22 February 2018
EMA/CHMP/148367/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Alpivab

International non-proprietary name: peramivir

Procedure No. EMEA/H/C/004299/0000

Note

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

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Table of contents

List of abbreviations

AS	Active substance
CHMP	Committee for Medicinal Products for Human use
CFU	Colony Forming Units
GC	Gas Chromatography
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
ICP	AES Inductively coupled plasma atomic emission spectroscopy
IR	Infrared
KF	Karl Fischer titration
mil	thousandth of an inch
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
Ph. Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
RRT	Relative retention time
SEM	Scanning Electron Microscopy
SM	Starting material
SmPC	Summary of Product Characteristics
TGA	Thermo-Gravimetric Analysis
WFI	Water for injection
XR(P)D X	Ray (Powder) Diffraction

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
AUC	Area under the time concentration curve
BID	Twice daily
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CFB	Change from baseline
CI	Confidence interval
CL	Clearance
CLcr	Creatinine clearance
Cmax	Maximum concentration
CSR	Clinical study report
CK / CPK	Creatine phosphokinase
COPD	Chronic obstructive pulmonary disease
CYP	Cytochrome
ECDC	European Centre for Disease Prevention and Control
Emax	Maximum effect
ET50	Time above IC50 that resulted in 50% of maximum possible effect

GCP	Good Clinical Practice
GI	Gastrointestinal
h	Hour(s)
HA	Haemagglutinin
IL	Interleukin
IM	Intramuscular
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
ITTI	Intent-to-Treat-Infected
IV	Intravenous
L	Litre(s)
LFT	Liver function test
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
NA	Neuraminidase
NAI	Neuraminidase inhibitor
NDA	New Drug Application
NOAEL	No observable adverse effect level
NSOIA Team	Novel Swine-Origin Influ A Virus H1N1 Investigation
OC	Oral contraceptive
OSE	Oseltamivir
OSE-C	Oseltamivir carboxylate
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetics
PT	Preferred term
QD	Once daily
RAT	Rapid antigen test
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SmPC	Summary of product characteristics
SOC	System organ class
SMQ	Standardised MedDRA Query
STC	Standard of care
t½	Half-life
TCID	Tissue Culture Infective Dose
TEAE	Treatment emergent adverse event
tmax	Time to maximum concentration
TNF	Tumour necrosis factor
TTAS	Time of alleviation of symptoms
UK	United Kingdom
US	United States
V (Vd)	Volume of distribution
WBC	White blood cell
WHO	World Health Organization
ZVR	zanamivir

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Biocryst UK Limited submitted on 22 December 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Alpivab, 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 24 September 2015.

The applicant applied for the following indication:

Treatment of influenza

Alpivab is indicated in adults 18 years and older with symptoms typical of influenza, when influenza virus is circulating in the community. Efficacy has been demonstrated when treatment is initiated within two days of first onset of symptoms.

Peramivir is not a substitute for influenza vaccination. The use of antivirals for the treatment of influenza should be determined on the basis of official recommendations, the variability of epidemiology, and the impact of the disease in different geographical areas and patient populations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that peramivir was considered to be a new active substance.

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/0340/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0340/2016 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 request(s) 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 peramivir 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 Scientific Advice from the CHMP on 24 May 2007. The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Robert James Hemmings Co-Rapporteur: Svein Rune Andersen

- The application was received by the EMA on 22 December 2016.
- The procedure started on 19 January 2017.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 31 March 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 April 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 21 April 2017.
- During the meeting on 18 May 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 11 August 2017.
- The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:

  GCP inspections at two investigator sites in Japan between 4-7 July 2017 and 10-13 July 2017. The outcome of the inspection carried out was issued on 14 September 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 18 September 2017.
- During the PRAC meeting on 5 October 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 12 October 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.

- The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 December 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 8 January 2018.
- During the CHMP meeting on 25 January 2018, the CHMP agreed on a second list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 31 January 2018.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 6 February 2018.
- During the meeting on 19-22 February 2018, 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 Alpivab on 22 February 2018.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Influenza virus is a member of the *orthomyxovirus* family and in humans causes an acute viral disease of the respiratory tract. Further details are outlined in the sub-sections 2.1.2- 2.1.5.

Peramivir is a selective inhibitor of influenza viral neuraminidase with activity against a broad range of influenza A and B subtypes.

