positive for influenza until Day 5 or later. However, the mean change from baseline in amount of viral RNA was statistically significantly greater in the baloxavir vs. placebo group from Days 2 through 9. In the comparison with oseltamivir, the mean change from baseline was statistically significantly greater in the baloxavir group on Days 2, 3 and 5. The same overall pattern was seen for those with type A/H3 virus. In the subgroup with type B virus, the mean change from baseline from Days 2 through 9 was slightly lower for baloxavir vs. placebo. When determined by RT-PCR, time to cessation of shedding was 216 h with baloxavir vs. 240 h with placebo and with oseltamivir, both comparisons reaching statistical significance.

Due to findings in the other Phase 3 treatment study (1602T0832; see below) that arose during a site audit for Study Centre 811, including critical and major deviations, the sponsor (Shionogi) decided to close this site. At time of closure, 10 patients had been enrolled into 1601T0831. At FDA's request, additional efficacy analyses of TTAS and time to cessation of viral shedding by virus titre were conducted after omitting data from Centre 811. These additional results are provided in the CSR; however, removal of the 10 patients did not impact on any study conclusions. For example, in the primary analysis, the difference in median TTAS between baloxavir and placebo was -26.4 h (p<0.0001).

HR

Primary endpoint

The primary endpoint was time to improvement, TTIS.

In the high-risk population, the time to improvement of symptoms was significantly shorter in the baloxavir marboxil group than in the placebo group, thus, the primary endpoint of the study was met. This was reflected by a shorter median time (95% CI) to improvement in the baloxavir marboxil, 73 hours (67-85 hours), as compared to the placebo group, 102 hours (93-113 hours). From day 1 through day 9, the proportion of patients, whose symptoms had improved, was higher in the baloxavir marboxil group as compared to placebo. Thus, in this high-risk population the difference between the groups was sustained throughout the study.

Table 18 HR Study T0832: Overview of Efficacy Results – Time to Event Endpoints (ITTI Population)

	Median [95% CI] (Hours)						
	Bxm (N = 388)	Placebo (N = 386)	Oseltamivir (N = 389)	Median Difference vs. Placebo (Hours) [a]	P-value [b]	Median Difference vs. Oseltamivir (Hours) [a]	P value [b]
Primary Endpoint							
Time to improvement of influenza symptoms	(n = 385) 73.2 [67.2, 85.1]	(n = 385) 102.3 [92.7, 113.1]	(n = 388) 81.0 [69.4, 91.5]	−29.1 [−42.8, −14.6]	<0.0001	−7.7 [−22.7, 7.9]	0.8347

A 95% CIs for the median difference are provided where available. Bootstrap estimates.

b P-values based on the stratified generalized Wilcoxon test: Stratification factors: region, composite symptom scores at baseline, and pre-existing and worsened symptom.

Table 19 HR T0832 Study: Proportion of Patients Whose Symptoms Had Improved at Each Time Point (ITTI Population)

Time Point	Treatment Group			P-value (vs. Placebo)	P-value (vs. Oseltamivir)
	Bxm (N = 388) No. (%)	Placebo (N = 386) No. (%)	Oseltamivir (N = 389) No. (%)		
12 hours	n = 297	n = 303	n=307		
	27 (9.1%)	26 (8.6%)	25 (8.1%)	0.7698	0.5777
24 hours	n = 357	n = 365	n = 367		
	67 (18.8%)	52 (14.2%)	72 (19.6%)	0.1112	0.6483
36 hours	n = 304	n = 304	n = 300		
	103 (33.9%)	64 (21.1%)	93 (31.0%)	0.0004	0.5625
48 hours	n = 363	n = 368	n = 363		
	138 (38.0%)	106 (28.8%)	145 (39.9%)	0.0072	0.6234
72 hours	n = 359	n = 359	n = 350		
	201 (56.0%)	150 (41.8%)	196 (56.0%)	0.0002	0.9547
96 hours	n = 352	n = 341	n = 350		
	232 (65.9%)	182 (53.4%)	214 (61.1%)	0.0012	0.1860
120 hours	n = 358	n = 342	n = 333		
	259 (72.3%)	221 (64.6%)	241 (72.4%)	0.0274	0.9635
144 hours	n = 347	n = 342	n = 330		
	271 (78.1%)	238 (69.6%)	256 (77.6%)	0.0081	0.7425
168 hours	n = 342	n = 326	n = 333		
	274 (80.1%)	237 (72.7%)	265 (79.6%)	0.0209	0.7448
192 hours	n = 341	n = 337	n = 327		
	285 (83.6%)	263 (78.0%)	280 (85.6%)	0.0644	0.4931
216 hours	n = 197	n = 174	n = 178		
	169 (85.8%)	137 (78.7%)	157 (88.2%)	0.0708	0.4024

Bxm = baloxavir marboxil.

[a] P-value by Mantel-Haenszel test. Stratification factors: region, composite symptom scores at baseline, and preexisting and worsened symptoms.

Source: Table 11-29 in HR T0832 CSR.

Secondary endpoints, ancillary results

Below, the secondary clinical and virological endpoints are summarised in tables. Thereafter, the secondary endpoints and subgroup analyses are presented in detail by graphs and description.

Secondary endpoints, clinical

Secondary clinical endpoints included time to improvement of 4 systemic symptoms (Headache, feverishness or chills, muscle or joint pain, and fatigue), of 3 respiratory symptoms (Cough, sore

throat and nasal congestion), or of individual symptoms (feverishness or chills, muscle or joint pain, fatigue, cough, sore throat, headache, nasal congestion). Furthermore, the proportion of patients, who experienced influenza-related complications was evaluated as a secondary clinical endpoint.

The times to improvement of different combinations or single influenza related symptoms are shown below:

Table 20 HR Study T0832: Overview of Efficacy Results – Time of Event Endpoints (ITTI Population)

	Median [95% CI] (Hours)						
	Bxm (N = 388)	Placebo (N = 386)	Oseltamivir (N = 389)	Median Difference vs. Placebo (Hours) [a]	P-value [b]	Median Difference vs. Oseltamivir (Hours) [a]	P value [b]
Secondary Clinical Endpoints							
Time to alleviation of symptoms	(n = 385)	(n = 385)	(n = 388)				
	77.0 [68.4, 88.3]	102.8 [93.2, 113.4]	85.6 [71.5, 94.8]	−25.8	<0.0001	−8.6	0.9127
Time to improvement of the 4 systemic symptoms [c]	(n = 385)	(n = 385)	(n = 388)				
	51.7 [45.0, 55.4]	66.8 [60.1, 70.0]	49.4 [44.2, 56.8]	−15.1	0.0013	2.3	0.8498
Time to improvement of the 3 respiratory symptoms [d]	(n = 385)	(n = 385)	(n = 388)				
	63.6 [55.9, 68.2]	87.8 [76.3, 98.9]	62.1 [54.0, 69.1]	−24.1	0.0001	1.5	0.9237
Time to improvement of individual symptoms:							
Cough	(n = 314)	(n = 312)	(n = 317)				
	47.3 [42.8, 52.7]	70.4 [56.5, 79.5]	47.5 [43.0, 55.4]	−23.1	0.0009	−0.2	0.4074
Sore throat	(n = 249)	(n = 243)	(n = 226)				
	40.2 [32.4, 46.1]	46.5 [39.0, 53.5]	39.3 [30.1, 42.8]	−6.3	0.2496	0.9	0.2963
Headache	(n = 251)	(n = 258)	(n = 266)				
	33.4 [29.1, 40.5]	43.9 [33.6, 46.2]	31.3 [28.6, 37.0]	−10.6	0.0390	2.0	0.7877
Nasal congestion	(n = 240)	(n = 267)	(n = 257)				
	45.6 [37.4, 54.3]	57.7 [48.7, 67.8]	44.0 [36.4, 50.3]	−12.1	0.0017	1.5	0.8119
Secondary Clinical Endpoints continued							
Time to improvement of individual symptoms cont.:							
Feverishness or chills	(n = 348)	(n = 347)	(n = 347)				
	28.3 [24.2, 31.8]	31.9 [28.6, 41.2]	29.1 [25.2, 30.8]	−3.6	0.0070	−0.7	0.9191
Muscle or joint pain	(n = 311)	(n = 302)	(n = 312)				
	37.2 [31.5, 41.6]	44.9 [42.2, 52.0]	33.2 [30.2, 39.5]	−7.7	0.0232	4.0	0.5436
Fatigue	(n = 332)	(n = 330)	(n = 325)				
	41.3 [35.2, 46.1]	48.8 [42.7, 55.4]	43.2 [39.3, 47.4]	−7.5	0.0207	−1.9	0.3710
Time to resolution of fever	(n = 380)	(n = 385)	(n = 383)				
	30.8 [28.2, 35.4]	50.7 [44.6, 58.8]	34.3 [30.0, 38.9]	−19.8 [−28.8, −12.5]	<0.0001	−3.5 [−9.1, 2.7]	0.2425

Bxm = baloxavir marboxil; CI = confidence interval; ITTI = Intention-to-Treat Infected; RT-PCR = reverse transcriptase-polymerase chain reaction

a 95% CIs for the median difference are provided where available. Bootstrap estimates.

b P-values based on the stratified generalized Wilcoxon test: Stratification factors: region, composite symptom scores at baseline, and pre-existing and worsened symptom.

c Headache, feverishness or chills, muscle or joint pain, and fatigue.

d Cough, sore throat and nasal congestion.

The proportion of patients, who experienced influenza-related complications, is shown below:

Table 21 HR T0832 Study: Overview of Efficacy Results – Additional Secondary Clinical Endpoints (ITTI Population)

Endpoint	Treatment Group			P-value [a] (vs. Placebo)	P-value [a] (vs. Oseltamivir)
	Bxm (N = 388) No. (%)	Placebo (N = 386) No. (%)	Oseltamivir (N = 389) No. (%)		
Proportion of patients with any systemic antibiotics for infections secondary to influenza infection					
	13 (3.4%)	29 (7.5%)	15 (3.9%)	0.0112	0.8478
Proportion of patients with influenza-related complications					
Any	11 (2.8%)	40 (10.4%)	18 (4.6%)	<0.0001	0.2558
Death	0	0	1 (0.3%)	-	1.0000
Hospitalization	3 (0.8%)	5 (1.3%)	4 (1.0%)	0.5047	1.0000
Sinusitis	1 (0.3%)	8 (2.1%)	2 (0.5%)	0.0205	1.0000
Otitis media	0	3 (0.8%)	1 (0.3%)	0.1235	1.0000
Bronchitis	7 (1.8%)	23 (6.0%)	9 (2.3%)	0.0027	0.8016
Pneumonia	0	3 (0.8%)	2 (0.5%)	0.1235	0.4994

Bxm = baloxavir marboxil.

[a] Fisher's exact test.

Secondary endpoints, virologic

Cessation of viral shedding either by virus titre or by RT-PCR was evaluated as multiple secondary endpoints, some of which are shown in Table 27:

Table 22 HR T0832 Study: Overview of Efficacy Results – Additional Secondary Virologic Endpoints (ITTI Population)

Endpoint	Treatment Group			P-value (vs. Placebo)	P-value (vs. Oseltamivir)
	Bxm (N = 355)	Placebo (N = 353)	Oseltamivir (N = 360)		
Proportion of patients with positive influenza virus titer at each time point (n, %) [a]					
Day 2	n = 336 197 (58.6%)	n = 344 299 (86.9%)	n = 344 299 (86.9%)	<0.0001	<0.0001
Day 3	n = 338 107 (31.7%)	n = 337 245 (72.7%)	n = 340 204 (60.0%)	<0.0001	<0.0001
Day 4 [c]	n = 130 24 (18.5%)	n = 122 61 (50.0%)	n = 124 41 (33.1%)	<0.0001	0.0044
Day 5	n = 326 52 (16.0%)	n = 322 99 (30.7%)	n = 333 68 (20.4%)	<0.0001	0.1146
Day 6 [c]	n = 115 5 (4.3%)	n = 106 17 (16.0%)	n = 105 12 (11.4%)	0.0046	0.0441
Day 9	n = 327 9 (2.8%)	n = 321 17 (5.3%)	n = 322 3 (0.9%)	0.0929	0.0907
Mean change from BL in virus titer at each time point (log_{10} [$TCID_{50}$/mL]) [b]					
Day 2	n = 336 –3.36	n = 343 –1.25	n = 344 –1.76	<0.0001	<0.0001
Day 3	n = 338 –3.92	n = 336 –2.99	n = 340 –3.26	<0.0001	0.0024
Day 4 [c]	n = 130 –3.99	n = 121 –3.79	n = 124 –3.75	0.9127	0.5361
Day 5	n = 326 –4.32	n = 321 –4.38	n = 333 –4.41	0.5739	0.5466
Day 6 [c]	n = 115 –4.07	n = 105 –4.68	n = 105 –4.39	0.0543	0.4677
Day 9	n = 327 –4.53	n = 320 –4.91	n = 322 –4.78	0.0266	0.1281

a Mantel-Haenszel test for analysis of the proportion of patients with positive influenza virus titer.

b van Elteren test for analysis of the change from baseline in virus titer.

c Days 4 and 6 were optional visits.

Stratification factors: composite symptom scores at baseline and region.

Subset of patients with a positive influenza virus titer at baseline is included in this analysis.

Day 1 was defined as the date of first dosing.

Ancillary analyses

Baloxavir significantly shorted the median TTAS vs. placebo but there was no statistically significant difference vs. oseltamivir.

Table 23 Time to Alleviation of Symptoms (ITTI Population)

	S-033188	Placebo	Oseltamivir
Summary statistics			
- n	385	385	388
- Median (hours)	77.0	102.8	85.6
- 95% CI (hours)	68.4, 88.3	93.2, 113.4	71.5, 94.8
Comparison with Placebo			
- Median difference (hours)	-25.8	---	---
- P-value derived from stratified generalized Wilcoxon test [a]	<.0001	---	---
Comparison with Oseltamivir			
- Median difference (hours)	-8.6	---	---
- P-value derived from stratified generalized Wilcoxon test [a]	0.9127	---	---

CI = confidence interval; ITTI = Intention-to-Treat Infected

[a] Stratification factors: region, composite symptom scores at baseline, and preexisting and worsened symptom.

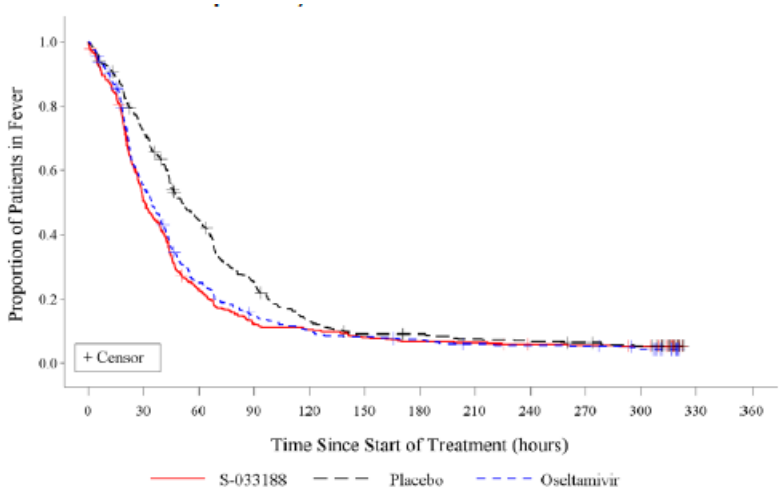
Patients who do not experience alleviation of symptoms were treated as censored at the last observation time point.

The TTIS by viral type indicated that the results for baloxavir vs. placebo in subgroups with A/H3 and B were very similar to those of the primary analysis. Whilst there was no difference vs. oseltamivir for A/H3, baloxavir gave a statistically significantly shorter TTIS vs. oseltamivir in those with type B, reflecting a longer median TTIS for oseltamivir against type B compared to type A/H3. Results for baloxavir and oseltamivir were similar in the small numbers with A/H1N1pdm and both gave much shorter median TTIS values vs. placebo.

The proportion of patients whose influenza symptoms improved was statistically significantly higher for baloxavir vs. placebo from 36-168 h post-dose but the difference narrowed over time, such that rates at 168 h were 80.1% in the baloxavir group vs. 72.7% in the placebo group (p = 0.0209). There were no statistically significant differences over time between baloxavir and oseltamivir.

There were statistically significant reductions in the time to improvement of the 4 systemic symptoms and 3 respiratory symptoms for baloxavir vs. placebo but no differences vs. oseltamivir.
The time to resolution of fever was shorter for baloxavir vs. placebo with no difference vs. oseltamivir.

Figure 18 Kaplan -Meier Curve: Time to Resolution of Fever (ITTI Population)



A statistically significantly lower proportion in the baloxavir group (2.8%) vs. placebo group (10.4%) had influenza-related complications.

Table 24 Incidences of Influenza-related Complications (ITTI Population)

		S-033188 N = 388	Placebo N = 386	Oseltamivir N = 389
Patients with any complications	Proportion	2.8% (11/388)	10.4% (40/386)	4.6% (18/389)
	95% CI (%)	1.4, 5.0	7.5, 13.8	2.8, 7.2
	Fisher's exact test			
	- P-value (vs Placebo)	<.0001	---	---
	- P-value (vs Oseltamivir)	0.2558	---	---
Death	Proportion	0.0% (0/388)	0.0% (0/386)	0.3% (1/389)
	95% CI (%)	0.0, 0.9	0.0, 1.0	0.0, 1.4
	Fisher's exact test			
	- P-value (vs Placebo)	---	---	---
	- P-value (vs Oseltamivir)	1.0000	---	---
Hospitalization	Proportion	0.8% (3/388)	1.3% (5/386)	1.0% (4/389)
	95% CI (%)	0.2, 2.2	0.4, 3.0	0.3, 2.6
	Fisher's exact test			
	- P-value (vs Placebo)	0.5047	---	---
	- P-value (vs Oseltamivir)	1.0000	---	---
Sinusitis	Proportion	0.3% (1/388)	2.1% (8/386)	0.5% (2/389)
	95% CI (%)	0.0, 1.4	0.9, 4.0	0.1, 1.8
	Fisher's exact test			
	- P-value (vs Placebo)	0.0205	---	---
	- P-value (vs Oseltamivir)	1.0000	---	---
Otitis media	Proportion	0.0% (0/388)	0.8% (3/386)	0.3% (1/389)
	95% CI (%)	0.0, 0.9	0.2, 2.3	0.0, 1.4
	Fisher's exact test			
	- P-value (vs Placebo)	0.1235	---	---
	- P-value (vs Oseltamivir)	1.0000	---	---
Bronchitis	Proportion	1.8% (7/388)	6.0% (23/386)	2.3% (9/389)
	95% CI (%)	0.7, 3.7	3.8, 8.8	1.1, 4.3
	Fisher's exact test			
	- P-value (vs Placebo)	0.0027	---	---
	- P-value (vs Oseltamivir)	0.8016	---	---
Pneumonia	Proportion	0.0% (0/388)	0.8% (3/386)	0.5% (2/389)
	95% CI (%)	0.0, 0.9	0.2, 2.3	0.1, 1.8
	Fisher's exact test			
	- P-value (vs Placebo)	0.1235	---	---

This overall difference for baloxavir vs. placebo in rates of complications was driven by rates for sinusitis (0.3% vs. 2.1%) and bronchitis (1.8% vs. 6.0%), with no important differences in rates of death, hospitalisation, otitis media or pneumonia. In the oseltamivir group 4.6% had complications with no statistically significant difference vs. baloxavir. The median time to return to pre-influenza status was not statistically significantly different between treatment groups although there was a numerical reduction for baloxavir vs. placebo of 23.4 h and medians were the same for baloxavir and oseltamivir.

Baloxavir gave statistically significant reductions in TTIS vs. placebo:

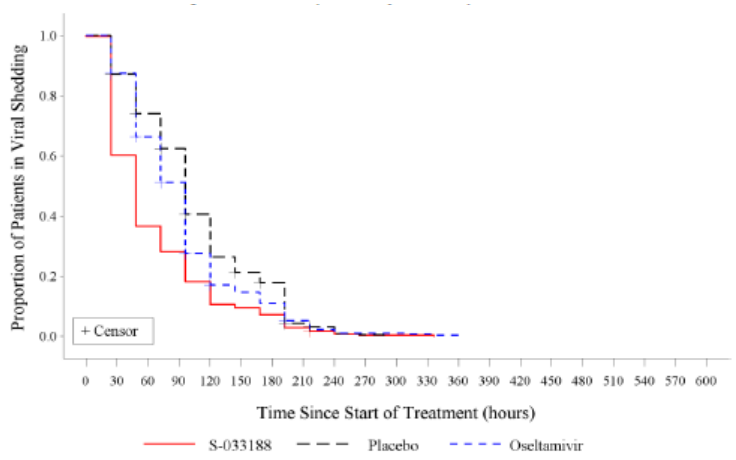
- In subgroups with baseline composite symptom score ≤ 14 (p-value = 0.0048) or ≥ 15 (p = 0.0039)
- In Asia and in North America/Europe
- In patients with or without pre-existing and worsened symptoms
- In the subgroup with asthma or chronic lung disease (74.6 h vs. 110.2 h; p-value = 0.0038) but not in subgroups with heart disease, endocrine disorders, metabolic disorders, aged ≥ 65 years or morbid obesity
- In each of the subgroups < 80 kg or ≥ 80 kg (p-values = 0.0348 and 0.0013)
- In patients who were dosed within 2 to 4 hours before or after food intake but did not reach significance in those dosed > 4 h or < 2 h before or after food
- In patients who were treated within 0 to 12 h (p = 0.0167), > 12 to 24 h (p = 0.0167) or > 24 to 36 h (p = 0.0004) from onset of symptoms, with a numerical reduction in median TTIS for patients who were treated within > 36 to 48 h

There were no significant differences for baloxavir vs. oseltamivir in these subgroups.