Initially, peramivir has been proposed for the treatment of adults with symptoms typical of influenza, when influenza virus is circulating in the community.

2.1.2. Epidemiology and risk factors, screening tools / prevention

In the EU influenza is a seasonal disease. There are several commercially available rapid diagnostic tests available but the vast majority of cases are diagnosed clinically. In humans, the infecting viruses are almost always of class A or B. Other classes may infect a wide range of species. Circulating virus can infect and cause clinically manifest disease in any human subjects without pre-existing protective immunity to the specific strain that is encountered. The influenza virus can lead to occasional pandemics when there has been an antigenic shift in a class A strain resulting in a large proportion of the population being non-immune to the circulating virus. Current epidemiology data are available for Europe from the ECDC. For the 2015/2016 influenza season, the ECDC report indicates that of the 5454 cumulative detections reported, 84% were attributed to influenza A and 16% to influenza B. Of the influenza A virus detections, 85.2% were attributed to H1N1pdm09 (the direct descendant of the strain that caused the 2009/10 pandemic) and 14.8% are attributed to H3N2. Of the influenza B detections, 61.7% were attributed to the Victoria lineage and 38.3% to the Yamagata lineage. The

mainstay of influenza prevention is vaccination but none of the available vaccines is exceptionally effective. Recommendations for annual vaccination of various population subsets vary between EU MS.

2.1.3. Aetiology and pathogenesis

Influenza virus is a member of the orthomyxovirus family and causes an acute viral disease of the respiratory tract. Influenza is characterized bronchoscopically by diffuse inflammation and oedema of the larynx, trachea, and bronchi; mucosal biopsies show lymphocytic and histiocytic inflammatory infiltrate and desquamation (Walsh *et al.,* 1961). The viral neuraminidase cleaves sialic acid groups from glycoproteins and facilitates viral escape from infected cells, making it possible for daughter virions to infect new host cells.

2.1.4. Clinical presentation, diagnosis and stage / prognosis

Typical influenza illness is characterised by abrupt onset of fever, headache, myalgia, sore throat and non-productive cough (Cox and Subbarao, 1999). Other symptoms may include nausea, vomiting and diarrhoea (NSOIA 2009). In otherwise healthy adults, the illness is usually self-limiting, with resolution of symptoms occurring within 5 to 7 days because immune defences shut down viral proliferation and shedding, clearing infected cells quickly. In uncomplicated influenza, tissue damage is limited, and secondary infections are uncommon. However, influenza is an important cause of morbidity and mortality in certain at-risk populations (including pregnant women, some types of immunosuppressed patients, the very young and the elderly). Virus-induced damage to the integrity of the respiratory tract can be severe in a minority of patients, leading to extensive viral pneumonia and impaired gas exchange. In addition, the disruption of normal defence mechanisms predisposes to secondary bacterial pneumonia. In each season influenza contributes to winter mortality rates. During the last pandemic season, which was a mild pandemic overall, the attributable mortality was estimated between 100,000 and 2000,000 persons.

2.1.5. Management

Management of uncomplicated influenza is usually confined to symptomatic treatment using over-the-counter NSAID preparations. Oral oseltamivir and inhaled zanamivir are licensed for treatment of influenza but policies on their use vary between EU MS. They have both been shown to shorten the duration of symptoms vs. placebo in uncomplicated cases. There are no licensed intravenous presentations of neuraminidase inhibitors in the EU although these may be available for compassionate use in severely ill patients, in whom their efficacy has not been established. Otherwise, treatment for severe influenza is supportive and may involve the need for assisted ventilation, circulatory support and antibacterial agents to treat or prevent secondary bacterial infections, such as staphylococcal pneumonia. In some countries amantadine and rimantadine (the adamantanes) are available but they are not active against influenza B strains and there is widespread resistance among H1N1 and H3N2 influenza A strains

About the product

Peramivir is an influenza virus neuraminidase (NA) inhibitor (NAI). It is active *in vitro* against influenza A, B and avian viruses. The median inhibitory activity of peramivir was assessed in a neuraminidase

assay. Against neuraminidase from influenza A/H1N1 virus, influenza A/H3N2 virus and influenza B virus clinical isolates the median IC_{50} values were 0.16 nM, 0.13 nM and 0.99 nM, respectively.

The applicant proposes that a single intravenous dose provides a shortening of the duration of the clinical disease vs. placebo in adults with uncomplicated influenza when it is given as a single intravenous dose within 48 hours of onset of symptoms.

Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment. This was based on the fact that CHMP was unable to agree with the applicant that the availability of single dose IV peramivir for treatment of uncomplicated influenza would be of major public health interest. Having this product available could be of use in some settings and it could provide adherence that would not be achieved with the licensed agents, which require 5 days dosing, but it still has to be given within a short window of onset of symptoms and the comparisons made with placebo and oseltamivir suggest that it is not more effective than licensed agents. Overall, it was concluded that peramivir would not address a clear unmet medical need and it was regarded as being of limited relevance for public health.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a concentrate for solution for infusion containing 200 mg of peramivir as active substance per vial. 1 mL concentrate for solution for infusion contains 10 mg peramivir (anhydrous base).

Other ingredients are: sodium chloride, water for injections, sodium hydroxide and hydrochloric acid (for pH adjustment).

The product is available in Type I clear glass vials with a coated bromobutyl-rubber stopper and an aluminium overseal with a plastic flip-off cap as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of peramivir (trihydrate) is (1*S*,2*S*,3*R*,4*R*)-3-[(1*S*)-1-(acetylamino)-2-ethylbutyl]-4-(carbamimidoylamino)-2-hydroxycyclopentanecarboxylic acid, trihydrate corresponding to the molecular formula $C_{15}H_{28}N_4O_4 \cdot 3H_2O$. It has a relative molecular mass of 382.00 g/mol and the following structure:

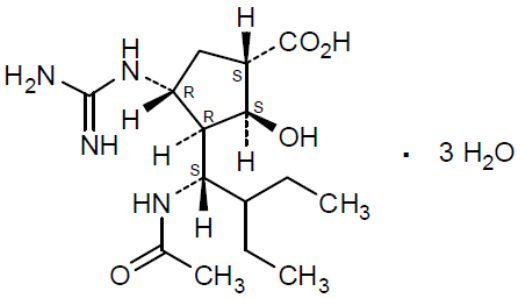


Figure 1. **Structural formula of peramivir trihydrate**

The chemical structure of peramivir was elucidated by elemental analysis, infrared (IR), ultraviolet (UV) and ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy, and mass spectrometry (MS).

Data from other analytical procedures such as scanning electron microscopy (SEM), X-ray powder diffraction (XRPD), thermogravimetric analysis (TGA), and solid state forms has been also presented to support the physicochemical characterization of peramivir.

Peramivir is a crystalline white to off-white or slightly beige hygroscopic powder It has pH-dependent solubility such that it is sparingly soluble in neutral pH range and freely soluble below its pKa . It is sparingly soluble in deionised water and 0.9% sodium chloride solution. The applicant provided additional data about solubility of Peramivir in various organic solvents.

Peramivir has five stereocentres. The C1 stereocenter is adjacent to the carboxylic acid function.The R-enantiomer is the active substance. Enantiomeric purity is controlled routinely by chiral HPLC.

The active substance peramivir is used to manufacture the finished product in the trihydrate form. Other forms may be produced by the use of other solvents during the crystallisation process. A polymorph screening study was carried out in an attempt to generate as many solid forms of peramivir as possible. The trihydrate is the thermodynamically most stable form.

Manufacture, characterisation and process controls

Peramivir is synthesized in a multi-step process using three well defined starting materials (SM1, SM2 and SM3) to form crude peramivir. After these steps, the crude peramivir is purified and dried to the desired trihydrate form, milled and screened. No re-processing, re-working, recycling, regeneration or other operations will be performed.

Initially, the active substance manufacturing process was developed and validated at one manufacturing site (site 1) and subsequently transferred to other site (site 2). For commercial production, only the latter (site 2) will be used. The chemical process used at both facilities is the same.