In the small subgroup aged < 18 years the oseltamivir group showed a reduction in median TTIS with no difference between baloxavir and placebo. The overall study results were driven by the large age group of adults aged <65 years. In the subgroup aged 65 to 74 years the median TTIS was similar among the 3 treatment groups but in those 75+ years there was a statistically significant difference for baloxavir vs. placebo and a comparable reduction in TTIS with baloxavir and oseltamivir.

The median time to cessation of viral shedding determined by virus titre (log_{10} $TCID_{50}$/mL) was 48.0 h for baloxavir vs. 96.0 h for both placebo and oseltamivir group. Similar results were observed in the supplemental analysis including PCR positive patients enrolled at Sites 206 and 225.

Figure 19 Kaplan-Meier Curve: Time to Cessation of Viral Shedding by Virus Titer (ITTI Population)



ITTI = Intention-to-Treat Infected

The median time to cessation of viral shedding determined by virus titre was statistically significantly shorter for baloxavir vs. placebo and vs. oseltamivir in the subgroups with A/H3 or B virus. However, within the baloxavir group the median time to cessation of viral shedding was longer for type B virus (72.0 h) than for type A/H3 virus (24.0 h).

The difference between baloxavir vs. placebo for median time to cessation of viral shedding determined by virus titre was statistically significant in subgroups with asthma or chronic lung disease, endocrine or metabolic disorders, heart disease, aged ≥ 65 years and with morbid obesity. There were also statistically significant differences for baloxavir vs. oseltamivir except in those with metabolic disorders.

The proportion of patients with positive influenza virus titres was statistically significantly lower in the baloxavir vs. placebo group from Days 2-6 and vs. oseltamivir from Days 2-4. In those with A/H3, statistically significant differences were seen for baloxavir vs. placebo on Days 2-5 and vs. oseltamivir on Days 2-3. In those with type B virus, statistically significant differences were seen for baloxavir vs. placebo on Days 2-4 and 6 and vs. oseltamivir on Days 2-4.

The mean change from baseline in the influenza virus titre was statistically significantly greater for baloxavir vs. placebo and vs. oseltamivir on Days 2-3. Similar findings applied in subgroups with A/H3 or type B virus. There were statistically significant differences in the mean AUC titre adjusted by baseline for baloxavir vs. placebo but not vs. oseltamivir.

Based on RT-PCR, the median time to cessation of viral shedding determined by RT-PCR was statistically significantly shorter for baloxavir vs. placebo but not vs. oseltamivir. Similar findings applied in those with A/H3 but the time to cessation of viral shedding was 240 h in each group for those with type B. The difference for baloxavir vs. placebo was also statistically significant for those with heart disease, aged ≥ 65 years or with morbid obesity but not in other subgroups and there were no differences vs. oseltamivir.

The proportion of patients with positive influenza virus RNA determined by RT-PCR was lower in the baloxavir vs. placebo group on Days 2 through 6 and Day 9, but the differences were statistically significant only on Day 9 ($p = 0.0017$). The differences in the proportion of patients with positive influenza virus RNA were very similar between the baloxavir and oseltamivir groups at each time point and were not statistically significant at any time point.

The GM ratios of influenza antibody titres were not different between the baloxavir, oseltamivir or placebo groups.

Gene substitutions during treatment

In the OwH and HR clinical studies, treatment-emergent PA/I38T substitution and additional I38 amino acid substitutions (PA/I38M, PA/I38F, and PA/I38N), collectively referred to as PA/I38X, were observed, and reverse genetic analysis demonstrated that these substitutions were associated with reduced baloxavir susceptibility.

In all three studies, the position in the PA gene most frequently affected by treatment-emergent amino acid substitutions was position 38. Overall, in patients treated with baloxavir marboxil, treatment-emergent amino acid changes at position 38 of the PA gene were detected in virus collected from 36/370 (9.7%) patients in OwH Phase 3 Study T0831, 4/182 (2.2%) patients in OwH Phase 2 Study T0821, and 15/290 (5.2%) patients in HR Phase 3 Study T0832; the denominators include baloxavir marboxil-treated patients with evaluable paired sequence samples collected at baseline and at the last time point with a positive RT-PCR result. No amino acid substitutions were found at position 38 in virus collected from placebo-treated patients.

In OwH studies T0831 and T0821, treatment-emergent amino acid substitutions in the PA gene exhibiting reduced susceptibility to baloxavir in recombinant strains were PA/I38T (A/H3N2 [fold change 48.90 - 56.59], A/H1N1 [fold change 27.24], B [fold change 5.76]), PA/I38F (A/H1N1 [fold change 10.61]), and PA/I38M (A/H3N2 [fold change 13.77]). In HR Study T0832, treatment-emergent amino acid substitutions in the PA gene exhibiting reduced susceptibility to baloxavir in recombinant strains were PA/I38T (A/H3N2 [fold change 20.33], B), PA/I38M (A/H3N2), and PA/I38N (A/H1N1 [fold change 3.66]). For all other treatment-emergent amino acid substitutions detected in these clinical studies, including all non-I38 substitutions, the fold change was <10 for type A virus and <5 for type B virus. Thus, overall, treatment-emergent amino acid substitutions in the PA gene exhibiting reduced susceptibility to baloxavir in the OwH and HR studies were PA/I38T, F, M, and N.

Clinical Impact of PA/I38 Substitutions

To assess the potential clinical impact of PA/I38X substitutions, primary efficacy endpoints were analysed for patients with and without I38 substitutions from OwH Phase 3 Study T0831 and HR Phase 3 Study T0832.

In between 2 and 10 % of the influenza infected OwH or HR patients, who were treated with baloxavir marboxil, changes in the viral PA gene were observed. No changes to the PA gene were found in the patients, who received placebo, or patients exposed to oseltamivir. Similarly, changes in the PB1 and PB2 genes were observed in a smaller number of virus samples from patients treated with baloxavir marboxil in the OwH-studies (data not shown)

The time to alleviation / improvement in patients with substitutions is shown below:

Table 25 Time to Alleviation of Symptoms and Time to Improvement of Symptoms by I38 Substitution (Studies T0831 and T0832, ITTI Population)

	OwH Study T0831			HR Study T0832		
	Baloxavir marboxil			Baloxavir marboxil		
	PA/I38X Substitution (N = 36)	No PA/I38X Substitution (N = 334)	Placebo (N = 231)	PA/I38X Substitution (N = 15)	No PA/I38X Substitution (N=275)	Placebo (N = 385)
TTAS (hours)						
Median [95% CI]	63.1 [52.2, 87.7]	51.0 [46.0, 56.0]	80.2 [72.6, 87.1]	65.2 [28.3, 87.7]	77.8 [68.4, 91.0]	102.8 [93.2, 113.4]
Median difference (hours)						
vs. No I38X substitution	12.0	-	-	-12.5	-	-
vs. placebo	-17.2	-29.2	-	-37.6	-25.0	-
TTIS (hours)						
Median [95% CI]	-	-	-	65.2 [28.3, 87.7]	73.2 [65.4, 86.9]	102.3 [92.7, 113.1]
Median difference (hours)						
vs. No I38X substitution	-	-	-	-8.0	-	-
vs. placebo	-	-	-	-37.1	-29.1	-

TTAS = time to alleviation of symptoms; TTIS = time to improvement of symptoms.

The analysis includes the subset of patients whose TTAS/TTIS was not missing. Patients who did not experience alleviation/improvement of symptoms were censored at the last observation time point.

For the baloxavir marboxil groups, the analysis includes the subset of patients with paired sequencing at baseline and post-treatment.Gene

Summary of main studies

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).

Summary of results in otherwise healthy patients (phase III)

Summary of Efficacy for Trial 1601T0831

Title: A Phase 3, Multicenter, Randomized, Double-blind Study of a Single Dose of S-033188 (Baloxavir Marboxil) Compared with Placebo or Oseltamivir 75 mg Twice Daily for 5 Days in Otherwise Healthy Patients with Influenza			
Study identifier	1601T0831 (T0831), CV40815, CAPSTONE-1		
Design	A randomized, double-blind, multicenter, parallel-group, placebo- and active-controlled study designed to evaluate the efficacy and safety of a single dose of baloxavir marboxil in otherwise healthy adult and adolescent patients with uncomplicated influenza. Eligible patients 20 to 64 years of age randomised in a ratio of 2:2:1 to receive a single weight-based dose of baloxavir marboxil, 75 mg BID of oseltamivir for 5 days, or placebo. Eligible patients 12 to 19 years of age were randomised in a ratio of 2:1 to receive a single weight-based dose of baloxavir marboxil or placebo. There was a maximum of 9 visits including 2 optional visits during a period to assess the efficacy and safety: 14 days for efficacy and 22 days for safety.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		22 days not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Baloxavir marboxil		• Baloxavir marboxil ○ 40-mg (weight < 80 kg) or ○ 80-mg (weight ≥ 80 kg). • 1 day duration N = 612 (plus oseltamivir matching placebo for patients aged 20-64 years; 5 days duration)
	Oseltamivir		• Oseltamivir 75-mg twice daily • 5 days duration N = 514 (Note: this treatment group only contains patients aged 20-64 years) (plus baloxavir matching placebo; 1 day duration)
	Placebo		• Baloxavir matching placebo ○ 1 day duration • Oseltamivir matching placebo (subgroup of patients aged 20-64 years) ○ 5 days duration N = 310
Endpoints and definitions	Primary endpoint	TTAS	Time to alleviation of symptoms.

			Defined as the time between the initiation of the study treatment and the alleviation of influenza symptoms. The alleviation of influenza symptoms was defined as the time when all of 7 influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) had been assessed by the patient as 0 (None) or 1 (Mild) in the patient eDiary, for a duration of at least 21.5 hours (24 hours − 10%).
	Secondary endpoint	TTRoF	Time to resolution of fever. Defined as the time between the initiation of the study treatment and the resolution of fever. The resolution of fever was defined as the time when the patient's self-measured axillary temperature became less than 37ºC and was maintained at less than 37ºC for a duration of at least 12 hours.
	Secondary endpoint	TTCVS-vt	Time to cessation of viral shedding by virus titer. Defined as the time between the initiation of the study treatment and first time when the virus titer was below the limit of detection.
	Secondary endpoint	TTCVS-rtpcr	Time to cessation of viral shedding by RT-PCR.Defined as the time between the initiation of the study treatment and the first time when virus RNA by RT-PCR was below the limit of detection.
Database lock	7th July 2017		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Intention-to-treat infected population (ITTI) Efficacy was assessed over 14 days The ITTI population consisted of the patients who received the study drug with a confirmed diagnosis of influenza. Confirmation of influenza was based on the results of RT-PCR on Day 1. The population was analyzed according to the treatment to which the patients were randomized.				
Descriptive statistics and estimate variability	Treatment group	Baloxavir marboxil	Placebo	Oseltamivir	Baloxavir marboxil (20-64 subgroup)
	Number of subject	455	230	377	375
	TTAS (Median (hours))	53.7	80.2	53.8	53.5
	95% confidence interval (hours)	49.5, 58.5	72.6, 87.1	50.2, 56.4	48.0, 58.5
Effect estimate per comparison	Primary endpoint - TTAS	Comparison groups	Baloxavir marboxil and Placebo		
		Difference in median	-26.5		

		time (hours)			
		95% confidence interval for median difference using bootstrap estimates (hours)	-35.8, -17.8		
		P-value using Stratified Generalized Wilcoxon test	<0.0001		
	Primary endpoint – TTAS (secondary analysis)	Comparison groups	Baloxavir marboxil (20-64 subgroup) and Oseltamivir		
		Difference in median time (hours)	-0.3		
		95% confidence interval for median difference using bootstrap estimates (hours)	-6.6, 6.6		
		P-value using Stratified Generalized Wilcoxon test	0.7560		
Notes	The stratification factors used in these analyses were: composite symptom score at baseline (≤ 11 or ≥ 12) and region (Japan/Asia or Rest of the world). The primary (baloxavir marboxil vs placebo) and secondary (baloxavir marboxil vs oseltamivir) comparisons were conducted in a hierarchical manner so as to maintain control of overall Type I error.				
Analysis description	**Secondary analysis (pre-specified)**				
Analysis population and time point description	Intention-to-treat infected Efficacy was assessed over 14 days The ITTI population consisted of the patients who received the study drug with a confirmed diagnosis of influenza. Confirmation of influenza was based on the results of RT-PCR on Day 1. The population was analyzed according to the treatment to which the patients were randomized.				
Descriptive statistics and estimate variability	Treatment group	Baloxavir marboxil	Placebo	Oseltamivir	Baloxavir marboxil (20-64 subgroup)
	Number of subject	448	230	374	369
	TTRoF (Median (hours))	24.5	42.0	24.0	24.4
	95% confidence interval (hours)	22.6, 26.6	37.4, 44.6	22.1, 25.9	22.2, 26.5
Effect estimate per comparison	Secondary endpoint - TTRoF	Comparison groups	Baloxavir marboxil and Placebo		
		Difference in median time (hours)	-17.5		

		95% confidence interval for median difference using bootstrap estimates (hours)			-21.1, -11.9
		P-value using Stratified Generalized Wilcoxon test			<0.0001
	Secondary endpoint - TTRoF	Comparison groups			Baloxavir marboxil (20-64 years subgroup) and Oseltamivir
		Difference in median time (hours)			0.5
		95% confidence interval for median difference using bootstrap estimates (hours)			-2.8, 3.4
		P-value using Stratified Generalized Wilcoxon test			0.9225
Notes	The stratification factors used in the analyses were: composite symptom score at baseline (≤ 11 or ≥ 12) and region (Japan/Asia or Rest of World). Analyses were not adjusted for type I error control.				
Analysis description	**Secondary analysis (pre-specified)**				
Analysis population and time point description	Intention-to-treat infected Efficacy was assessed over 14 days The ITTI population consisted of the patients who received the study drug with a confirmed diagnosis of influenza. Confirmation of influenza was based on the results of RT-PCR on Day 1. The population was analyzed according to the treatment to which the patients were randomized.				
Descriptive statistics and estimate variability	Treatment group	Baloxavir marboxil	Placebo	Oseltamivir	Baloxavir marboxil (20-64 subgroup)
	Number of subject	426	209	357	351
	TTCVS-vt (Median (hours))	24.0	96.0	72.0	24.0
	95% confidence interval (hours)	24.0, 48.0	not available	72.0, 96.0	24.0, 48.0
Effect estimate per comparison	Secondary endpoint – TTCVS-vt	Comparison groups		Baloxavir marboxil and Placebo	
		Difference in median time (hours)		-72.0	
		95% confidence interval for median difference using bootstrap		-72.0, -48.0	

		estimates (hours)			
		P-value using Stratified Generalized Wilcoxon test	<0.0001		
	Secondary endpoint – TTCVS-vt	Comparison groups	Baloxavir marboxil (20-64 subgroup) and Oseltamivir		
		Difference in median time (hours)	-48.0		
		95% confidence interval for median difference using bootstrap estimates (hours)	-72.0, -24.0		
		P-value using Stratified Generalized Wilcoxon test	<0.0001		
Notes	The stratification factors used in the analyses were: composite symptom score at baseline (≤ 11 or ≥ 12) and region (Japan/Asia or Rest of World). Analyses were not adjusted for type I error control.				
Analysis description	**Secondary analysis (pre-specified)**				
Analysis population and time point description	Intention-to-treat infected Efficacy was assessed over 14 days The ITTI population consisted of the patients who received the study drug with a confirmed diagnosis of influenza. Confirmation of influenza was based on the results of RT-PCR on Day 1. The population was analyzed according to the treatment to which the patients were randomized.				
Descriptive statistics and estimate variability	Treatment group	Baloxavir marboxil	Placebo	Oseltamivir	Baloxavir marboxil (20-64 subgroup)
	Number of subject	455	230	375	375
	TTCVS-rtpcr (Median (hours))	216.0	240.0	240.0	216.0
	95% confidence interval (hours)	216.0, 240.0	240.0, 336.0	216.0, 240.0	192.0, 240.0
Effect estimate per comparison	Secondary endpoint – TTCVS-rtpcr	Comparison groups	Baloxavir marboxil and Placebo		
		Difference in median time (hours)	-24.0		
		95% confidence interval for median difference using bootstrap estimates (hours)	-120.0, 0.0		
		P-value using Stratified Generalized Wilcoxon test	0.0020		

	Secondary endpoint – TTCVS-rtpcr	Comparison groups	Baloxavir marboxil (20-64 subgroup) and Oseltamivir
		Difference in median time (hours)	-24.0
		95% confidence interval for median difference using bootstrap estimates (hours)	-48.0, 24.0
		P-value using Stratified Generalized Wilcoxon test	0.0102
Notes	The stratification factors used in the analyses were: composite symptom score at baseline (≤ 11 or ≥ 12) and region (Japan/Asia or Rest of World). Analyses were not adjusted for type I error control.		

Summary of results in high-risk patients (phase III)

Summary of Efficacy for Trial 1602T0832

Title: A Phase 3, Multicenter, Randomized, Double-blind Study of a Single Dose of S-033188 Compared with Placebo or Oseltamivir 75 mg Twice Daily for 5 Days in Patients with Influenza at High Risk of Influenza Complications		
Study identifier	1602T0832 (T0832), CV40818, EudraCT 2016-002688-32, CAPSTONE-2	
Design	A randomized, double-blind, multicenter, parallel-group, placebo-, and active-controlled study designed to evaluate the efficacy and safety of a single oral dose of baloxavir marboxil (S-033188) (40 or 80 mg depending on patient's body weight and administered within 48 hours of symptom onset) in patients ≥ 12 years of age with influenza A and/or B infection at high risk of developing influenza complications. Eligible patients were randomized in a 1:1:1 ratio to receive a single, weight-based oral dose of baloxavir marboxil, oseltamivir (75 mg BID for 5 days), or placebo. There was a maximum of 9 visits, including 2 optional visits, during a 22-day period to assess the efficacy and safety.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	22 days not applicable not applicable
Hypothesis	Superiority	
Treatments groups	Baloxavir marboxil	• Baloxavir marboxil ○ 40-mg (weight < 80 kg) or 80-mg (weight ≥ 80 kg). • 1 day duration • n = 729 (plus oseltamivir matching placebo; 5 days duration)
	Placebo	• Baloxavir matching placebo ○ 1 day duration • Oseltamivir matching placebo ○ 5 days duration

			• n = 728
	Oseltamivir		• Oseltamivir 75-mg twice daily • 5 days duration • n = 725 (plus baloxavir matching placebo; 1 day duration)
Endpoints and definitions	Primary endpoint	TTIS	Time to improvement of influenza symptoms, defined as the time from the start of study treatment to the improvement of influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue). The improvement of influenza symptoms was defined as the time when all of a patient's influenza symptoms had been alleviated, maintained, or improved for a duration of at least 21.5 hours (24 hours − 10%) as follows: • Preexisting symptoms that were judged by the patient to be worse at baseline must have improved at least 1 score from baseline severity • Preexisting symptoms that were judged by the patient to NOT be worse at baseline must have maintained baseline severity • For new symptoms at baseline, alleviation, which meant the symptom score was none or mild, of symptoms must have been achieved
	Secondary endpoint	TTAS	Time to alleviation of symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue), defined as the time between the initiation of the study treatment and the alleviation of influenza symptoms, defined as the time when all 7 influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) had been assessed by the patient as 0 (none) or 1 (mild) in the patient eDiary, for a duration of at least 21.5 hours (24 hours −10%).
	Secondary endpoint	TTRoF	Time to resolution of fever. Defined as the time between the initiation of the study treatment and the resolution of fever. The resolution of fever was defined as the time when the patient's self-measured axillary temperature became less than 37ºC and was maintained for at least 12 hours.
	Secondary endpoint	TTCVS-vt	Time to cessation of viral shedding by virus titer (TTCVS-vt). Defined as the time between the initiation of the study treatment and first time when the virus titer was below the limit of detection.
	Secondary endpoint	TTCVS-rtpcr	Time to cessation of viral shedding by RT-PCR (TTCVS-rtpcr). Defined as the time between the initiation of the study treatment and the first time when virus RNA by RT-PCR was below the limit of detection.

	Secondary endpoint	IRC rate	Incidence of influenza-related complications (death, hospitalization, sinusitis, bronchitis, otitis media, and radiologically confirmed pneumonia), defined as the percentage of patients in the analysis population who experienced each influenza-related complication (any influenza-related complication, death, hospitalization, sinusitis, otitis media, bronchitis, or radiologically confirmed pneumonia) as an AE that developed after the initiation of the study treatment.
	Secondary endpoint	Proportion requiring antibiotics	Proportion of patients requiring systemic antibiotics for infections secondary to influenza infection, defined as the percentage of patients who took antibiotics for any of the predefined complications (sinusitis, otitis media, bronchitis, and pneumonia).
Database lock	25th June 2018		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intention-to-treat Infected (ITTI) population Efficacy was assessed for 14 days The ITTI population consisted of all patients who received the study drug with a confirmed diagnosis of influenza virus infection and were enrolled at sites with GCP compliance. Confirmation of influenza virus infection was based on the results of RT-PCR on Day 1. The population was analyzed according to the treatment to which the patients were randomized.			
Descriptive statistics and estimate variability	Treatment group	Baloxavir marboxil	Placebo	Oseltamivir
	Number of subject	385	385	388
	TTIS (Median (hours))	73.2	102.3	81.0
	95% confidence interval (hours)	67.2, 85.1	92.7, 113.1	69.4, 91.5
Effect estimate per comparison	Primary endpoint - TTIS	Comparison groups	Baloxavir marboxil and Placebo	
		Difference in median time (hours)	-29.1	
		95% confidence interval for median difference using bootstrap estimates (hours)	-42.8, -14.6	
		P-value using Stratified Generalized Wilcoxon test	<0.0001	
	Primary endpoint – TTIS	Comparison groups	Baloxavir marboxil and Oseltamivir	
		Difference in median time (hours)	-7.7	
		95% confidence interval for median difference using bootstrap estimates (hours)	-22.7, 7.9	

		P-value using Stratified Generalized Wilcoxon test	0.8347
Notes	The stratification factors used in the analyses were: region (Asia, North America/Europe, Southern Hemisphere), composite symptom scores at baseline (≤ 14 or ≥ 15) and preexisting and worsened symptoms (yes or no). The primary endpoint was first compared between the baloxavir marboxil and placebo groups (primary analysis). Together with the primary efficacy analysis, the comparison between the baloxavir marboxil and the oseltamivir groups (secondary analysis) was conducted. The secondary analysis was only performed if a statistically significant difference was observed in the primary analysis, in order to maintain control of overall type I error. During the study it was determined that two siteswould be closed due to GCP noncompliance and all patients were excluded from the ITTI population. Therefore, a supplemental analysis of the ITTI population including PCR positive patients enrolled at the two closed sites was performed. The median time to improvement of symptoms was significantly reduced in the baloxavir marboxil group (73.0 hours) compared with the placebo group (102.4 hours) (generalized Wilcoxon test, p-value < 0.0001; log-rank test p-value = 0.0003). There was no significant difference in the median time to improvement of symptoms between the baloxavir marboxil group and the oseltamivir (generalized Wilcoxon test, p-value = 0.6784; log-rank test p-value = 0.7136).		
Analysis description	**Secondary analysis (pre-specified)**		
Analysis population and time point description	Intention-to-treat infected Efficacy assessed over 14 days The ITTI population consisted of all patients who received the study drug with a confirmed diagnosis of influenza virus infection and were enrolled at sites with GCP compliance. Confirmation of influenza virus infection was based on the results of RT-PCR on Day 1. The population was analyzed according to the treatment to which the patients were randomized.		
Descriptive statistics and estimate variability	Treatment group	Baloxavir marboxil	Placebo	Oseltamivir
	Number of subject	385	385	388
	TTAS (Median (hours))	77.0	102.8	85.6
	95% confidence interval (hours)	68.4, 88.3	93.2, 113.4	71.5, 94.8
Effect estimate per comparison	Secondary endpoint - TTAS	Comparison groups	Baloxavir marboxil and Placebo	
		Difference in median time (hours)	-25.8	
		Variability statistic	not reported	
		P-value using Stratified Generalized Wilcoxon test	<0.0001	
	Secondary endpoint - TTAS	Comparison groups	Baloxavir marboxil and Oseltamivir	
		Difference in median time (hours)	-8.6	
		Variability statistic	not reported	
		P-value using Stratified Generalized Wilcoxon test	0.9127	

Notes	The stratification factors used in the analyses were: region (Asia, North America/Europe, Southern Hemisphere), composite symptom score at baseline (≤ 14 or ≥ 15) and preexisting and worsened symptoms (yes or no). Multiplicity relating to multiple items or time points for the secondary endpoints was not considered.			
Analysis description	**Secondary analysis (pre-specified)**			
Analysis population and time point description	Intention-to-treat infected Efficacy assessed over 22 days The ITTI population consisted of all patients who received the study drug with a confirmed diagnosis of influenza virus infection and were enrolled at sites with GCP compliance. Confirmation of influenza virus infection was based on the results of RT-PCR on Day 1. The population was analyzed according to the treatment to which the patients were randomized.			
Descriptive statistics and estimate variability	Treatment group	Baloxavir marboxil	Placebo	Oseltamivir
	Number of subject	380	385	383
	TTRoF (Median (hours))	30.8	50.7	34.3
	95% confidence interval (hours)	28.2, 35.4	44.6, 58.8	30.0, 38.9
Effect estimate per comparison	Secondary endpoint - TTRoF	Comparison groups	Baloxavir marboxil and Placebo	
		Difference in median time (hours)	-19.8	
		95% confidence interval for median difference using bootstrap estimates (hours)	-28.8, -12.5	
		P-value using Stratified Generalized Wilcoxon test	<0.0001	
	Secondary endpoint - TTRoF	Comparison groups	Baloxavir marboxil and Oseltamivir	
		Difference in median time (hours)	-3.5	
		95% confidence interval for median difference using bootstrap estimates (hours)	-9.1, 2.7	
		P-value using Stratified Generalized Wilcoxon test	0.2425	
Notes	The stratification factors used in the tests were: region (Asia, North America/Europe, Southern Hemisphere), composite symptom scores at baseline (≤ 14 or ≥ 15) and preexisting and worsened symptoms (yes or no). Multiplicity relating to multiple items or time points for the secondary endpoints was not considered.			
Analysis description	**Secondary analysis (pre-specified)**			

<table>
<tr><td>Analysis population and time point description</td><td colspan="4">Intention-to-treat infected
Efficacy was assessed over 22 days
The ITTI population consisted of all patients who received the study drug with a confirmed diagnosis of influenza virus infection and were enrolled at sites with GCP compliance. Confirmation of influenza virus infection was based on the results of RT-PCR on Day 1. The population was analyzed according to the treatment to which the patients were randomized.</td></tr>
<tr><td rowspan="4">Descriptive statistics and estimate variability</td><td>Treatment group</td><td>Baloxavir marboxil</td><td>Placebo</td><td>Oseltamivir</td></tr>
<tr><td>Number of subject</td><td>352</td><td>352</td><td>356</td></tr>
<tr><td>TTCVS-vt (Median (hours))</td><td>48.0</td><td>96.0</td><td>96.0</td></tr>
<tr><td>95% confidence interval (hours)</td><td>not available</td><td>not available</td><td>72.0, 96.0</td></tr>
<tr><td rowspan="9">Effect estimate per comparison</td><td rowspan="4">Secondary endpoint – TTCVS-vt</td><td colspan="2">Comparison groups</td><td>Baloxavir marboxil and Placebo</td></tr>
<tr><td colspan="2">Difference in median time (hours)</td><td>-48.0</td></tr>
<tr><td colspan="2">95% confidence interval for median difference using bootstrap estimates (hours)</td><td>-48.0, -48.0</td></tr>
<tr><td colspan="2">P-value using Stratified Generalized Wilcoxon test</td><td><0.0001</td></tr>
<tr><td rowspan="4">Secondary endpoint – TTCVS-vt</td><td colspan="2">Comparison groups</td><td>Baloxavir marboxil and Oseltamivir</td></tr>
<tr><td colspan="2">Difference in median time (hours)</td><td>-48.0</td></tr>
<tr><td colspan="2">95% confidence interval
for median difference using bootstrap estimates (hours)</td><td>-48.0, -24.0</td></tr>
<tr><td colspan="2">P-value using Stratified Generalized Wilcoxon test</td><td><0.0001</td></tr>
<tr><td>Notes</td><td colspan="4">The stratification factors used in the analyses were: region (Asia, North America/Europe, Southern Hemisphere), composite symptom score at baseline (≤ 14 or ≥ 15) and preexisting and worsened symptoms (yes or no).
Multiplicity relating to multiple items or time points for the secondary endpoints was not considered.
Similar results were observed in the supplemental analysis of the ITTI population including PCR positive patients enrolled at two sites.</td></tr>
<tr><td>Analysis description</td><td colspan="4">Secondary analysis (pre-specified)</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="4">Intention-to-treat infected
Efficacy was assessed over 22 days
The ITTI population consisted of all patients who received the study drug with a confirmed diagnosis of influenza virus infection and were enrolled at sites with GCP compliance. Confirmation of influenza virus infection was based on the results of RT-</td></tr>
</table>

	PCR on Day 1. The population was analyzed according to the treatment to which the patients were randomized.			
Descriptive statistics and estimate variability	Treatment group	Baloxavir marboxil	Placebo	Oseltamivir
	Number of subject	385	385	384
	TTCVS-rtpcr (Median (hours))	216.0	240.0	216.0
	95% confidence interval (hours)	192.0, 240.0	216.0, 312.0	216.0, 240.0
Effect estimate per comparison	Secondary endpoint – TTCVS-rtpcr	Comparison groups	Baloxavir marboxil and Placebo	
		Difference in median time (hours)	-24.0	
		95% confidence interval for median difference using bootstrap estimates (hours)	-96.0, 0.0	
		P-value using Stratified Generalized Wilcoxon test	0.0006	
	Secondary endpoint – TTCVS-rtpcr	Comparison groups	Baloxavir marboxil and Oseltamivir	
		Difference in median time (hours)	0.0	
		95% confidence interval for median difference using bootstrap estimates (hours)	-48.0, 24.0	
		P-value using Stratified Generalized Wilcoxon test	0.2370	
Notes	The stratification factors used in the analyses were: region (Asia, North America/Europe, Southern Hemisphere), composite symptom score at baseline (≤ 14 or ≥ 15) and preexisting and worsened symptoms (yes or no). Multiplicity relating to multiple items or time points for the secondary endpoints was not considered.			
Analysis description	**Secondary analysis (pre-specified)**			
Analysis population and time point description	Intention-to-treat infected Efficacy was assessed over 22 days The ITTI population consisted of all patients who received the study drug with a confirmed diagnosis of influenza virus infection and were enrolled at sites with GCP compliance. Confirmation of influenza virus infection was based on the results of RT-PCR on Day 1. The population was analyzed according to the treatment to which the patients were randomized.			
Descriptive statistics and estimate variability	Treatment group	Baloxavir marboxil	Placebo	Oseltamivir
	Number of subject	388	386	389
	IRC rate (Proportion)	2.8% (11/388)	10.4% (40/386)	4.6% (18/389)

	95% confidence interval (%)	1.4, 5.0	7.5, 13.8	2.8, 7.2

Effect estimate per comparison	Secondary endpoint – IRC rate	Comparison groups	Baloxavir marboxil and Placebo
		Test Statistic	not reported
		Variability Statistic	not reported
		P-value using Fisher's exact test	<0.0001
	Secondary endpoint – IRC rate	Comparison groups	Baloxavir marboxil and Oseltamivir
		test statistic	not reported
		variability statistic	not reported
		P-value using Fisher's exact test	0.2558
Notes	Multiplicity relating to multiple items or time points for the secondary endpoints was not considered.		
Analysis description	**Secondary analysis (pre-specified)**		
Analysis population and time point description	Intention-to-treat infected Efficacy was assessed over 22 days The ITTI population consisted of all patients who received the study drug with a confirmed diagnosis of influenza virus infection and were enrolled at sites with GCP compliance. Confirmation of influenza virus infection was based on the results of RT-PCR on Day 1. The population was analyzed according to the treatment to which the patients were randomized.		

Descriptive statistics and estimate variability	Treatment group	Baloxavir marboxil	Placebo	Oseltamivir
	Number of subject	388	386	389
	Proportion requiring antibiotics	3.4% (13/388)	7.5% (29/386)	3.9% (15/389)
	95% confidence interval (%)	1.8, 5.7	5.1, 10.6	2.2, 6.3

Effect estimate per comparison	Secondary endpoint – Proportion requiring antibiotics	Comparison groups	Baloxavir marboxil and Placebo
		test statistic	not reported
		variability statistic	not reported
		P-value using Fisher's exact test	0.0112
	Secondary endpoint – Proportion requiring antibiotics	Comparison groups	Baloxavir marboxil and Oseltamivir
		test statistic	not reported
		variability statistic	not reported
		P-value using Fisher's exact test	0.8478
Notes	Multiplicity relating to multiple items or time points for the secondary endpoints was not considered.		

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

Clinical studies in special populations

The Applicant has not presented studies in patients with renal or hepatic impairment. Paediatric studies with regard to treatment of influenza have not been presented either. In the high-risk group, the median age was 55 years, 53 years, and 53 years in the baloxavir marboxil, placebo, and oseltamivir groups, respectively. There were 29%, 27% and 27% patients aged ≥ 65 years in the three groups. As age ≥ 65 years is a high-risk factor, the results in elderly are not presented separately.

Supportive study

The phase II dose-finding study, T0821, in otherwise healthy patients supports the phase III studies. A summary of numbers analysed and the time to alleviation in the T0821 study is presented below. The shorter time to alleviation in the baloxavir marboxil group as compared to placebo was confirmed.

Numbers analysed:

Table 26 Efficacy Analysis Population (All Randomized Patients)

	S-033188 10 mg N=100 n (%)	S-033188 20 mg N=100 n (%)	S-033188 40 mg N=100 n (%)	Placebo N=100 n (%)	P-value[a]
Patients included in ITTI	100 (100.0)	100 (100.0)	100 (100.0)	100 (100.0)	---
Patients excluded from ITTI	0	0	0	0	
Patients included in PPS	89 (89.0)	92 (92.0)	96 (96.0)	91 (91.0)	0.2987
Patients excluded from PPS	11 (11.0)	8 (8.0)	4 (4.0)	9 (9.0)	
Reason for exclusion					
- Ineligible	1 (1.0)	2 (2.0)	1 (1.0)	0	
- Non-compliance of treatment	9 (9.0)	4 (4.0)	3 (3.0)	7 (7.0)	
- Insufficient follow-up	1 (1.0)	2 (2.0)	0	2 (2.0)	

a Fisher's exact test.

Time to alleviation:

Table 27 Analysis of Time of Alleviation of Symptoms (ITTI)

	S-033188 10 mg	S-033188 20 mg	S-033188 40 mg	Placebo
Summary statistics				
- n	100	100	100	100
- Median (hrs)	54.2	51.0	49.5	77.7
- 95% confidence interval (hrs)	47.7, 66.8	44.5, 62.4	44.5, 64.4	67.6, 88.7
- Difference (vs Placebo) (hrs)	-23.4	-26.6	-28.2	---
Stratified Generalized Wilcoxon test vs placebo[a]				
- P-value	0.0085	0.0182	0.0046	---
Cox proportional hazards model vs placebo[b]				
- Hazard ratio	0.758	0.810	0.817	---
- 95% confidence interval	0.571, 1.007	0.608, 1.078	0.614, 1.087	---
- P-value	0.0561	0.1488	0.1650	---

a Stratified factors: smoking habit, composite symptom scores at baseline.
b Covariates: smoking habit, composite symptom scores at baseline.

2.5.2. Clinical efficacy in the post-exposure prophylaxis (PEP) indication

2.5.2.1. Dose response

The baloxavir marboxil single dose administrations used in study T0834 are the approved doses used for treatment of influenza virus infection outside EU. The doses have been found to have an acceptable safety profile. Dosing recommendations include dosing in children < 12 years of age.

2.5.2.2. Main study

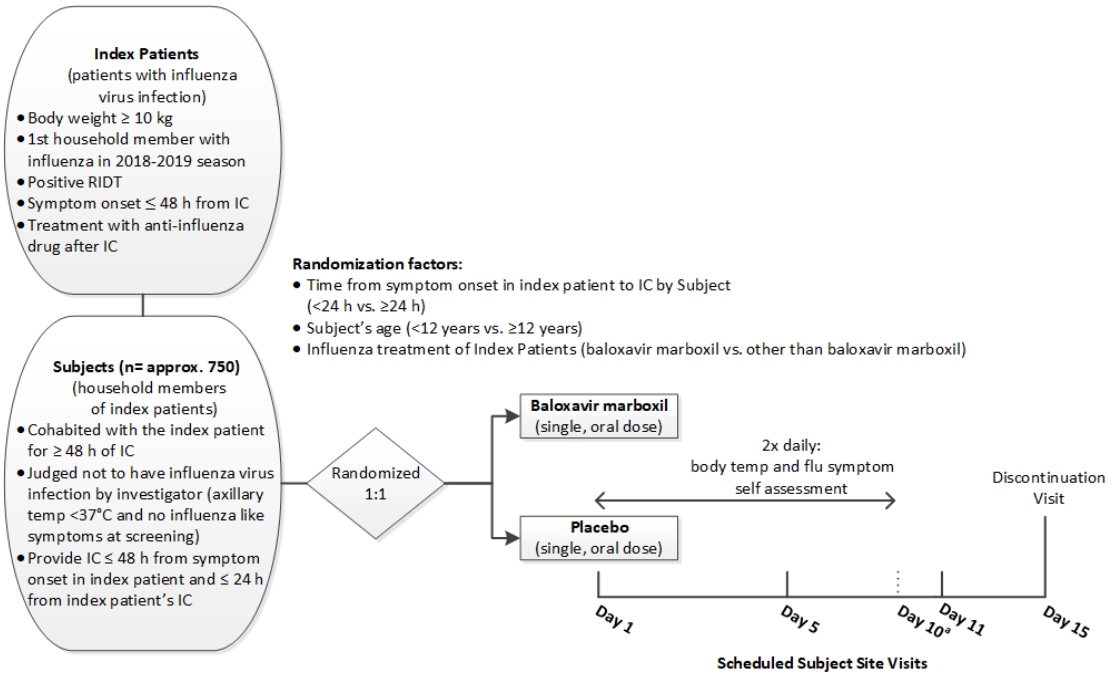
The efficacy of Post-exposure prophylaxis (PEP) treatment with baloxavir marboxil in household members of index patients with confirmed influenza was investigated in study T0834.

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 (BLOCKSTONE)

Methods

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 in household members (subjects) of index patients with confirmed influenza. The study was conducted in the 2018-2019 N. hemisphere winter season and involved 52 study sites, all of which were located in Japan.

Overview of Post-Exposure Prophylaxis Study T0834 Design



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.

Study Participants

Main inclusion criteria

Index patients:

- The first patient (any age, but > 10 kg) in a household with influenza virus infection in the 2018-2019 influenza season (November 2018 to April 2019).
- Influenza diagnosed with a positive rapid influenza diagnostic test by nasopharyngeal (if difficult, nasal or throat) swabs.
- Onset of symptoms within 48 hours at the time of informed consent (defined as the time when body temperature first rose to 37.5°C or higher).
- Were to receive any treatment with anti-influenza drugs after informed consent was obtained
- Body weight of at least 10 kg

Subjects:

- Adults and children who had lived with the index patient for 48 hours or more prior to the time of informed consent.
- Judged not to have influenza virus infection at inclusion
- 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

Main exclusion criteria

Subjects:

- Previously diagnosed with influenza during the 2018-2019 influenza season
- Lived with household member(s) other than index patient with influenza symptoms
- underlying diseases requiring systemic (oral or injectable), or nasal treatment of antipyretics/analgesics, corticosteroids, or immunosuppressive agents.
- Anti-influenza treatment within 30 days prior to screening.
- Pregnant or lactating women.

Treatments

Baloxavir marboxil 20-mg tablets, granules, or matching placebo were orally administered to subjects as a single dose on Day 1 (see Table 9-1). Subjects were randomised 1:1

Table 28 Study Drug Administration by Treatment Group

Subjects ≥ 12 years of age at Screening

Subject's body weight at Screening	Dose	Baloxavir marboxil group	Placebo group
Weight < 80 kg	40 mg	2 baloxavir marboxil 20-mg tablets	2 placebo tablets
Weight ≥ 80 kg	80 mg	4 baloxavir marboxil 20-mg tablets	4 placebo tablets

Subjects < 12 years of age at Screening

Subject's body weight at Screening	Dose	Baloxavir marboxil group	Placebo group
Weight < 10 kg	1 mg/kg	Baloxavir marboxil 2% granules 1 mg/kg (50 mg/kg[a])	Placebo granules (50 mg/kg[a])
Weight 10 to < 20 kg	10 mg	Baloxavir marboxil 2% granules 10 mg (0.5 g[a] [1 packet])	1 placebo granules packet (0.5 g[a])
Weight 20 to < 40 kg	20 mg	1 baloxavir marboxil 20-mg tablet	1 placebo tablet
Weight ≥ 40 kg	40 mg	2 baloxavir marboxil 20-mg tablets	2 placebo tablets

a: Amount of drug/placebo granules

The use of antipyretics/analgesics, anti-influenza drugs, systemic corticosteroids, immunosuppressive agents, influenza vaccines and other study drugs including over-the-counter drugs with equivalent efficacy was prohibited from the time of informed consent until completion of assessments on Day 11.

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 (hereinafter referred to as "subjects") of influenza-infected patients (hereinafter referred to as "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 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

Using an electronic thermometer, axillary temperature was measured twice daily and recorded in the subject diary (ePRO system) from pre-dose on Day 1 until Day 10. Subjects aged ≥ 12 years self-assessed the 7 symptoms associated with influenza on a 4-point rating scale. For subjects aged < 12 years, the subject's guardian assessed 2 symptoms (cough, nasal discharge/nasal congestion) on the same 4-point rating scale. Assessments were performed twice daily from pre-dose Day 1 until Day 10.

Nasopharyngeal swabs from subjects were collected by trained staff pre-dose on Day 1, Day 5, at a subject's visit between Day 1 (post-dose) and Day 10 (if influenza suspected based on temperature ≥ 37.5°C and moderate or severe influenza-like symptoms) and Day 11. A central virology testing laboratory performed RT-PCR for virus typing and serology. Gene sequencing of virus was performed using the first positive sample from a subject.

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 (not prioritised):

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

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.

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.

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

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

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 titer 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)

Randomisation and Blinding (masking)

Subjects who were qualified for entry in the study were randomly assigned to either the baloxavir marboxil group or the placebo group in a 1:1 ratio, using the IWRS. The randomization used the stochastic minimization method for balancing the following 3 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, other than baloxavir marboxil)
- Subject's age (<12 years vs. ≥12 years)

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

Statistical methods

All statistical tests were to be performed at the two-sided significance level of 0.05, unless otherwise noted. No multiplicity adjustments were made in this study.

The risk ratio in the baloxavir marboxil group vs. the placebo group, its 95% confidence interval (CI), and P value was calculated using the modified Poisson regression approach of a binary response (whether all of the following were 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 or other than baloxavir marboxil] and age of subject [continuous variable]) as covariates.

Two-sided P value was calculated for the null hypothesis that the true risk ratio was 1. In the primary analysis, the proportion of subjects who were infected with influenza virus (RT-PCR positive), and presented with fever and at least one respiratory symptom in the baloxavir marboxil group were compared with that in the placebo group. The modified Poisson regression approach used the sandwich variance estimator.

The mITT (modified intent-to-treat) population included 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. Subjects were analysed according to the treatment to which they were randomized.

The Per-protocol Set (PPS) includes all randomized subjects who were included in the mITT population and did not have protocol deviations affecting the primary efficacy endpoint.

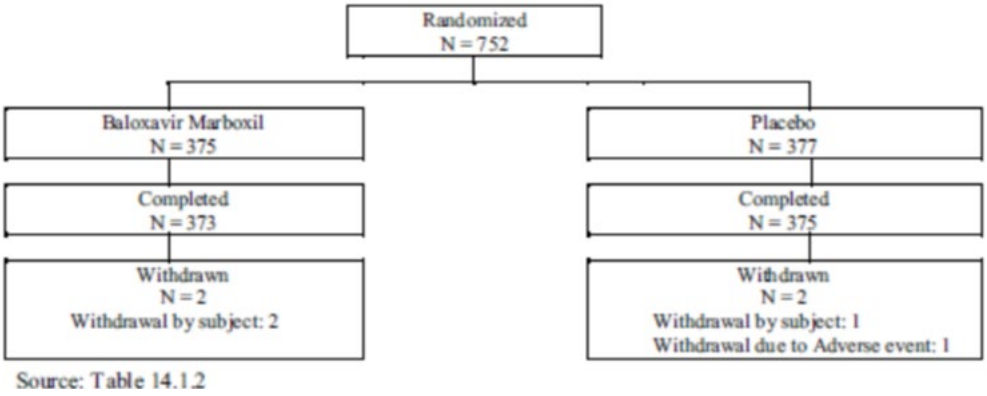
The mITT population was the primary efficacy analysis population.

Results

Participant flow

A total of 752 subjects (375 in the baloxavir marboxil group and 377 in the placebo group) were randomized as household members of 545 index patients.

Figure 20 Subject Disposition (All Randomized Subjects)



Baseline data

The majority of subjects (>75%) were female and were parents of index patients (71.4% and 67.2%). The mean age was ~34 years, only 19% were aged <12 years and only 2-4% were ≥ 65 years. The proportions with high risk factors (undefined) were 12-14%. More than 90% were negative for influenza virus (93.0% and 90.4%) based on RT-PCR. The majority (~73%) was enrolled within 24 h of influenza onset in the index case.

Table 29 Demographics and Baseline Characteristics of Subjects (mITT Population)

		Baloxavir Marboxil N=374 n (%)	Placebo N=375 n (%)
Age (years)	n	374	375
	Mean	33.5	33.6
	SD	15.8	17.0
	Min	1	1
	Median	37.0	38.0
	Max	87	85
	<5	14 (3.7)	20 (5.3)
	<10	55 (14.7)	52 (13.9)
	>=10 to <20	30 (8.0)	42 (11.2)
	>=20 to <30	20 (5.3)	14 (3.7)
	>=30 to <40	108 (28.9)	108 (28.8)
	>=40 to <50	131 (35.0)	130 (34.7)
	>=50 to <65	22 (5.9)	14 (3.7)
	>=65	8 (2.1)	15 (4.0)
	<12	71 (19.0)	71 (18.9)
	>=12	303 (81.0)	304 (81.1)
Weight (kg)	n	374	375
	Mean	51.62	51.28
	SD	17.16	17.72
	Min	10.3	8.0
	Median	52.95	52.30
	Max	96.8	113.4
	<10	0	1 (0.3)
	>=10 to <20	19 (5.1)	30 (8.0)
	>=20 to <40	57 (15.2)	43 (11.5)
	>=40 to <80	280 (74.9)	283 (75.5)
	>=80	18 (4.8)	18 (4.8)
BMI (kg/m^2)	n	374	375
	Mean	21.43	21.44
	SD	4.29	4.39
	Min	11.6	12.4
	Median	20.95	20.90
	Max	36.2	37.8
Sex	Male	77 (20.6)	85 (22.7)
	Female	297 (79.4)	290 (77.3)
Ethnicity	Hispanic or Latino	0	0
	Not Hispanic or Latino	374 (100.0)	375 (100.0)
Race	Asian	374 (100.0)	375 (100.0)
	Other	0	0
Relation to index patient	Parent	267 (71.4)	252 (67.2)
	Sibling	83 (22.2)	89 (23.7)
	Child	5 (1.3)	10 (2.7)
	Spouse	13 (3.5)	14 (3.7)
	Other	6 (1.6)	10 (2.7)
Current Smoking habits	Yes	38 (10.2)	37 (9.9)
	No	336 (89.8)	338 (90.1)
Influenza vaccination status within the previous 6 months	Yes	131 (35.0)	124 (33.1)
	No	243 (65.0)	251 (66.9)

Table 30 Demographics and Baseline Characteristics of Subjects (mITT Population) (cont.)

		Baloxavir Marboxil N=374 n (%)	Placebo N=375 n (%)
High risk factor	Presence	46 (12.3)	52 (13.9)
	Absence	328 (87.7)	323 (86.1)
Time from onset of influenza virus infection of index patient to informed consent of subject (hours)	<24	272 (72.7)	271 (72.3)
	>=24	102 (27.3)	104 (27.7)
Influenza virus subtype based on RT-PCR	Positive	26 (7.0)	36 (9.6)
	A/H1N1pdm	2 (0.5)	11 (2.9)
	A/H3NX	16 (4.3)	16 (4.3)
	A/ND	8 (2.1)	9 (2.4)
	B	0	0
	Mixed infection	0	0
	Negative	348 (93.0)	339 (90.4)
	Unable to be analyzed	0	0

ND = not determined; RT-PCR = reverse transcription polymerase chain reaction

Source: Table 11-2 and Table 14.1.6.1 in PEP T0834 CSR.

Table 31 Demographics and Baseline Characteristics of Index Patients (All Index Patients with at Least one Randomized Subject)

Demographics and Baseline Characteristics of Index Patients
Project: 1602T0834 (XV41428)

		Overall N = 545 n(%)
Age (years)	n	545
	Mean	11.3
	SD	12.51
	Min	0
	Median	8.0
	Max	81
	<10	336 (61.7)
	>=10 to <20	158 (29.0)
	>=20 to <30	12 (2.2)
	>=30 to <40	11 (2.0)
	>=40 to <50	8 (1.5)
	>=50 to <65	12 (2.2)
	>=65	8 (1.5)
	<6	160 (29.4)
	>=6 to <12	241 (44.2)
	>=12	144 (26.4)
Household size including index patient (people)	n	545
	Mean	4.2
	SD	1.11
	Min	2
	Median	4.0
	Max	10
	1	0
	2	30 (5.5)
	3	83 (15.2)
	>=4	432 (79.3)
Sex	Male	290 (53.2)
	Female	255 (46.8)
Style of living	Student	472 (86.6)
	Worker	34 (6.2)
	Not student or worker	39 (7.2)
Current Smoking habits	Yes	8 (1.5)
	No	537 (98.5)
Influenza vaccination status within the previous 6 months	Yes	170 (31.2)
	No	375 (68.8)
Actual treatment for influenza virus infection	Baloxavir Marboxil	287 (52.7)
	Oseltamivir	171 (31.4)
	Zanamivir	23 (4.2)
	Laninamivir	51 (9.4)
	Peramivir	13 (2.4)
	Amantadine	0
	Not taken	0
Influenza virus subtype by rapid influenza diagnostic test	A	535 (98.2)
	B	10 (1.8)
	A and B	0
	Missing	0
	Negative	0
	Unknown	0
Influenza virus subtype based on RT-PCR	A/H1N1pdm	255 (46.8)
	A/H3NX	265 (48.6)
	A/ND	1 (0.2)
	B	5 (0.9)
	Mixed infection	12 (2.2)
	Negative	7 (1.3)
	Unable to be analyzed	0
Virus titer [log10(TCID50/mL)]	n	545
	Mean	5.40
	SD	1.994
	Min	0.7
	Median	5.50
	Max	9.5

ND = not determined; RT-PCR = reverse transcription polymerase chain reaction

Program: root/clinical_studies/RO7191686/CDT70160/XV41428/data_analysis/CSR/prod/program/t_dm_indx_xv41428.sas
Output: root/clinical_studies/RO7191686/CDT70160/XV41428/data_analysis/CSR/prod/output/t_dm_indx_xv41428.out
27SEP2019 18:55 Page 1 and 2 of 2

Numbers analysed

Almost all (>99%) randomised subjects were included in the mITT population.

Table 32 Efficacy Analysis Populations (All Randomized Subjects)

	Baloxavir Marboxil N=375 n (%)	Placebo N=377 n (%)
Subjects included in mITT Population	374 (99.7)	375 (99.5)
Subjects excluded from mITT Population	1 (0.3)	2 (0.5)
Reason for exclusion		
- Subject with GCP noncompliance	0	1
- Subject who received no study drug	1	1
Subjects included in PPS	370 (98.7)	371 (98.4)
Subjects excluded from PPS	5 (1.3)	6 (1.6)
Reason for exclusion		
- Subject with GCP noncompliance	0	1
- Subject who received no study drug	1	1
- Subject with study procedure violations	4	4

GCP = Good Clinical Practice; mITT = modified intention-to-treat; PPS = per protocol set

Subjects who have the reason for exclusion more than once in different categories were counted once by each category.

Outcomes and estimation

Primary endpoint

In the mITT population, 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 statistically significantly lower in the baloxavir marboxil group than in the placebo group (1.9% vs. 13.6%; adjusted risk ratio 0.14 [95% CI: 0.06, 0.30], $p < 0.0001$).

When the primary analysis was repeated in the subgroup of subjects who had negative RT-PCR at baseline and whose index patients had positive RT-PCR the result was similar to that in the overall mITT population. The infection rates were 1.5% (5/344 subjects) in the baloxavir group and 11.6% (39/337 subjects) in the placebo group (adjusted risk ratio: 0.13 [95% CI: 0.05, 0.31], $p < 0.0001$).

Table 33 Summary of Primary and Secondary Efficacy Endpoint Results (mITT Population)

	Baloxavir Marboxil (N = 374)	Placebo (N = 375)
Primary Endpoint		
Proportion of subjects with influenza virus infection (RT-PCR positive), fever, and at least one respiratory symptom		
No. (%)	7 (1.9%)	51 (13.6%)
95% CI (%) [a]	[0.8%, 3.8%]	[10.3%, 17.5%]
Comparison with placebo:		
Adjusted risk ratio [b]	0.14	-
95% CI for adjusted risk ratio [b]	[0.06, 0.30]	-
P-value [b]	< 0.0001	-
Secondary Endpoints		
Proportion of subjects with influenza virus infection (RT-PCR positive) and fever or at least one influenza symptom		
No. (%)	20 (5.3%)	84 (22.4%)
95% CI (%) [a]	[3.3%, 8.1%]	[18.3%, 27.0%]
Comparison with placebo:		
Adjusted risk ratio [c]	0.24	-
95% CI for risk ratio [c]	[0.15, 0.38]	-
P-value [c]	< 0.0001	-
Proportion of subjects with influenza virus infection (RT-PCR positive) regardless of symptoms		
No. (%)	49 (13.1%)	114 (30.4%)
95% CI (%) [a]	[9.9%, 16.9%]	[25.8%, 35.3%]
Comparison with placebo:		
Adjusted risk ratio [d]	0.43	-
95% CI for risk ratio [d]	[0.32, 0.58]	-
P-value [d]	< 0.0001	-
Proportion of subjects with asymptomatic influenza virus infection (RT-PCR positive)		
No. (%)	29 (7.8%)	29 (7.7%)
95% CI (%) [a]	[5.3%, 10.9%]	[5.2%, 10.9%]
Comparison with placebo:		
Adjusted risk ratio [e]	1.00	-
95% CI for risk ratio [e]	[0.61, 1.64]	-
P-value [e]	0.9917	-

Table 33 Summary of Primary and Secondary Efficacy Endpoint Results (mITT Population) (cont.)

CI = confidence interval; RMST = restricted mean survival time; RT-PCR = reverse transcription polymerase chain reaction.

[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.

[c] Modified Poisson regression approach of a binary response (whether the following are confirmed for a subject or not; occurrence of fever or at least one influenza symptom, and influenza virus infection) on a study treatment for subject with randomization factors (as described in [b]) as covariates.

[d] Modified Poisson regression approach of a binary response (whether influenza virus infection is confirmed for a subject or not) on a study treatment for subject with randomization factors (as described in [b]) as covariates.

[e] Modified Poisson regression approach of a binary response (whether asymptomatic influenza is confirmed for a subject or not) on a study treatment for subject with randomization factors (as described in [b]) as covariates.

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

Source: Tables 11-4, 11-7, 11-8, 11-9, 11-10, and 11-11 in PEP T0834 CSR.*Ancillary analyses*

Secondary endpoints

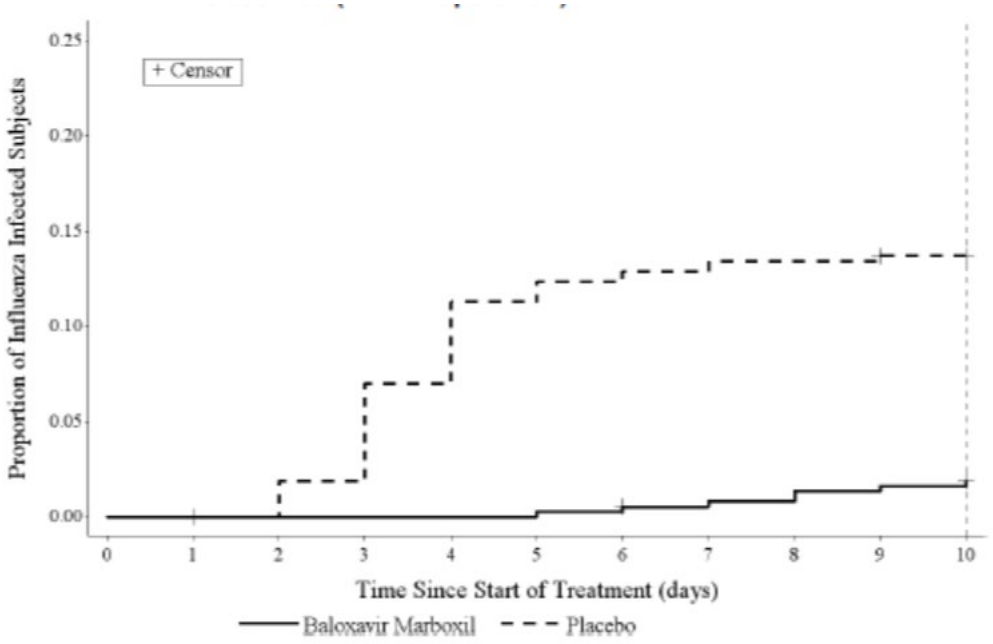
The results of the analyses of the secondary efficacy endpoints in the mITT population were generally supportive of the primary endpoint results. Beneficial effects of baloxavir marboxil were observed compared with placebo for all secondary endpoints except the proportion of subjects with asymptomatic influenza virus infection, which was similar in both groups (Table 68).

Ancillary analyses

As shown in the figure below, the restricted mean survival time (RMST) from study treatment to the time when fever, at least one respiratory symptom and influenza virus infection (RT-PCR positive) were observed up to Day 10 in the mITT population was 10.0 days (95% CI: 9.9, 10.0) in the baloxavir group and 9.1 days (95% CI: 8.9, 9.4) in the placebo group (difference 0.8 days [95% CI: 0.6, 1.0], p < 0.0001).

The proportions with asymptomatic influenza were similar between the treatment groups, with 7.8% (29/374) in the baloxavir group and 7.7% (29/375) in the placebo group (adjusted risk ratio: 1.00 [95% CI: 0.61, 1.64], p = 0.9917). Also, the proportions who were RT-PCR positive regardless of symptoms were 13.1% (49/374) in the baloxavir group and 30.4% (114/375) in the placebo group (adjusted risk ratio: 0.43 [95% CI: 0.32, 0.58], p < 0.0001).

Figure 21 Kaplan-Meier Plot of Time from Study Treatment to the Time When Fever, at least One Respiratory Symptom and Influenza Virus Infection (RT-PCR positive) were observed (mITT Population)



RT-PCR = reverse transcription polymerase chain reaction
Source: Figure 14.4.1

Subgroup analyses

Key subgroup analyses were

- Subject age (< 12 or ≥ 12 years)
- HR factors for developing influenza-related complications (present or absent per CDC criteria)
- Index patient influenza virus type (RT-PCR)
- Index patient treatment for influenza virus infection

When the primary endpoint was analysed according to the treatment given to the index case, rates in the baloxavir group were 2.7% when the index case had received baloxavir and 1.2% when they were given other treatments. Corresponding rates in the placebo group were 11.1% and 17.2% (standardized risk ratio: 1.31 [95% CI: 0.65, 2.64], p = 0.4498).

When the primary endpoint was analysed separately for the two influenza subtype groups, both showed statistically significantly lower case rates for baloxavir (A/H1N1pdm 1.1% vs. 10.6%, p = 0.0023; A/H3NX 2.8% vs. 17.5%, p < 0.0001)

The proportion that was 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 group in subjects aged < 12 years (4.2% vs. 15.5%, p = 0.0339) and subjects aged 12+ years (1.3% vs 13.2%, p < 0.0001).

- Lower in the baloxavir group in subjects with (2.2% vs. 15.4%, p = 0.0435) and without (1.8% vs. 13.3%, p < 0.0001) high risk factors

The results in the other subgroups were similar to the result in the overall mITT population.

Table 34 Subgroup Analysis of Primary Efficacy Endpoint by Subject Age (mITT Population)

	Baloxavir Marboxil (N = 374)	Placebo (N = 375)
Subject < 12 years		
n	71	71
No. (%) of subjects with influenza virus infection (RT-PCR positive), fever, and at least one respiratory symptom	3 (4.2%)	11 (15.5%)
95% CI (%) [a]	[0.9%, 11.9%]	[8.0%, 26.0%]
Comparison with placebo:		
Adjusted risk ratio [b]	0.27	-
95% CI for adjusted risk ratio [b]	[0.08, 0.90]	-
P-value [b]	0.0339	-
Subject ≥ 12 years		
n	303	304
No. (%) of subjects with influenza virus infection (RT-PCR positive), fever, and at least one respiratory symptom	4 (1.3%)	40 (13.2%)
95% CI (%) [a]	[0.4%, 3.3%]	[9.6%, 17.5%]
Comparison with placebo:		
Adjusted risk ratio [b]	0.10	-
95% CI for adjusted risk ratio [b]	[0.04, 0.28]	-
P-value [b]	<0.0001	-

Table 35 Subgroup Analysis of Primary Efficacy Endpoint by High Risk Factors for Developing Influenza-related Complications (mITT Population)

	Baloxavir Marboxil (N = 374)	Placebo (N = 375)
Presence of high risk factor [a] in subject		
n	46	52
No. (%) of subjects with influenza virus infection (RT-PCR positive), fever, and at least one respiratory symptom	1 (2.2%)	8 (15.4%)
95% CI (%) [b]	[0.1%, 11.5%]	[6.9%, 28.1%]
Comparison with placebo:		
Adjusted risk ratio [c]	0.13	-
95% CI for adjusted risk ratio [c]	[0.02, 0.94]	-
P-value [c]	0.0435	-
Absence of high risk factor in subject		
n	328	323
No. (%) of subjects with influenza virus infection (RT-PCR positive), fever, and at least one respiratory symptom	6 (1.8%)	43 (13.3%)
95% CI (%) [b]	[0.7%, 3.9%]	[9.8%, 17.5%]
Comparison with placebo:		
Adjusted risk ratio [c]	0.14	-
95% CI for adjusted risk ratio [c]	[0.06, 0.32]	-
P-value [c]	<0.0001	-

Table 36 Subgroup Analysis of Primary Efficacy Endpoint by Influenza Virus Subtype (RT-PCR) of Index Patients (mITT Population)

	Baloxavir Marboxil (N = 374)	Placebo (N = 375)
Index patient infected with A/H1N1pdm influenza virus		
n	176	180
No. (%) of subjects with influenza virus infection (RT-PCR positive), fever, and at least one respiratory symptom	2 (1.1%)	19 (10.6%)
95% CI (%) [a]	[0.1%, 4.0%]	[6.5%, 16.0%]
Comparison with placebo:		
Adjusted risk ratio [b]	0.11	-
95% CI for adjusted risk ratio [b]	[0.03, 0.45]	-
P-value [b]	0.0023	-
Index patient infected with A/H3NX influenza virus		
n	181	183
No. (%) of subjects with influenza virus infection (RT-PCR positive), fever, and at least one respiratory symptom	5 (2.8%)	32 (17.5%)
95% CI (%) [a]	[0.9%, 6.3%]	[12.3%, 23.8%]
Comparison with placebo:		
Adjusted risk ratio [b]	0.15	-
95% CI for adjusted risk ratio [b]	[0.06, 0.39]	-
P-value [b]	<0.0001	-
Index patient infected with B influenza virus		
n	2	3
No. (%) of subjects with influenza virus infection (RT-PCR positive), fever, and at least one respiratory symptom	0 (0.0%)	0 (0.0%)
95% CI (%) [a]	[0.0%, 84.2%]	[0.0%, 70.8%]

Table 37 Subgroup Analysis of Primary Efficacy Endpoint by Treatment for Influenza Virus Infection of Index Patient (mITT Population)

	Baloxavir Marboxil (N = 374)	Placebo (N = 375)
Baloxavir marboxil		
n	195	197
No. (%) of subjects with influenza virus infection (RT-PCR positive), fever, and at least one respiratory symptom	5 (2.6%)	21 (10.7%)
95% CI (%) [b]	[0.8, 5.9]	[6.7, 15.8]
Comparison with placebo:		
Adjusted risk ratio [c]	0.24	-
95% CI for adjusted risk ratio [c]	[0.09, 0.61]	-
P-value [c]	0.0030	-
Other than baloxavir marboxil		
n	179	178
No. (%) of subjects with influenza virus infection (RT-PCR positive), fever, and at least one respiratory symptom	2 (1.1%)	30 (16.9%)
95% CI (%) [b]	[0.1, 4.0]	[11.7, 23.2]
Comparison with placebo:		
Adjusted risk ratio [c]	0.07	-
95% CI for adjusted risk ratio [c]	[0.02, 0.27]	-
P-value [c]	0.0002	-

Amino acid substitution

Of the 374 baloxavir marboxil-treated subjects in the mITT population of Study T0834, 63 subjects had RT-PCR confirmed influenza either at baseline or post-dose (26 at baseline and 37 post-dose).
Amino acid changes at position 38 of the PA gene (PA/I38X) were detected in virus from a total of 10 baloxavir marboxil-treated subjects.
Amino acid changes at position 23 of the PA gene (PA/E23K) were detected in virus collected from 5 RT-PCR positive baloxavir marboxil-treated subjects.
No amino acid substitutions were found at positions 38 or 23 of the PA gene in virus collected from RT-PCR positive placebo-treated subjects.

Summary of main study(ies)

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).

Summary of Efficacy for the Phase 3 PEP Trial 1719T0834

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 prophylaxis trial. 1:1 randomization.		
	Duration of main phase:		15 days
Hypothesis	Superiority vs placebo		
Treatments groups	Baloxavir marboxil		• Baloxavir marboxil (subjects ≥ 12 years of age) ○ 40-mg (weight < 80 kg) or ○ 80-mg (weight ≥ 80 kg). • 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 = 375
	Placebo		Baloxavir matching Placebo. 1 day duration, N = 377
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	374	375

	Proportion symptomatic infected (%)		1.9		13.6
	95% confidence interval using the Clopper-Pearson method (%)		0.8, 3.8		10.3, 17.5
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		0.14
			95% confidence interval using modified Poisson regression approach of a binary response		0.06, 0.30
			P-value using modified Poisson regression approach of a binary response		<0.0001
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.				
Analysis description	**Subgroup Analysis (pre-specified)**				
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 (< 12 years of age subgroup)	Placebo (< 12 years of age subgroup)	Baloxavir marboxil (≥ 12 years of age subgroup)	Placebo (≥ 12 years of age subgroup)
	Number of subject	71	71	303	304
	Proportion symptomatic infected (%)	4.2	15.5	1.3	13.2
	95% confidence interval using the Clopper-Pearson method (%)	0.9, 11.9	8.0, 26.0	0.4, 3.3	9.6, 17.5

Effect estimate per comparison	Primary endpoint – Proportion symptomatic infected (subgroup analysis)	Comparison groups	Baloxavir marboxil (< 12 years of age subgroup) and Placebo (< 12 years of age subgroup)		
		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		
	Primary endpoint – Proportion symptomatic infected (subgroup analysis)	Comparison groups	Baloxavir marboxil (≥ 12 years of age subgroup) and Placebo (≥ 12 years of age subgroup)		
		Risk ratio using modified Poisson regression approach of a binary response	0.10		
		95% confidence interval using modified Poisson regression approach of a binary response	0.04, 0.28		
		P-value using modified Poisson regression approach of a binary response	<0.0001		
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) and treatment for influenza virus infection in the index patient (baloxavir marboxil, other than baloxavir marboxil or no treatment when index patients didn't take any treatment). No multiplicity adjustments were made in this study.				
Analysis description	**Subgroup Analysis (pre-specified)**				
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 (with high risk factor of subject)	Placebo (with high risk factor of subject)	Baloxavir marboxil (without high risk factor of subject)	Placebo (without high risk factor of subject)
	Number of subjects	46	52	328	323

	Proportion symptomatic infected (%)	2.2	15.4	1.8	13.3
	95% confidence interval using the Clopper-Pearson method (%)	0.1, 11.5	6.9, 28.1	0.7, 3.9	9.8, 17.5

Effect estimate per comparison	Primary endpoint – Proportion symptomatic infected (subgroup analysis)	Comparison groups	Baloxavir marboxil (with high risk factor of subject) and Placebo (with high risk factor of subject)
		Risk ratio using modified Poisson regression approach of a binary response	0.13
		95% confidence interval using modified Poisson regression approach of a binary response	0.02, 0.94
		P-value using modified Poisson regression approach of a binary response	0.0435
	Primary endpoint – Proportion symptomatic infected (subgroup analysis)	Comparison groups	Baloxavir marboxil (without high risk factor of subject) and Placebo (without high risk factor of subject)
		Risk ratio using modified Poisson regression approach of a binary response	0.14
		95% confidence interval using modified Poisson regression approach of a binary response	0.06, 0.32
		P-value using modified Poisson regression approach of a binary response	<0.0001
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 didn't take any treatment) and age of the subject (continuous variable). No multiplicity adjustments were made in this study.		

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

Clinical studies in special populations

The majority of subjects included in study T0834 did not have any risk factors, e.g. only one subjects with kidney disorder was included and 11 with liver disorder.

Most subjects were between 30 and 50 years of age. Paediatric subjects under 12 years of age accounted for 19% of subjects in both treatment groups while elderly subjects aged 65 years and older accounted for 2.1% and 4.0% of subjects in the baloxavir marboxil and placebo groups, respectively. The proportion of subjects under 5 years of age was 3.7% in the baloxavir marboxil group and 5.3% in the placebo group.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies- Treatment of influenza infection

Demonstration of clinical efficacy of baloxavir marboxil in the proposed indication of treatment of influenza infection is based on two pivotal studies; study T0831, treatment of influenza infection in otherwise healthy patients (OwH), and study T0832, treatment of influenza infection in a group of patients at higher risk of influenza complications (HR). A phase II dose-finding study in OwH-patients, T0821, is considered supportive.

The studies T0831 and T0832 were multicentre, randomised, double-blind, controlled, pivotal, Phase 3 studies comparing baloxavir marboxil to placebo and subsequently to oseltamivir in terms of time to alleviation/improvement of symptoms in patients infected with influenza. The objective of the study T0831 in otherwise healthy patients was to investigate if baloxavir marboxil decreases the time to alleviation of influenza symptoms, which is a generally accepted measure of treatment efficacy in influenza studies. In the HR patients, the endpoint was slightly modified being 'time to improvement of symptoms', since HR patients commonly have 'influenza-like symptoms' at baseline (e.g. cough and fatigue in COPD patients). The objectives are adequately reflected in the primary endpoints and the primary efficacy analysis, the modified endpoint 'time to improvement of symptoms' in HR patients is discussed further below. Overall these designs are considered acceptable.

The inclusion and exclusion criteria of the T0831, OwH, study selected a population without any acute or chronic concomitant disease whose main medical problem was clinically suspected influenza infection. In comparison, the inclusion and exclusion criteria of the T0832, HR, study selected patients at increased risk of influenza-related complications. Principally, the selection criteria for high-risk patients followed the criteria defined by the Centre for Disease Control, however, not all CDC-listed patient groups were eligible, e.g. cancer patients. Moreover, only a single item on the list needed to be met for eligibility. Based on these criteria, some patients were eligible for reason(s) expected to have only a very minor, if any, impact on their risk of developing complications of influenza. For example, any otherwise healthy patient aged 65 years would be eligible as would any patient with diabetes regardless of type, duration and degree of control.

Patients were randomised to receive either baloxavir marboxil, 40 mg or 80 mg (depending on body weight below or above 80 kg) once + placebo for four additional days, oseltamivir for five days, or matching placebo all five days. Treatment was to be initiated within 48h after influenza onset. Both study medications and placebo are adequately described. The choice of oseltamivir as active comparator is considered relevant as an approved medicinal product in EU for the sought indication.

The primary endpoint was the time to alleviation (TTAS) or time to improvement (TTIS) of all seven influenza symptoms defined as cough, sore throat, nasal congestion, headache, feverishness or chills, muscle/joint pain, and fatigue. Fever was defined as ≥ 38ºC (axillary) in the predose examinations or > 4 hours after dosing of antipyretics if they were taken. All patients were to record their symptoms in

a diary pre-dose on Day 1, twice daily (morning and evening) until Day 9, and once daily (evening) from Days 10 to 14. It is generally accepted that TTAS is an adequate measure of treatment efficacy of influenza and is considered acceptable. However, in HR patients the endpoint was modified as being to improvement of influenza symptoms (TTIS), which consisted of three categories: Alleviation of new symptoms that were not present before the onset of influenza, Improvement of pre-existing symptoms that were judged by the patient to have been worsened by influenza, and/or Maintenance of pre-existing symptoms that were judged by the patient to have NOT been worsened by influenza.

As in prior treatment studies that have supported NAI approvals, the primary analysis was conducted in the ITTI population, comprising all treated subjects with a positive RT-PCR on day 1. It is acceptable that culture confirmation was not required for inclusion in the primary analysis. However, in contrast to several prior studies with NAIs, the inclusion criteria did not require that a rapid diagnostic test (RDT) conducted at the study site was used to determine study eligibility. The exception was in 1602T0832 in which (by amendment) subjects enrolled in the US were to have a positive RDT or a documented exposure to a case of influenza to be eligible. As a result, a substantial proportion of the total enrolled (~25% in 1601T0831 and near to 50% in 1602T0832) were excluded from the ITTI populations

Secondary endpoints included clinical and virological endpoints, namely time to alleviation/improvement of individual symptoms or number of complications (clinical), and viral shedding as assessed by virus titre and virus-PCR. Especially the risk of complications appears clinically relevant, since treatment may be initiated specifically to avoid complications in high risk patients. However, the Applicant did not prioritise the secondary endpoints or adjust for multiplicity in the analyses of significance of treatment for each endpoint. Therefore, the secondary endpoints are considered exploratory.

Whilst the two studies were conducted in different regions (Japan and N. America being common to both) and in different seasons, the difference in proportion confirmed to be eligible for the primary analysis is not discussed. In this regard, additional central laboratories participated in 1602T0832. The applicant confirmed that in-house RT-qPCR tests were used at the central laboratories, and the test used did not change between studies. According to the applicant, the possible explanation for the difference in the percentage included in the primary analysis, is a result of higher flu confirmation rates in Japan than rest of the world countries. The stated LOD and LLOQ should be satisfactory to pick up influenza virus.

The sample size calculations were based on results of previous studies. The Applicant considered that a 28 % decrease in disease duration to be clinically significant. The sample size calculations are endorsed. Patients were randomised according to age group (12-19 years and 20-64 years), region (Japan/Asia, Rest of the world), body weight (< 80 kg, ≥ 80 kg), and baseline symptom score, which in the OwH population was ≤ 11, ≥ 12, while it in the HR-group was ≤ 14, ≥ 15. These measures are considered clinically relevant.

The use of the FAS (full analysis set) for the primary analysis is agreed. However, the Applicant excluded some subjects after randomisation, since they had been treated at a site with GCP non-compliance, which is usually not acceptable, but the Applicant adequately clarified the reasons for the GCP non-compliance and provided additional analyses for the primary endpoints In addition, all "time to alleviation/improvement" endpoints were tested for statistically significant difference between treatment arms by generalised Wilcoxon tests (endorsed) but the effect estimates were reported as difference between medians. The applicant was asked to apply the three-step approach suggested in "Robust Design and Analysis of Clinical Trials with Non-proportional Hazards: A Straw Man Guidance from a Cross-pharma Working Group" (arXiv:1908.07112v1) and present the results.
In short the applicant was required to perform (1) the MaxCombo test. However, no package for conducting the MaxCombo test was available for R/SAS. Therefore, the applicant has instead provided

an assessment based on the MaxCombo principle. It was argued that, since the pattern of the studies T0831 and T0832 was described as "early separation", the G1,0 test covered by the MaxCombo test is approximately equivalent to the Peto-Prentice test already used. (2) The Grambsch-Therneau test should be used to evaluate if the proportional hazards assumption is reasonable. The applicant did not perform this step, as proportionality of hazards was not assumed to begin with. Lastly, the applicant was asked to (3) Estimate the treatment effect. This was done by Restricted Mean Survival Time analysis (RMST) demonstrating TTAS/TTIS improvement of 18-21 hours in patients treated with baloxavir when compared to placebo. Overall, the statistical analysis plan is endorsed.

GCP issues

The CSR for 1601T0831 reports that findings of a site audit for a Study Centre (which was in both trials) as part of monitoring of 1602T0832, including critical and major deviations, led Shionogi to close the site when 10 patients had been enrolled. Subsequently, additional efficacy analyses were conducted after omitting data from that Centre, which did not impact on study conclusions. This much seems clear. It does not seem that audits of any other sites in 1601T0831 raised GCP concerns but this should be confirmed with a list of all audits conducted.

According to section 9.8.1 of the CSR of 1602T0832, site audits identified critical and major deviations at three Sites and Shionogi decided to close these sites. However, the data indicate that the ITTI population eliminated 107 patients enrolled at 7 sites and this number included 32 with positive RT-PCR (i.e. would not otherwise have been excluded from the ITTI population). The CSR sections that mention site closure and exclusion of data refer to appendix 16.1.8. However, this appendix provides only single page certificates recording that an audit was conducted, with no details of findings or explanation for decisions on elimination of data. There is no further explanation found in the CSR, *Clinical overview* or applicant's *Summary of efficacy*.

Both treatment studies involved a very (and unusually) large number of study sites. The fact that site audits were conducted and action was taken is acknowledged but, with such a large number of sites, the applicant have reported the numbers/percentages that were audited. Also, since baloxavir has been approved for treatment of influenza by the US FDA, and FDA also inspected some sites, for which details have been provided. Even with such a large number of sites, it is unusual that data are excluded from 7 sites. The applicant has explained why data from two sites were not excluded.

Overall, the issues concerning GCP have been fully addressed by the applicant and it does not seem necessary to trigger a GCP-inspection on data integrity.

Efficacy data and additional analyses - Treatment of influenza infection

Included patients were generally representative of the proposed indication, although it should be observed that the defined 'high-risk' group of patients did not fully correspond to the patient group defined be CDC-criteria (please refer to discussion above). The three study groups, baloxavir marboxil, oseltamivir, and placebo, were well balanced in term of demographics, previous medical history, and protocol deviations in both the OwH- and HR-populations.

The studies met their primary objectives. Baloxavir marboxil decreased the time to alleviation (OwH patients) or time to improvement (high-risk patients) significantly as compared to placebo. There was no difference in times to alleviation/improvement between patients treated with baloxavir marboxil or the active comparator, oseltamivir. In the primary analyses comparing baloxavir marboxil with placebo, the Hodges-Lehmann location shift demonstrated that the average time to alleviation/improvement of

symptoms among all patients is reduced by 22.3 hours and 19.9 hours in Studies T0831 and T0832 compared with placebo treatment, respectively. It appears that in the otherwise healthy population approx. 80% of patients treated with baloxavir marboxil recovered faster than patients, who received placebo. In both the baloxavir marboxil and placebo groups, approx. 80% of patients recovered by day 5 after treatment initiation (i.e. 5-7 days after influenza onset). In the high-risk population patients recovered more slowly; by day 7 after treatment initiation, 80% of the baloxavir marboxil patients and 73% of the placebo patients had recovered. Finally, time to alleviation was also measured in the high-risk population and was shorter in the high-risk population.

As noted, corrections for multiplicity were not used. Thus, the secondary endpoints are considered exploratory. Notwithstanding this limitation, all secondary endpoints appeared to favour treatment with baloxavir marboxil as compared to placebo, while the baloxavir marboxil and oseltamivir appeared similar also with regard to the secondary endpoints. Among analyses of secondary endpoints, the following should be noted:

Efficacy by "baseline symptom score"

The baseline stratification by symptom score was accounted for in the two primary analyses but the strata were defined differently in the two studies. Nevertheless, sub-group analyses showed that baloxavir gave statistically significant reductions in TTAS vs. placebo in the subgroups with baseline composite symptom scores ≤ 11 (19.1 h) and ≥ 12 (27.0 h) in 1601T0831 and statistically significant reductions in TTIS vs. placebo in the subgroups with baseline composite symptom score ≤ 14 (-14 h; 64.4 vs. 78.4 h) or ≥ 15 (-23.6 h; 101.4 vs. 125 h) in 1602T0832. The marked difference in median TTIS values according to baseline score that was observed regardless of treatment group in this second study is notable and raises the question whether symptom scores showed a relationship to age, such that older patients were less likely to record high scores at baseline and post-baseline, resulting in them being more likely to be in the <15 category at baseline and to achieve resolution more quickly (see below regarding results in those aged 65+years in this study). This might be explained by differences in the proportions of patients from Asia and Europe/ North America between the three age groups.

Regarding efficacy in subgroups, the following should be observed:

The effect of baloxavir marboxil on time to alleviation (OwH)/ improvement (HR), i.e. the primary endpoints, was maintained across age, sex, and race (Japanese vs. American). It is noted that males recovered faster than females, which has also been described in literature, and that Japanese patients possibly recovered faster American patients. However, this was also noted in the placebo and oseltamivir groups. Thus, even though Japanese subjects were exposed to higher levels of baloxavir marboxil (please refer to the PK-section of this AR), the higher exposure was not translated into a different recovery rate between Japanese and American (evaluated as percentage shorter disease duration). However, there do not appear to be any obvious differences in age, virus type/subtype or medical history between the low and high baseline symptom score groups explaining the differences between Japanese and American subjects. The effect of baloxavir marboxil on time to alleviation (OwH)/ improvement (HR) was also maintained across body weight (above or below 80 kg).

Efficacy by "at risk" categorisation in 1602T0832

In 1602T0832 the median TTIS was also displayed by the applicant's "at risk" categorisations. With asthma and other respiratory disorders predominating (~150 ITTI patients per group), baloxavir gave a statistically significant reduction in median TTIS in this subgroup (74.6 h vs. 110.2 h), very similar to the primary analysis. Whilst differences did not reach statistical significance in the smaller subgroups (note it is unclear if patients were counted in several analyses if they had multiple reasons to be study

eligible), the actual difference in median TTIS for baloxavir vs. placebo was also comparable with primary analysis results in the sub-groups with endocrine disorders (the applicant should clarify if most in this group only had diabetes), heart disorders or morbid obesity.

In contrast, the difference in those aged 65+years (~100 per group) was -17.8 h, reflecting median values of 70 h vs. 87.8 h, i.e. a difference impacted by an unexpectedly short median TTIS for placebo. The CSR also reports that in the subset aged 65+ years who also had other risk factors the median TTIS was 67.9 h for baloxavir vs. 78.4 h for placebo. Furthermore, in the ~50 per group with metabolic disorders the median TTIS values were unusually short and showed no numerical benefit for baloxavir (56.8 h vs. 57.4 h).

Median TTIS data by age subsets showed that there were 75-85 per group aged 65-74 years and 27 per group aged 75+ years. The overall result for the 65+ years subset is driven by those aged from 75+ years (-50.7 h; 65.1 h vs. 115.8 h) such that there was no apparent benefit of treatment in those aged 65-74 years (-6.1; 73 h vs. 79.1 h). It is very likely that these subgroup differences are not related to age *per se* but to differences in other factors. Most of the subjects aged 75+ years were enrolled in Japan but no host factors explained the observed difference. Meanwhile, it is not considered necessary to impose an upper age limit based on these dubious subgroup analyses. However, it cannot be ruled out from current data confined to one treatment study that the benefit of baloxavir may be less as age increases.

Efficacy by time from onset to enrolment/dosing

In 1601T0831 and in 1602T0832 only ~20% were enrolled when 36+ h had elapsed since symptom onset. Baloxavir gave statistically significant reductions in TTAS vs. placebo in 1601T0831 regardless of the time elapsed but the difference in median TTAS was 32.8 h when treatment started within 24 h compared to only 13.2 h when treatment started between 24 and 48 h. The applicant provided median TTAS broken down into the four 12-h intervals for 1601T0831 suggesting a waning effect of baloxavir as time between onset of symptoms and treatment, lengthens.
In 1602T0832, baloxavir gave statistically significant reductions in TTIS vs. placebo in patients who were treated within 0 to 12 h, > 12 to 24 h or > 24 to 36 h with a numerical reduction for those treated within > 36 to 48 h but the actual differences were -47.7 h, -29.4 h, -39.5 h and -9.2 h in respective subgroups. Taking into account the data from both studies, the SmPC recommendation that treatment should be started within 48 h is acceptable.

Efficacy in adolescents

In 1601T0831 ~17% of the total ITTI population were aged 12-19 years. Baloxavir gave statistically significant reductions in TTAS vs. placebo in both adolescents (aged 12-17 years) and adults. Although the median TTAS in those who received baloxavir was 54 h in both age subsets, the median TTAS in the placebo group of only 27 adolescents was longer vs. adults who received placebo so the actual difference in median TTAS was greater in the adolescents vs. adults (38.6 h vs. 25.6 h).
In 1602T0832 only ~5% of patients were aged 12-19 years. With 13 baloxavir and 12 placebo patients in this age range, no benefit for baloxavir was observed. However, the median TTIS was exceptionally long in the baloxavir and placebo groups (188 and 192 h) but exceptionally short in the oseltamivir group (73.4 h). In such small numbers these results may have occurred by chance. The underlying conditions that made these adolescents eligible for the study has been presented and overrepresentation of immunocompromised subjects in the baloxavir group does not appear to be the explanation of the observed differences.

Efficacy in other special populations

Efficacy has not been studied in patients with severe hepatic and/or renal impairment, in patients with cancer or cancer within the last 5 years, or in pregnant women. These patients are defined as patients at high risk of influenza-related complications by the CDC criteria. T0832 included patients with a wide range of conditions with very different risk levels for complications of influenza and overall. Thus, the HR-population included in the studies, is actually a subpopulation of the 'entire' population at high-risk of influenza complications. Limited data on efficacy in patients with impaired renal or hepatic function has been obtained in the development program. Available data suggest that impaired renal or moderate impaired hepatic function does not affect efficacy of baloxavir. The efficacy of baloxavir in patients with severe hepatic function has not been established.

Effect of prior vaccination against influenza

In 1601T0831 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.

Virological data from treatment studies

A/H3 was very predominant (~85%) in 1601T08312. A/H3 predominated to a lesser extent in 1602T0832 (just under 50%) with < 10% having H1N1. Numbers with type B infection in the Phase 2 study and in 1601T0831 were small 24 and 38, respectively, per study had type B and received 40 mg baloxavir). The proportion with type B in 1602T0832 was much higher (~40% per group). Overall, there were no concerns regarding type-specific clinical effects of baloxavir.

Baseline susceptibility to baloxavir and oseltamivir was determined at central laboratories. The median baloxavir EC_{50} values for baseline isolates compared to reference strains indicate no substantial shifts. Both the plaque assay applied in Phase 2 and Virospot assay applied in Phase 3 showed that median EC_{50} values for baloxavir were about 4-5-fold higher for type B vs. type A strains. However, the ranges indicated that some strains had 10-40-fold higher baloxavir EC_{50} values compared to the median value.

Despite the occurrence of strains with unusually high EC_{50} values, the applicant's summary of efficacy states that *no baseline substitutions (vs. references strains) were associated with reduced susceptibility to baloxavir*. Genotypic testing was conducted for at least for baloxavir-treated patients with virus having higher EC_{50} values and that some phenotypic testing was conducted. The conclusions are limited by the small numbers with EC_{50} FC values ≥10. However, these is no consistent relationship visualised between FC EC_{50} and TTAS or TTIS and it does not seem that any one substitution can explain the FC EC_{50} values. There was also no clear relationship between baseline EC_{50} values and changes in $TCID_{50}$ over time based on these few data.

Importantly, using a neuraminidase inhibition assay, there was no evidence of shifts in median IC_{50} values for oseltamivir for isolates from the Phase 3 studies. Also, the upper end of the ranges indicated no more than a 7-fold increase vs. reference strains, indicating the comparisons of antiviral and clinical effects between baloxavir and oseltamivir were not confounded by resistance to oseltamivir. However, median IC_{50} values were 6-7-fold higher for type B vs. type A strains.

In between 2 and 10 % of the influenza infected OwH or HR patients, who were treated with baloxavir marboxil, changes in the viral PA gene were observed. No changes to the PA gene were found in the patients, who received placebo, or patients exposed to oseltamivir. Similarly, changes in the PB1 and PB2 genes were observed in a smaller number of virus samples from patients treated with baloxavir marboxil in the OwH-studies. The possible clinical impact of these gene changes could not be properly evaluated due to the relatively low number of patients, who were infected with a virus that expressed the gene changes (the sample sizes were also reduced due to exclusion of patients without virus samples both at pre- and post-dosing). However, such changes could indicate a selection pressure and be of importance in case of an influenza epidemic, where treatment would be used continuously over months. A recently published study indicates that influenza A/H1N1 2009 pandemic (A/H1N1pdm) and A/H3N2 viruses, carrying an I38T mutation in the polymerase acidic protein were fit and transmissible through respiratory droplets; the study indicates the clinical relevance of the mutation in terms of return of symptoms and transmitting bxm-resistant strains (Imai M. et al. Nature Microbiology 5, 27-33 (2020)). The Applicant has presented all available evidence including literature data (human and animal) related to resistance development. The presented data suggest that baloxavir-resistant viruses rarely emerge and I38T mutant viruses become a minority due to reduced fitness compared to the wildtype virus.

Protocol deviations

In both Phase 3 treatment studies the most common protocol deviation was administration of prohibited concomitant medications. It is likely that most of these transgressions involved use of symptomatic treatments other than the allowed paracetamol or low dose aspirin. However, these patients were excluded from the per protocol (PP) population. It is therefore important to note that both studies showed statistically significant differences for baloxavir vs. placebo on TTAS/TTIS in the PP populations.

Design and conduct of clinical studies - Post-exposure Prophylaxis

A single study, T0834, has been included in the MAA to support the indication of baloxavir marboxil for post-exposure prophylaxis of influenza in individuals aged 12 and above.

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. Subjects were included if 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, i.e. within 48 hours. Baloxavir marboxil dosing was dependent on age and body weight at screening. The baloxavir marboxil single dose administrations used in study T0834 are the approved doses used for treatment of influenza virus infection outside EU. The doses have been found to have an acceptable safety profile. Dosing recommendations in the study include dosing in children < 12 years of age whereas the PEP indication is confined to adolescents from 12 years and adults. 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 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. In total, 752 subjects were included in the study, and 749 were included in the mITT population. Few subjects were excluded and there were no apparent differences in subjects being excluded across treatment groups.

The case definition and duration of capture for 1-10 days is appropriate. The index case was to have had had onset within 48 h and three quarters of subjects were enrolled within 24 h of symptom onset in the index case. In the SmPC it is stated that baloxavir marboxil should be taken as soon as possible within the 48-h window after close contact with an individual known or suspected to have influenza, which is acceptable. It is specified in section 5.1 of the SmPC that the majority of index patients were included within 24 hours of onset of symptoms.

Not all household members of the recruited index patients were included in the study. For the majority of index patients (71.6%), only one subject was included from the household. It could be argued that there would be a larger risk of influenza in larger households where all members are not either treated or receive prophylaxis. An alternative option to the treatment assignment in T0834, all household members could have been randomized to either baloxavir or placebo, such that all members of the same household would receive the same drug or control in line with FDA guidance for Developing Drugs for Treatment and/or Prophylaxis. Even though the study design implied risk of intra-household-correlation, such a relation was not demonstrated.

The baloxavir and placebo subject groups were comparable. The study was conducted in Japan and all subjects were Asian of origin. It should be noted that 55 (14.7 %) and 52 (13.9 %) of subjects were below 10 years of age in the baloxavir and placebo group respectively. The youngest subjects were 1 year old. The study has 71 subjects < 12 years of age in both treatment groups reflecting close to 20 % of included subjects and these subjects are included in the primary endpoint. The number of paediatric subjects included in study T0834 is beyond what was requested in the PIP. No waiver has been granted by PDCO for neither the treatment nor the PEP indication.

The proposed age restriction in the indication, i.e. post-exposure prophylaxis of influenza in individuals aged 12 and above is therefore not fully understood, since study T0834 has been completed with 142 paediatric subjects < 12 years of age included.

Few elderly subjects have been included. In total 23, (8 subjects ≥ 65 years in the baloxavir group and 15 subjects in the placebo group) were included in the study.

Less than 1 % of index patients had influenza B. The predominant subtypes were A/H3NX (48.6%) and A/H1N1pdm (46.8%) in accordance with the most prevalent subtypes in the 2018-2019 influenza season (global WHO data for the same period (95.4% influenza A, 4.6% influenza B).

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 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. A list of subgroup analyses were prespecified e.g. 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) and High risk factor of subject (Presence or Absence). Secondary endpoints with different variations of influenza symptoms and time from study treatment to subjects presenting with fever or at least one influenza symptom were also analysed.

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. As no multiplicity adjustment is made in T0834 only the primary endpoint is controlled for and all secondary endpoints are considered exploratory.

The applicant used a modified intent-to-treat (ITT) population instead of following the intent-to-treat principle and including all randomised subjects. However, the requirement of post baseline observation lead to exclusion of three subjects out of 752 from the randomised analysis set. Given the low number it is not considered to affect the result of the trial and therefore the ITT analysis is not requested. Additional analyses have been performed in order to evaluate the implications of the stochastic minimisation allocation method and to evaluate the robustness of the primary analysis method. The supplementary analyses have confirmed the robustness of the primary analysis method.

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

Efficacy data and additional analyses - Post-exposure Prophylaxis

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

In the mITT population, 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 statistically significantly lower in the baloxavir marboxil group than in the placebo group (1.9% vs. 13.6%; adjusted risk ratio 0.14 [95% CI: 0.06, 0.30], $p < 0.0001$). A risk reduction of 86 % is considered clinically relevant, and in absolute numbers, the number needed to treat to prevent one case of influenza is 9 (ARR= 13.6 – 1.9 = 11,7 %, NNT = 1/ 0.117 = 8.5). However, the risk reduction of 86 % is in a population where the index patient also is administered an anti-influenza treatment.

The number of events is low, 7 and 51 subjects with influenza in baloxavir and placebo respectively. This limits the interpretation of the study and analysis of subgroup.

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, but again numbers are limited.

The number of subjects with high risk factors (CDC criteria) was 12.3% and 13.9%. The majority of subjects were low risk patients. Twelve subjects showed a confirmed influenza type or subtype different from their respective index patient. The index cases showed an equal split between A/H1N1pdm and A/H3NX, which is described in the CSR as an unidentified subtype of neuraminidase. The tests used could not determine the N type. However, in most cases it was assumed that the N type was N2 as this was the predominant circulating type. Baloxavir marboxil has been shown to be effective against a wide range of influenza viruses. While influenza viruses vary somewhat from season to season, baloxavir targets the cap-dependent endonuclease inhibitor which is a highly conserved internal component of the virus and not subject to the antigenic drift that is a feature of external virus components such as haemagglutinin. No subjects were infected with influenza B virus in either treatment group. The prevalence of influenza B virus was low in the influenza season, where the study was conducted. Efficacy against influenza B virus has been demonstrated in the treatment trials.

In contrast to standard of care in EU, all index patients received anti-influenza treatment, 52.7 % baloxavir marboxil. It is therefore difficult to conclude on the prophylactic effect of baloxavir if the index patients are not treated. The adjusted risk ratio for primary endpoint was 0.24 in the subgroup of subjects where the index patient was treated with baloxavir compared to 0.07 in the subgroup where the index patient was treated with another anti-influenza product. Though numbers are small, the result is noteworthy. It is also note-worthy that none of the placebo-treated subjects had amino acid substitutions compared to 10 and 5 for PA/I38X and PA/E23K respectively in subjects treated with baloxavir. This raises concerns of selection pressure and influenza strain resistance to baloxavir. It is acknowledged that for the individual, tolerance to baloxavir administered as a single dose not is

expected to be a concern. However, as seen in the subgroup analysis, subjects had a trend of higher influenza risk if the index patient had been treated with baloxavir compared to other anti-influenza products. However, since only 3 out of 26 subjects were found to have virus with I38X substitutions later in the study and since baseline data were not available for 2 of the 3 of interest, nothing can be concluded on the risk of RAMs in baseline positives given baloxavir.

There was no apparent difference in efficacy in the subgroup analysis of vaccination status in either index patient or subject.

The secondary efficacy endpoint results overall support the primary endpoint results. The difference in RMST between the treatment groups of 0.8 days is difficult to interpret and, therefore, these data has not been included in the discussion of the clinical relevance and are not included in the SmPC.

A puzzling result is that the proportion of subjects with asymptomatic influenza virus infection was similar in both groups, but this reflects that a larger proportion of subjects in the baloxavir group who catch influenza compared to the placebo group will be asymptomatic, i.e. 29/49 (59%) vs 29/114 (25 %). Available virology data from study T0834 cannot address the question is baloxavir marboxil can have an impact on viral transmission. This issue is under investigation in a clinical study. It is agreed that viral shedding and transmission would be expected to be lower in asymptomatic individuals.

Based on the results of a real-world-data study with oseltamivir, the Applicant does not expect retreatment to be likely. Simulations of various retreatment scenarios predicted minimal accumulation of baloxavir marboxil during weekly retreatment. No accumulation of baloxavir was expected for retreatment every 2 or 4 weeks. Additionally, findings from CP40617 did not raise safety concerns when baloxavir marboxil were administered on Day 1, Day 4, and Day 7 if required, in combination with standard-of-case neuraminidase inhibitor. However, no clinical data are available for the efficacy or safety of retreatment in the PEP setting. Therefore, retreatment is not recommended in the PEP setting. This has been specified in section 4.2 of the SmPC.

The prerequisites of a single pivotal trial ((CPMP/EWP/2330/99)) and whether the proposed indication can be adequately supported by study T0834 alone needs be taken into consideration. These include both the internal validity and external validity of the study. The internal validity of study T0834 is considered appropriate and the efficacy results of the study convincing, though numbers are small. However, the external validity of the study could be questioned as study T0834 was conducted in Japan, mainly in subjects < 65 years of age, with extrapolation from one influenza season without incidences of B-influenza to all influenza seasons, and since all index patients had anti-influenza treatment. Extrapolation to a broader population is justified by reasonably comparable exposure. Extrapolation to other influenza types and subtypes is justified based on in vitro data and efficacy in treatment studies in different seasons. Finally, treatment of index patients may reduce viral transmission lowering the risk of infection of household members. Therefore, extrapolation to a setting with non-treated index patients with potentially (slightly) higher transmission is acceptable**.**

Assessment of paediatric data on clinical efficacy

Both the treatment and post-exposure prophylaxis indications are proposed from 12 years of age. Adults and adolescents from 12 years of age were included in study T0831 (OwH) + T0832 (HR), and the paediatric development in the treatment indication is ongoing. In study T0834 - conducted to support the PEP indication - smaller children (> 10 kg) were included and the study has been finalised. PK data from paediatric subjects < 12 years are available but have not been submitted.

2.5.4. Conclusions on the clinical efficacy

From a treatment of influenza infection point of view, the studies met their primary endpoint, i.e. the time to alleviation (otherwise healthy patients) or time to improvement (high-risk patients) was significantly decreased in baloxavir marboxil treated patients as compared to placebo treated patients. There was no difference in times to alleviation/improvement between baloxavir marboxil and the active comparator, oseltamivir.

While the secondary endpoints are considered exploratory due to insufficient handling of these, they all in all supported a favourable outcome in the baloxavir marboxil group as compared to placebo, e.g. time with viral shedding, time with fever and respiratory symptoms, and the number of complications in the HR groups was reduced.

With regard to prophylaxis, a single pivotal study has been submitted to support the PEP indication for baloxavir marboxil. Study T0834 met its primary endpoint and efficacy is supported by the supplementary analysis.

The single PEP study followed on from two successful treatment studies and used the same dose as for treatment, which is considered acceptable. The fact that the study was confined to Japan is not a major concern, and both the internal and external validity of the trial has been clarified.
In conclusion, no outstanding issues remain.

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

Xofluza resistance reports should be submitted annually to EMA as a post-marketing requirement (to be discussed in the PSUR)

2.6. Clinical safety

For the safety assessment of baloxavir marboxil in other-wise healthy (OwH) patients, the safety data from the two OwH Studies T0831 and T0821 were pooled, resulting in a total of 1632 patients in the safety population. From the baloxavir marboxil group in Study T0821, only the patients who received a 40 mg dose (n = 100) were included in the pooled dataset as this is one of the to-be marketed doses.

For the safety assessment of baloxavir marboxil in patients at high risk of developing influenza-related complications (HR patients), the pivotal Phase 3 Study T0832 provided safety data from 2178 HR adult and adolescent patients comprising the safety population.

For the safety assessment of baloxavir marboxil in household members of influenza-infected patients the phase 3 PEP (post-exposure prophylaxis) Study T0834 provided safety data from 749 subjects.

Patient exposure

In 12 phase 1 studies 329 adults received single 6 mg to 80 mg doses of baloxavir marboxil; and in 2 paediatric studies 140 children below 12 yoa received baloxavir marboxil in weight-adjusted doses.

Table 43 shows the number of subjects exposed to one dose of baloxavir marboxil in the 4 main studies (T0821, T0831, T0832, and T0834) by age and gender. Females constituted 56% of the total exposed population, 79% of the exposed PEP population. In total 71 (3.5%) children below 12 were included, while 109 (5.4%) of the subjects were 12-17 years old.

Table 38 Extent of Exposure by Age Group and Gender

Age Group	Male	Female	Total
Cumulative for All Indications			
28 days – 23 months	1 (0.1%)	0	1 (0.0%)
2 – 11 years	33 (3.7%)	37 (3.3%)	70 (3.5%)
12 – 17 years	58 (6.5%)	51 (4.5%)	109 (5.4%)
18 – 64 years	687 (77.5%)	930 (82.5%)	1617 (80.3%)
65 – 74 years	77 (8.7%)	83 (7.4%)	160 (7.9%)
75 – 84 years	31 (3.5%)	23 (2.0%)	54 (2.7%)
≥ 85 years	0	3 (0.3%)	3 (0.1%)
Total All Indications	**887 (100%)**	**1127 (100%)**	**2014 (100%)**
Treatment Indication			
Otherwise Healthy Population (Studies T0831 and T0821)			
12 – 17 years	41 (8.5%)	35 (8.2%)	76 (8.4%)
18 – 64 years	440 (91.5%)	394 (91.8%)	834 (91.6%)
Total OwH Population	**481 (100%)**	**429 (100%)**	**910 (100%)**
High Risk Population (HR Study T0832)			
12 – 17 years	13 (4.0%)	8 (2.0%)	21 (2.9%)
18 – 64 years	208 (63.2%)	292 (72.8%)	500 (68.5%)
65 – 74 years	77 (23.4%)	78 (19.5%)	155 (21.2%)
75 – 84 years	31 (9.4%)	21 (5.2%)	52 (7.1%)
≥ 85 years	0	2 (0.5%)	2 (0.3%)
Total HR Population	**329 (100%)**	**401 (100%)**	**730 (100%)**
Post-exposure Prophylaxis Indication (Study T0834)			
28 days – 23 months	1 (1.3%)	0	1 (0.3%)
2 – 11 years	33 (42.9%)	37 (12.5%)	70 (18.7%)
12 – 17 years	4 (5.2%)	8 (2.7%)	12 (3.2%)
18 – 64 years	39 (50.6%)	244 (82.2%)	283 (75.7%)
65 – 74 years	0	5 (1.7%)	5 (1.3%)
75 – 84 years	0	2 (0.7%)	2 (0.5%)
≥ 85 years	0	1 (0.3%)	1 (0.3%)
Total PEP Indication	**77 (100%)**	**297 (100%)**	**374 (100%)**

Percentages are based on column subtotals.

Adverse events

The AE profile was similar between treatment groups and between the OwH and HR populations. No new safety signals were identified. As expected, a slightly higher incidence of AEs was observed in the HR population across all treatment groups compared with the pooled OwH population, Table 39

Table 39 Overall Summary of Adverse Events in Pooled OwH Studies T0831/T0821 and HR Study T-832 (Safety Population)

	Pooled OwH Studies T0831/T0821			HR Study T0832		
	Baloxavir marboxil N = 710 n (%)	Placebo N = 409 n (%)	Oseltamivir N = 513 n (%)	Baloxavir marboxil N = 730 n (%)	Placebo N = 727 n (%)	Oseltamivir N = 721 n (%)
Patients with any AE	152 (21.4)	105 (25.7)	127 (24.8)	183 (25.1)	216 (29.7)	202 (28.0)
95% CI (%)	(18.4, 24.6)	(21.5, 30.2)	(21.1, 28.7)	(22.0, 28.4)	(26.4, 33.2)	(24.8, 31.4)
Number of AEs, n	201	158	179	282	342	332
Treatment-related AEs	33 (4.6)	22 (5.4)	43 (8.4)	41 (5.6)	60 (8.3)	57 (7.9)
95% CI (%)	(3.2, 6.5)	(3.4, 8.0)	(6.1, 11.1)	(4.1, 7.5)	(6.4, 10.5)	(6.0, 10.1)
Number of AEs, n	44	33	53	49	76	72
SAEs[a]	2 (0.3)	0	0	5 (0.7)	9 (1.2)	8 (1.1)
Number of AEs, n	2	0	0	7	9	15
Treatment-related SAEs	0	0	0	0	2 (0.3)	2 (0.3)
Number of AEs, n	0	0	0	0	2	2
Deaths	0	0	0	0[b]	0	1 (0.1)
AEs that resulted in discontinuation of study drug[a]	2 (0.3)	1 (0.2)	2 (0.4)	5 (0.7)	5 (0.7)	4 (0.6)
Number of AEs, n	3	4	2	6	6	7
Patients with any AE related to Hepatic Function	12 (1.7)	12 (2.9)	13 (2.5)	15 (2.1)	13 (1.8)	18 (2.5)
Patients with any Neuropsychiatric AE	17 (2.4)	12 (2.9)	8 (1.6)	16 (2.2)	19 (2.6)	27 (3.7)

AE = adverse event; CI = confidence interval; SAE = serious adverse event.

[a] Events in the pooled OwH dataset occurred in Study T0831 only.

[b] One patient (0.1%) in the baloxavir marboxil group died due to an SAE of acute myocardial infarction. The SAE onset was prior to drug administration on Day 1 and resulted in the patient's death on Day 24. The SAE was considered non-treatment emergent.

By preferred term, the most common AEs (≥ 2%) in baloxavir marboxil-treated patients were bronchitis (2.4%) and diarrhoea (2.8%) in the OwH population, and bronchitis (2.9%), diarrhoea (2.7%), and nausea (2.7%) in the HR population. In all cases, the incidence was similar to or lower than the incidence in the placebo and oseltamivir groups.

The severity of AEs was consistent between the OwH and HR populations. In both patient populations, the majority of AEs were mild (Grade 1) or moderate (Grade 2). Also, the incidence of treatment-related AEs was consistent between the pooled OwH studies and the HR study.

The incidence of abnormal changes in liver function tests (< 2% in any population and treatment group) and AEs related to hepatic disorders was low (< 3%) and generally similar between treatment groups and between the OwH and HR populations. Finally, the incidence of AEs related to neuropsychiatric disorders was low (< 4% in any population and treatment group) and generally similar between treatment groups and between the OwH and HR populations.

Regarding the PEP study, the overall incidence of AEs and treatment-related AEs (assessed by the investigator) was also almost similar between the baloxavir marboxil and placebo, Table 45.

Influenza virus infection itself was not reported as an AE. Regarding symptoms of influenza infection (cough, sore throat, headache, nasal discharge/nasal congestion, feverishness or chills, muscle or joint pain, and fatigue), these were reported as AEs unless both of the following conditions were met at the study visit: 1) The subject was diagnosed with influenza virus infection using a rapid influenza

diagnostic test (RIDT positive) and 2) The symptom was related to influenza virus infection, in the opinion of the investigator. If both conditions were met, the symptom was not reported as an AE in the CRF.

Table 40 Overall Summary of Adverse Events in PEP Study T0834 (Safety Population)

	Baloxavir marboxil N = 374 n (%)	Placebo N = 375 n (%)
Subjects with:		
Any AE	83 (22.2)	77 (20.5)
95% CI (%)	(18.1, 26.7)	(16.6, 25.0)
Number of AEs, n	102	99
Treatment-related AEs	7 (1.9)	6 (1.6)
95% CI (%)	(0.8, 3.8)	(0.6, 3.4)
Number of AEs, n	7	7
SAEs	0	1 (0.3)
Number of SAEs, n	0	1
Treatment-related SAEs	0	0
Deaths	0	0
AEs that resulted in discontinuation of study	0	1 (0.3)
Number of AEs, n	0	1

AE = adverse event; CI = confidence interval; SAE = serious adverse event.

The most commonly reported AEs (≥ 1% of subjects in either treatment group) were nasopharyngitis (baloxavir marboxil: 6.4% and placebo: 6.7%), headache (2.1% and 1.6%), blood urine present (1.6% and 0.3%; all blood urine present AEs were Grade 1 in severity and were recorded in female subjects only), pharyngitis (1.1% and 0.3%), and ALT increased (1.1% and 0.3%).

All AEs were Grade 1–2 in the baloxavir marboxil and placebo groups, with the exception of one Grade 3 AE (psychotic disorder) in the placebo group. The vast majority of AEs resolved or were resolving by the end of the study (98.0% in both treatment groups) for QC bxm total 102 AEs – 1 unknown – 1 not recovered = 98.0% pbo 99 AEs – 2 not recovered = 98.0%.

The incidence of abnormal changes in liver function tests was ≤ 1% in either treatment group; in the baloxavir marboxil group, no Grade 3 or 4 abnormalities in ALT, AST, or total bilirubin occurred. No subject experienced ALT or AST > 3 x ULN simultaneously with a total bilirubin > 2 x ULN.

Serious adverse event/deaths/other significant events

No fatal SAEs were reported in the OwH studies. In HR Study T0832, 1 patient in the oseltamivir group had a fatal SAE of pneumonia (onset on Day 12 and death on Day 38) and 1 patient in the baloxavir marboxil group had a fatal SAE of acute myocardial infarction (SAE onset prior to study drug administration on Day 1 and death on Day 24).

The incidence of SAEs was overall low in both the pooled OwH studies and the HR study. Two patients (0.3%) in the pooled OwH Studies T0831/T0821, both in the baloxavir marboxil group of Study T0831, experienced SAEs of viral meningitis and incarcerated inguinal hernia, neither of which were considered related to study treatment. The incidence of SAEs (excluding death) in HR Study T0832 was low and

similar across the 3 treatment groups, occurring in 5 patients (0.7%) in the baloxavir marboxil group, 9 patients (1.2%) in the placebo group, and 8 patients (1.1%) in the oseltamivir group

In the PEP Study T0834 no deaths were reported; and there were no SAEs reported in the baloxavir marboxil group; one SAE (psychotic disorder) was reported in the placebo group, which had not resolved by the end of study.

Laboratory findings

Within each study (T0831, T0821, and T0832), no clinically relevant differences between treatment groups were observed in haematology, chemistry, or urinalysis laboratory parameters. The most common laboratory abnormalities were elevated C-reactive protein and abnormalities in differential white blood cell counts; however, these are common during infections. The abnormalities occurred most frequently at the baseline visit, were similar in all treatment groups within each of the three studies, and returned to normal levels by the last study visit in the majority of patients.

In the PEP study no clinically, relevant differences were found in changes from baseline or in proportion of subjects with abnormalities in haematology, blood chemistry, or urinalysis laboratory parameters between the baloxavir marboxil and the placebo group. The incidence of Grade 3 and 4 laboratory abnormalities was low at each measured timepoint (Days 1, 5, and 15) in the baloxavir marboxil group (maximum 0.8%) and the placebo group (maximum 1.6%) for each parameter tested

Safety in special populations

For the pooled OwH studies (T0831/T0821), subgroup AE analyses were performed by *age* (T0831 only: < 18 or ≥ 18 years), *body weight* at baseline (< 80 kg or ≥ 80 kg), *gender* (male or female), *race* (Asian or Non-Asian), and *region* (Japan or United States). For the HR T0832 study, subgroup AE analyses were performed by *age* (<18, 18 – 64, 65 – 74, or ≥ 75 years), *body weight* at baseline (< 80 kg or ≥ 80 kg), *gender* (male or female), *race* (Asian or Non-Asian), *HR category* (asthma or chronic lung disease, endocrine disorders, ≥ 65 years of age, heart disease, morbid obesity, metabolic disorders), and *region* (Asia or North America / Europe).

Overall, in both OwH and HR populations, there were no apparent or clinically meaningful differences found in the age, body weight, gender, HR category (T0832 only), or race subgroup analyses.

In OwH Study T0831 infections and infestations were the most frequent SOC in the age-group ≥ 18 years with around 10% affected followed by GI disorders, appr 7%, in all three arms. For the age group < 18 infections/infestations were reported in 4% in the baloxavir group, in 15% in the placebo group. GI disorders were more equally represented with appr 6% in both groups. In the HR Study T0832 only a total of 13 patients in the age group < 18 years had any AE. For the age groups 18-64 and 65-74 appr 27% had any AE in all 3 arms. Again infections/infestations were the most frequently represented SOC. For the age group ≥ 75 years many more patients had any AE: 30-45%. GI disorders was the most frequent SOC with most patients reporting nausea.

By region, across all treatment groups in the pooled OwH population, patients in the Japan subgroup (baloxavir marboxil: 24.4%, placebo: 27.1% oseltamivir: 26.5%) had a higher incidence of AEs compared with the United States subgroup (baloxavir marboxil: 16.1%, placebo: 22.5% oseltamivir: 22.2%). However, most AEs occurred at low frequencies and no particular AE was markedly higher in the Japan subgroup compared to the United States subgroup. In the HR T0832 study, there were generally no clinically meaningful differences in the incidence or nature of AEs by region (between regions or between treatment groups within regions).

In the PEP study subgroup analysis was performed by age using < 12 and ≥ 12 years of age subgroups. Of the 749 subjects in the safety population, 142 were < 12 years of age. In both treatment groups, a slightly higher proportion of subjects aged < 12 years experienced an AE (25.4% in both treatment groups) compared with the ≥ 12 years subgroup (baloxavir marboxil: 21.5% and placebo: 19.4%). However, no relevant differences in the nature of AEs was observed across the age subgroups. Across treatment groups, similar proportions of subjects experienced an AE for patients weighing < 20 kg (baloxavir marboxil: 42.1%, placebo: 32.3%), 20 to < 40 kg (17.5% and 18.6%), 40 to < 80 kg (21.8% and 20.1%), and ≥ 80 kg (22.2% and 11.1%, respectively). The frequency of AEs was higher in the age group weighing < 20 kg; however, the number was very low. Of the 749 subjects, 78.4% were female. In both treatment groups, a similar proportion female (baloxavir marboxil: 22.9% and placebo: 22.1%) and male (baloxavir marboxil: 19.5% and placebo: 15.3%) subjects experienced an AE.

Safety related to drug-drug interactions and other interactions

Drug interaction studies including Study T0814 (interaction study with midazolam), Study T0815 (itraconazole), Study T0818 (oseltamivir phosphate), T081C (probenecid), and T081D (digoxin and rosuvastatin) did not reveal any safety or tolerability findings when these drugs were administered concomitantly with baloxavir marboxil.

Discontinuation due to adverse events

The incidence of AEs leading to withdrawal of study drug was < 1% in both the OwH Study T0831 and the HR Study T0832. In the PEP study no AE led to discontinuation in the baloxavir marboxil group; in the placebo group one subject had an AE (psychotic disorder) that led to discontinuation.

Post marketing experience

The first authorisation of baloxavir marboxil was in Japan for the treatment of influenza A or B virus infection in otherwise healthy patients on 23 February 2018.

Since March 2018, an estimated cumulative total of 5,902,702 patients (5,653,250 in Japan, 240,266 in the US, and 9,186 in rest of the world countries) have received baloxavir marboxil in the post-marketing setting.

The Applicant has evaluated the post-marketing data received since the initial commercial distribution of baloxavir marboxil on 14 March 2018 up to 22 August 2019 (approximately 18 months after the international birth date [IBD]).

Hypersensitivity reactions (including anaphylaxis) was confirmed as a safety signal from post-marketing data and has been added as an ADR to the product label as a risk mitigation action. The Applicant continues to monitor such events for any change in nature, frequency, or severity. The Applicant considers haemorrhagic events, in association with use of baloxavir marboxil, to be a validated signal from post-marketing data, and a full evaluation is ongoing.

2.6.1. Discussion on clinical safety

The safety of Baloxavir Marboxil was evaluated in three phase 3 studies (Studies T0831, T0832 and T0834) and one phase 2 dose-finding study (Study T0821). The applicant has for the purpose of the SCS pooled the safety data from Studies T0831 and T0821. The target population for Studies T0831/T0821 (n=1632) was OwH patients with influenza symptoms aged 12 to 64 years (Study T0831) or aged 20 to 64 years (Study T0821). Patients with severe underlying diseases and patients

who had any of the risk factors as defined in the CDC criteria were excluded. The target population of Study T0832 (n=2178) was patients ≥ 12 years of age (no upper age limit) with influenza symptoms and considered at high risk of developing influenza-related complications (criteria adapted from the CDC criteria). The target population for the prophylaxis study T0834 (n=749) was subjects of all ages who were household members of influenza-infected patients.

Baseline demographics and disease characteristics were well balanced across the treatment groups within each population / each study; and results were generally similar to those described for the ITTI population in the SCE. In the pooled OwH population only 29% were white, while this was the case for 59% in the HR population. In total white subjects constituted 46% (1759/3810) of the two populations – and of these 1759 white patients, 638 were exposed to baloxavir marboxil. As the PEP study was conducted in Japan only no further white persons were included in the safety-populations. In the HR study the disease seemed to be more serious with a higher symptom score, but the frequency of patients tested negative for influenza virus was significantly higher than in the pooled OwH studies.

Treatment of influenza with baloxavir marboxil was overall well tolerated and no apparent safety concerns were identified. The safety profile was overall consistent between treatment groups and between the pooled OwH population and the HR population, see above.

A slightly higher incidence of AEs was observed in the HR population compared with the pooled OwH population across all treatment groups. However, the incidence of treatment-related AEs was consistent between the pooled OwH studies and the HR study. In both populations, the incidence of treatment-related AEs was higher in the oseltamivir-group as compared to the baloxavir marboxil group.

The most commonly reported AEs were bronchitis, sinusitis, diarrhoea, nausea (Study T0831 & T0832), nasopharyngitis, seasonal allergy, vertigo, headache, diarrhoea, gastritis (Study T0821). The AE-pattern was consistent among treatment groups. No AE was reported in ≥ 5% in any treatment group in any study. The majority of the AEs were Grade 1-2, and the majority resolved. In Study T0821 no dose-dependent increases in AEs were observed.

SAEs were reported in 2 patients only in the pooled OwH studies (viral meningitis, incarcerated inguinal hernia; not related to study drug). Thirty-one SAEs were reported in the HR study; however, none of the 7 SAEs occurring in 5 patients in the baloxavir marboxil group were treatment-related. The severity of AEs was consistent between the OwH and HR populations. In both patient populations, the majority of AEs were mild (Grade 1) or moderate (Grade 2).

No fatal AEs were reported in the OwH studies. In HR Study T0832, 1 patient in the oseltamivir group had a fatal AE of pneumonia (onset on Day 12 and death on Day 38) and 1 patient in the baloxavir marboxil group had a fatal AE of acute myocardial infarction (AE onset prior to study drug administration on Day 1 and death on Day 24).

The incidences of AEs leading to withdrawal of study drug were low in all treatment groups in both the OwH studies and in the HR study.

The incidence of abnormal changes in liver function tests, AEs related to hepatic disorders and the incidence of AEs related to neuropsychiatric disorders was low and generally similar between treatment groups and between the OwH and HR populations.

Regarding laboratory data, it is concluded that within each study, no clinically relevant differences between treatment groups were observed in haematology, chemistry, or urinalysis laboratory parameters. The most common laboratory abnormalities were elevated C-reactive protein and abnormalities in differential white blood cell counts, which are common during infections. These abnormalities occurred most frequently at the baseline visit, were similar in all treatment groups within

each of the three studies, and returned to normal levels by the last study visit in the majority of patients.

In Study T0821 clinically significant abnormal ECG findings were noted in 4 patients. There was one case of baloxavir-unrelated bradycardia. The remaining 3 cases were "considered to be caused by their existing medical condition at baseline." However, as the patients were per inclusion criteria "otherwise healthy" the applicant clarified on request, that the ECGs showed ventricular extrasystoles (1 pt) and right bundle branch block (2 pts). As these ECG diagnoses are clinically insignificant, it was acceptable to include the patients

Analyses of AEs by Intrinsic factors (age, body weight, gender, race, high risk category) and Extrinsic factor (region) revealed no apparent differences in frequencies and nature of AEs among treatment groups and studies. Only 638 white patients have been exposed to baloxavir marboxil and from the analyses of AEs by race it appears that diarrhoea, vomiting, bronchitis and sinusitis were more frequent among non-Asian patients. However, the overall incidence of AEs appears higher in the Asian population compared with the non-Asians within each of the treatment groups. Taking into account the size of each comparator group and the low numbers of AEs reported, and comparing the overall AE incidence for each race subgroup across treatment groups, the rate was higher in the placebo subgroups compared with the corresponding baloxavir marboxil subgroups.

No ADRs were identified as for no AEs both criteria for ADRs were met in any of the OwH + HR safety populations.

In PEP Study T0834 the pattern of AEs was the same as described above: The overall incidence of AEs and treatment-related AEs (assessed by the investigator) was similar between the baloxavir marboxil and placebo groups (22.2% vs. 20.5% and 1.9% vs. 1.6%, respectively). Pharyngitis, headache, blood urine present, and ALT increased were numerically higher in the baloxavir marboxil group than in the placebo group; however, the Sponsor assessment of causality which was based on both individual and aggregate case review of events revealed that these AEs were most likely related to factors other than baloxavir marboxil.

All AEs in the PEP study were Grade 1–2 with the exception of one Grade 3 AE (psychotic disorder) in the placebo group; the vast majority of AEs resolved or were resolving by the end of the study (98.0% in both treatment groups) for QC bxm total 102 AEs – 1 unknown – 1 not recovered = 98.0% pbo 99 AEs – 2 not recovered = 98.0%. No deaths were reported; and only one SAE (psychotic disorder) was reported in the placebo group - which led to discontinuation of study drug. Furthermore, the incidence of abnormal changes in liver function tests was low ($\leq$1% in either treatment group); in the baloxavir marboxil group, no Grade 3 or 4 abnormalities in ALT, AST, or total bilirubin occurred. No subject experienced ALT or AST $>$ 3 $\times$ ULN simultaneously with a total bilirubin $>$ 2 $\times$ ULN. None of 20 neuropsychiatric AEs were considered treatment-related.

None of the AEs fulfilled the criteria for an ADR – and consequently no AEs reported in the 4 main studies should be included in the SmPC section 4.8.

Further to the four phase 2 and 3 studies the applicant has in the SCS included information about 12 phase 1 studies: 329 healthy subjects or patients with moderate hepatic impairment received single 6 to 80 mg doses of baloxavir marboxil. No deaths or other SAEs occurred in any of the studies. Most of the AEs were mild, and of the AEs that occurred in $\geq$ 2 subjects in any of the studies (increased ALT, increased eosinophils, increased white blood cells, dizziness, nausea, headache, and nasopharyngitis), only headache occurred in more than 1 study.

Two paediatric studies have been completed in which a total of 140 children received baloxavir marboxil. In both studies, there were no deaths, SAEs, or AEs leading to withdrawal. All AEs were Grade 1–2 and most of them resolved by the end of the study. The most common AE was vomiting, all

of which were Grade 1 in severity and were not considered related to study drug. No significant safety concerns were identified and baloxavir marboxil was generally well tolerated.

Post-marketing data: Baloxavir marboxil was approved in Japan for the treatment of influenza A or B virus infection in otherwise healthy patients across all age ranges (body weight ≥ 10 kg) on 23 February 2018. Since then, baloxavir marboxil has been approved in a number of other countries around the world, including the United States, for the treatment of influenza in patients aged 12 and above who have been symptomatic for no more than 48 hours. In Thailand, baloxavir marboxil is also approved for treating patients who are at high risk of developing influenza-related complications. It is estimated that a total of 5,902,702 patients (5,653,250 in Japan, 240,266 in the US, and 9,186 in rest of the world countries) have received baloxavir marboxil.

During the reporting period a total of 6831 AEs were received spontaneously of which 820 were considered serious. In addition, 316 solicited events (of which 8 were serious) from non-interventional studies were reported (studies which will be reported when evaluated).

Almost one third of the 7147 reported AEs belonged to the SOC Gastrointestinal disorders.

The applicant identified hypersensitivity reactions as a safety signal, conducted a thorough evaluation of all relevant data, and consequently updated the SmPC to include hypersensitivity reactions. As haemorrhagic events were also considered a validated signal, a full evaluation was also conducted.

The applicant has at Day 121 submitted Drug Safety Reports concerning hypersensitivity reactions and haemorrhagic events. Based on the review of the post-marketing data the Applicant believes that baloxavir marboxil is likely to be causally associated with hypersensitivity reactions characterized by the features of urticaria, angioedema and anaphylaxis/anaphylactic reaction and recommends an update to the company core datasheet. Severe cutaneous reactions, along with other hypersensitivity reactions, will continue to be closely monitored via routine signal detection activities.

Regarding haemorrhagic events:

Following a close evaluation of the cases received at both an individual case level and in aggregate, the data were not considered to suggest a causal association with the use of baloxavir marboxil. No additional risk minimization measures are considered required. Events reporting bleeding will continue to be evaluated.

The applicant was asked to update the post-marketing data at the time of responding to the D120 LOQ and to re-appraise and justify the content of section 4.8 of the SmPC accordingly. Subsequently, an updated evaluation of post-marketing data from all sources for the period 23 August 2019 to 22 February 2020 has been undertaken to inform the first Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report (PBRER/PSUR). Exposure is now estimated to be in excess of 7.2 million patients with the majority (approximately 6.8 million) in Japan. It is concluded, that based on the cumulative and interval data, no further safety updates are proposed for Section 4.8 of the SmPC.

SmPC

There are no safety warnings in section 4.4 of the SmPC, apart from those related to excipient warnings whilst section 4.3 contraindicates use in patients known to be hypersensitive to baloxavir or excipients

Based on post-marketing data, anaphylaxis, anaphylactic reactions, hypersensitivity and angioedema have been added as ADRs to section 4.8. Based on the clinical trial data, urticaria has been added to section 4.8 of the SmPC with a frequency of uncommon.

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

2.6.2. Conclusions on the clinical safety

The safety of baloxavir marboxil in the treatment of influenza has been evaluated in 12 phase 1 studies (329 subjects), 2 paediatric studies (140 children < 12 yoa), one phase 2 study in adults (100 subjects), two phase 3 studies (including 1432 and 2178 subjects, respectively) and in one phase 3 prophylaxis study (749 subjects). No AEs fulfilling the definition of ADRs were reported in the clinical studies. Post marketing data have become available since February 2018, where the product was first approved in Japan, and it is estimated that approximately 6 million people have received baloxavir marboxil. Due to a number of post marketing reports of hypersensitivity a thorough evaluation of all relevant data has resulted in inclusion of hypersensitivity as an ADR in the SmPC section 4.8. Furthermore, a full evaluation of haemorrhagic events is ongoing. No safety concerns precluding a favourable risk-benefit.

2.7. Risk Management Plan

The applicant submitted an updated EU Risk Management Plan for Xofluza (baloxavir marboxil), version number 1.1, data lock point for current RMP 22 August 2019, dated 2 October 2020.

Safety concerns

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

Pharmacovigilance plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
Category 1 — Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorization				
Not applicable				
Category 2 — Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 — Required additional pharmacovigilance activities (by a competent authority such as CHMP/PRAC or NCA) — i.e., studies that investigate a safety concern or evaluate the effectiveness of risk minimization activities				
Not applicable				

Risk minimisation measures

Not applicable (no additional risk minimization activities).

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.1 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 23.02.2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of baloxavir marboxil with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers baloxavir marboxil to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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.*

2.10.2. Labelling exemptions

Not applicable.

2.10.3. Quick Response (QR) code

Not applicable.

2.10.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Xofluza (baloxavir marboxil) is included in the additional monitoring list as it contains a new active substance.

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 influenza in patients aged 12 and above, including patients at high risk of developing influenza-related complications.

Xofluza is indicated for the post-exposure prophylaxis of influenza in individuals aged 12 and above.

Influenza is an acute febrile illness caused by infection with influenza type A and/or B viruses that occurs in outbreaks of varying severity every winter in temperate climates and year-round in tropical climates. Influenza viruses are highly contagious with efficient person-person spread within communities and the potential for significant public health challenges due to severe morbidity and mortality from both seasonal flu and pandemics.

Annual influenza epidemics are thought to result in between 3 and 5 million cases of severe illness and between 290,000 and 650,000 deaths every year around the world (WHO 2018a).

Baloxavir marboxil is an anti-influenza virus drug with a novel mechanism of action. 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.

3.1.2. Available therapies and unmet medical need

Two classes of influenza anti-viral medications have been approved in Europe: M2 blockers and neuraminidase inhibitors (NAIs). Widespread, transmissible resistance has rendered the M2 blockers entirely ineffective. NAIs act principally at the end of the viral life cycle to prevent release of the virus from the infected cell. This mechanism of action delivers relatively modest antiviral activity. Viral replication inhibitors are thought to be more effective than either virus entry or exit inhibitors. A simplified dosing regimen (e.g., single oral dose) for influenza anti-viral medications is also desirable for patient convenience. This could maximize patient adherence.

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. For these reasons, having the option to provide treatment and prevention with an anti-influenza virus drug is necessary and especially important in populations at high risk of developing influenza-related complications (both hospitalized and outpatients).

There is therefore an unmet need for an easily administered (e.g., single oral dose) antiviral drug with good antiviral efficacy and a new mechanism of action–ideally with a high barrier to resistance, but at a minimum lacking cross-resistance with NAIs.

3.1.3. Main clinical studies

Treatment:

The evidence for treatment efficacy derives from three studies; one phase 2 study and two phase 3 studies:

- 1 randomised, double-blind, placebo controlled, pivotal, Phase 2 studies on the treatment of diagnosed influenza in otherwise healthy subjects (OwH).
- 2 multicentre, randomised, double-blind, placebo- and comparator controlled, pivotal, Phase 3 studies on the treatment of diagnosed influenza in otherwise healthy subjects and in patients at high-risk of developing complications (HR).

Treatment was a single dose of baloxavir marboxil initiated within 48 h of influenza onset. The primary endpoint was time to recovery in terms of time to alleviation of symptoms (OwH) or improvement of symptoms (HR).

PEP:

The main evidence of efficacy is a single pivotal, randomized, double-blind, placebo-controlled Phase 3 study T0834 in subjects of all ages who were household members of all ages of influenza-infected patients with symptoms < 48 hours. Treatment was a single dose baloxavir marboxil. The study was conducted in Japan in the 2019/2019 influenza season. With two successful treatment studies, a single pivotal PEP study vs. placebo is considered acceptable.

3.2. Favourable effects

Treatment:

In the otherwise healthy population, treatment with baloxavir marboxil reduced the time with influenza-related symptoms. The median time with influenza symptoms was 54 h (50-59 h) in the baloxavir marboxil group as compared to 80 h (73-87 h) in the placebo group.

Similarly, in the high-risk population, treatment with baloxavir marboxil reduced the time with influenza-related symptoms. The median time with influenza symptoms was 73 h (67-85 h) in the baloxavir marboxil group as compared to 102 h (93-113 h) in the placebo group.

The overall faster recovery was also reflected in the secondary endpoints. The time to alleviation/improvement of systemic symptoms (headache, feverishness or chills, muscle or joint pain, and fatigue), respiratory symptoms (cough, sore throat and nasal congestion), and individual symptoms (all of the above) was shorter in the baloxavir marboxil group than the placebo group in both the otherwise healthy and high-risk populations.

In the high-risk population, the number of influenza-related complications was decreased in patients treated with baloxavir marboxil; 3% (11/388) in baloxavir marboxil group vs. 10% (40/386) in placebo group. In addition, the proportion of patients, who received systemic antibiotics for infections secondary to influenza infection, was lower in the baloxavir marboxil group; 3% (13/388) in baloxavir marboxil group vs. 8% (29/386) in placebo group.

Finally, the proportion of patients, who had a positive influenza virus titre at each time point after treatment initiation, was reduced in the baloxavir groups as compared to the placebo groups in both the otherwise healthy and high-risk populations.

There was no difference between the baloxavir marboxil and the active comparator, oseltamivir, groups.

PEP:

A single dose of baloxavir to household members of index patients maintained preventive exposure levels for 10 days and a beneficial effect of baloxavir marboxil compared with placebo in the prevention of symptomatic influenza infection has been shown in study T0834. The study was effectively a measure of prevention of clinically manifest infection with influenza A in parents who were randomised within 24 h of onset of disease in paediatric index cases and were negative for influenza (based on RT-PCR) at baseline. The minority of randomised subjects consisted of paediatric contacts of index cases (19%) and less than 5% were aged 65+years.
A significant lower proportion of subjects were infected with symptomatic influenza (RT-PCR positive influenza and symptoms of fever and at least one respiratory symptom during the period) in the baloxavir marboxil group compared to the placebo group (1.9% vs. 13.6%; adjusted risk ratio 0.14 [95% CI: 0.06, 0.30], $p < 0.0001$). 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.

A risk reduction of 86 % is considered clinically relevant, and in absolute numbers, the number needed to treat to prevent one case of influenza is 9 (ARR= 13.6 – 1.9 = 11,7 %, NNT = 1/ 0.117 = 8.5).

3.3. Uncertainties and limitations about favourable effects

Treatment:

There is solid evidence for the primary endpoint in both the otherwise healthy and the high-risk populations. It was prespecified and adequately tested.

In comparison, the secondary endpoints were not prioritised before study initiation and the analyses of the endpoint were not adjusted for multiple testing. Therefore, the secondary endpoints are considered exploratory. Nevertheless, the secondary endpoints, which were predominantly subgroups of the primary endpoint (time to resolution headache, feverishness or chills, muscle or joint pain, fatigue, cough, sore throat, nasal congestion, or viral shedding), all favoured baloxavir marboxil over placebo.

Similarly, the proportion of patients, who had a positive influenza virus titre at each time point after treatment initiation, and the proportion of patients, who received systemic antibiotics for infections secondary to influenza infection, in the high-risk population were non-prioritised and non-adjusted for multiplicity. Therefore, less emphasis may be put on these results, even though they are plausible in the light of the outcome of the primary endpoint. This is regrettable since a reduction of influenza-related complications is of high clinical relevance.

Finally, the proposed indication includes a broader population than the one studied in the pivotal studies. Specifically, only patients with uncomplicated influenza were included. The indication should reflect this. Furthermore, while the selection criteria for high-risk patients generally followed the criteria defined by the Centre for Disease Control, not all CDC-listed patient groups were eligible for inclusion. Thus, the entire spectrum of high-risk patients was not studied.

PEP:

Only results from one single pivotal study are available and numbers of events are small, 7 and 51 subjects presented with influenza virus infection (RT-PCR positive), fever, and at least one respiratory symptom in the baloxavir and placebo group respectively. Retreatment is expected to be uncommon

for the Post-exposure prophylaxis and 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 was 48 hours, efficacy beyond this timeframe is not known.

3.4. Unfavourable effects

No ADRs (defined as treatment-emergent AE incidence of ≥ 1% in the baloxavir marboxil group and a higher incidence than in the placebo group plus medical judgment indicating the AE was likely due to the drug) were reported in the three treatment studies or in the post-exposure prophylaxis study.

A slightly higher incidence of AEs was observed in the HR population compared with the pooled OwH population; however, this was the case in all treatment groups. In both populations, the incidence of treatment-related AEs was higher in the oseltamivir-group as compared to the baloxavir marboxil group.

The most commonly reported AEs were bronchitis, sinusitis, diarrhoea, nausea, nasopharyngitis, seasonal allergy, vertigo, headache, and gastritis. However, the AE-pattern was consistent among treatment groups. No AE was reported in ≥ 5% in any treatment group in any study. The majority of the AEs were Grade 1-2, and the majority resolved. In Study T0821 no dose-dependent increases in AEs were observed.

No SAEs reported in the pooled OwH studies or in the HR study were treatment-related. One patient in the HR study treated with baloxavir died; however, the AE (AMI) had onset prior to study drug administration. The severity of AEs was consistent between the OwH and HR populations. In both patient populations, the majority of AEs were mild (Grade 1) or moderate (Grade 2).

3.5. Uncertainties and limitations about unfavourable effects

A number of limitations related to the study populations may restrict the possibility to catch all potential AEs or other unfavourable effects adhered to baloxavir marboxil:

In the treatment studies no subject was below 12 year of age (yoa), in the PEP study this was the case for 71 subjects. However, the applicant does not apply with this application for an indication in children below 12. A paediatric development plan (PIP) including children from birth to < 12 years has been approved by the PDCO.

Only 57 subjects above 75 yoa were exposed to study drug; however, there are no indications of a higher risk of AEs among older subjects.

A number of exclusion criteria were included in the clinical study protocols which inherently imply the risk of "missing" some unfavourable effects. Excluded were

1. Women who were pregnant or within 2 weeks post-partum; however, Section 4.6 of the SmPC advises against the use of baloxavir marboxil during pregnancy, unless the potential benefit for the mother outweighs the potential risk to the foetus.
2. Women who were breastfeeding; however, Section 4.6 of the SmPC advises that the potential benefit of baloxavir marboxil to the nursing mother and the potential risk to the infant should be taken into account.
3. Patients who had a severe influenza virus infection requiring inpatient treatment. Due to this exclusion criterion it is recommended to amend the indication to read: Treatment of *uncomplicated* influenza ……

It was demonstrated in Study T0821 that the frequency of AEs did not increase with increasing dose.

3.6. Effects Table

Table 41 Effects Table for Xofluza for treatment and prophylaxis of influenza.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects: treatment of influenza						
Reduced time to alleviation Primary endpoint	Otherwise healthy population: Time to recovery from influenza related symptoms	Hours 95% CI	54 h (50-59 h)	Placebo: 80 h (73-87 h) Oseltamivir: 54 h (50-56 h)	Firm evidence	SCE table 9 + Table 10
Reduced time to improvement Primary endpoint	High-risk population: Time to improvement of symptoms – reduction to baseline level of symptoms	Hours 95% CI	73 h (67-85 h)	Placebo: 102 h (93-113 h) Oseltamivir: 81 h (69-92 h)	Firm evidence	SCE Table 19
Reduced number of complications Secondary endpoint	High-risk population: Number of influenza-related complications	% (n/N)	3% (11/388)	Placebo: 10% (40/386) Oseltamivir: 5% (15/389)	Exploratory investigations	SCE Table 20
Favourable Effects: Prevention of influenza						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Proportion of subjects with influenza infection, fever, and at least one respiratory symptom Primary endpoint (total population) < 12 years 12+ years only	Clinical significant Influenza events in household members to index patients mITT	% (n/N)	1.9% (7/374) 4.2% 1.3%	Placebo: 13.6% (51/375) 15.5% 13.2 %	Firm evidence	SCE Table 68
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	% (n/N)	5.3% (20/374)	Placebo: 22.4% (84/375)	Exploratory investigation (secondary endpoints not prioritised)	SCE Table 68
Proportion of subjects with influenza infection regardless of symptoms Secondary endpoint	Influenza events n household members to index patients mITT	% (n/N)	13.1% (49/374)	Placebo: 30.4% (114/375)	Exploratory investigation (secondary endpoints not prioritised)	SCE Table 68
Unfavourable Effects						
Hypersensi-tivity reactions	Anaphylaxis Urticaria		< 1/1000	Post-marketing data		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Compared to placebo, baloxavir marboxil statistically significantly reduced the time with influenza-related symptoms. The median reduction (compared to placebo) in time with influenza symptoms was approximately 24 hours, slightly more for HR than for OwH. This reduction is considered clinically relevant and comparable to what is seen for other drugs for this indication. Potentially of greater importance is the beneficial effect of baloxavir marboxil on the number of influenza-related complications and proportion of patients, who received systemic antibiotics for infections secondary to influenza infection, as these secondary endpoints suggest a beneficial effect on the more serious consequences of influenza. Although the numerical difference between active and placebo suggests that this effect is indeed clinically relevant, the results must be interpreted with caution as the analyses of secondary endpoints were not controlled for multiplicity.

The single PEP study followed on from two successful treatment studies and used the same dose as for treatment, which is considered acceptable. The fact that the study was confined to Japan is not a concern. Whilst the study included subjects aged <12 years, the majority was aged 12+ years and efficacy was shown overall and in the latter group.

A single dose of baloxavir to household members of index patients maintained preventive exposure levels for 10 days. A significant lower proportion of subjects were infected with symptomatic influenza. A risk reduction of 86 % is considered clinically relevant, and in absolute numbers, the number needed to treat to prevent one case of influenza is 9 (ARR= 13.6 – 1.9 = 11,7 %, NNT = 1/ 0.117 = 8.5).

The unfavourable effects of baloxavir marboxil appears to be very limited and clinically manageable. No AE was reported in ≥ 5% in any treatment group in any study. The majority of the AEs were Grade 1-2, and the majority resolved. No AEs fulfilling the definition of ADRs were reported in the clinical studies. Post marketing data have become available since February 2018, where the product was first approved in Japan, and it is estimated that approximately 7.2 million people have received baloxavir marboxil. Due to a number of post marketing reports of hypersensitivity a thorough evaluation of all relevant data has resulted in inclusion of hypersensitivity as an ADR in the SmPC section 4.8. Furthermore, a full evaluation of haemorrhagic events has been conducted. Data were not considered to suggest a causal association with the use of baloxavir marboxil. The information about the safety of baloxavir marboxil in pregnant and lactating women as well as children (below the age of 12) and elderly (above the age of 65) is currently limited. However, these uncertainties are considered manageable if the SmPC includes adequate warnings and restrictions.

3.7.2. Balance of benefits and risks

The benefit/risk balance for the proposed treatment indication is considered positive for both the treatment and PEP indication.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of Xofluza is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Xofluza is favourable in the following indication:

Treatment of influenza

Xofluza is indicated for the treatment of uncomplicated influenza in patients aged 12 years and above.

Post-exposure prophylaxis of influenza

Xofluza is indicated for post-exposure prophylaxis of influenza in individuals aged 12 years and above.

Xofluza should be used in accordance with official recommendations.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other 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.

The marketing authorisation holder shall submit aperiodic safety update report for this product within 6 months following authorisation.

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

Risk Management Plan (RMP)

The 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that baloxavir marboxil is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.