The proposed starting materials SM2SM3 were adequately justified and considered acceptable. However, the data and justification provided to support the selection of SM1 as starting material was considered insufficient. This molecule contributes substantially to the structure of the final active substance and, the synthetic process from the point of introduction of SM1 involves only one isolated intermediate, crude peramivir, with no further synthesis steps (formation/breaking of bonds), which provides limited opportunities for purification. This poses the risk that impurities, resulting from changes to the from non-GMP manufacturing process, which may not necessarily be detected by

routine analytical testing, are introduced into the final active substance. In addition, the synthesis of this proposed starting material SM1 includes critical steps which may affect the quality of the active substance and requires appropriate control in order to ensure that the process and its associated control strategy will consistently provide active substance of satisfactory quality during the lifecycle of the product. As a result, the CHMP raised a major objection during the evaluation of this application requesting the applicant to redefine SM1 further back in the synthesis in line with ICH Q11 and include those critical steps in the GMP manufacturing process (3.2.S.2.2.), to ensure that the conditions necessary to maintain the validity of the control strategy do not change over time. In response, the applicant committed to redefine this starting material SM1 two steps further back in the synthesis within 6 months after approval

By going back two steps from the proposed SM1, all the impurities in the final active substance, with the exception of three related substances will be formed under GMP. These are not genotoxic impurities. All related substances formed upstream of the redefined starting material have been controlled in batches of the originally proposed SM1 and in the final active substance with a limit of no more than the ICH Q3A identification threshold (0.10%).
Taking into account the risk-benefit of the finished product, the proposed commitment to re-definition of the starting material (SM1)two steps back post-approval within 6 months of the Commission decision is considered acceptable. Concerns were also raised on the specification for SM1 (to be redefined). These concerns were resolved.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

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. The impurity profile of the active substance is well documented and supported by the results of appropriate stress studies. The active substance is stable under conditions of light, heat and humidity and unstable under acid , alkali and oxidising conditions. The initial submission did not contain information on potential genoxotic impurities. This constituted a major objection, and as a result the applicant presented data from genotoxic studies supporting that there are no concerns for genotoxicity. In line with ICH M7 a review of active substance and impurity structures as well as the reagents used during the manufacture of peramivir did not highlight any structural alerts with the exception of one reagent. The supplier of the reagent conducted an AMES testand concluded that the compound is nonmutagenic. In addition, in toxicology studies, there were no indications of mutagenicity, clastogenicity or carcinogenicity found throughout the development program; peramivir is administered as a single dose, and as such, there is no long-term exposure to peramivir and therefore, no accumulation. Given the toxicology profile of Peramivir, it is considered highly unlikely that any carcinogenicity could occur from a single dose. Furthermore, no related carcinogenic safety signals were detected in the ~2 million patients treated with Peramivir since 2009 worldwide. Based on the above it was concluded that there are no potential mutagenic impurities in peramivir which could increase the carcinogenic risk.

The active substance manufacturing process was developed and validated at site 1 and subsequently transferred to site 2 . For commercial production, onlysite 2 will be used. The chemical process used at both facilities is the same. There are, however, minor differences which have been described. It has been demonstrated that the change(s) did not have a significant impact on the quality of the product. A comprehensive overview on manufacturers, manufacturing dates, batch sizes and synthetic routes of

batches used in nonclinical and clinical trials as well as in primary stability studies and registration lots at both the development site and the commercial site has been provided in the dossier.

The differences between the processes have been described and flow charts for the different development routes have been provided in the dossier.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program.

The primary packaging (inner and outer) fulfils the requirements of EU Regulation 10/2011 on plastic food contact materials and articles and Ph. Eur. monograph 3.2.2 Plastic Containers and Closures for Pharmaceutical Use.

Specification

The active substance specification includes tests for description, identity (IR, HPLC), assay (HPLC), impurities (HPLC), enantiomeric purity (HPLC), residual solvents (GC), residue on ignition (Ph. Eur.), catalyst residues (ICP-AES), pH of solution, water content (KF), bacterial endotoxins and microbial limits (Ph. Eur.).

The omission of limits for particle size and polymorphic form has been adequately justified. Adequate control of residual solvents has been justified .Control of particle size has been omitted from the active substance specification on the basis that the finished product is presented as a 10 mg/ml concentrate for solution for infusion. At this concentration, the active substance is soluble and the product does not contain any undissolved active substance (ref. Decision Tree 3 of ICH Q6A).

The omission of polymorphic form has been justified in line with Decision Tree 4 of ICH Q6A. The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the used reference standards has been presented.

Batch analysis data from a sufficient number of batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three commercial scale batches of active substance from the proposed manufacturer (site 2) and three additional commercial scale batches from the other manufacturer used only during development (site 1) have been presented.

Samples were stored for up to 60 months under long term conditions (30ºC / 65% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines. The container closure system for the stability samples is of the same materials but a smaller size than the proposed commercial container closure system of the bulk active substance. It is considered representative of that intended for the market.

Stability batches were tested for description, assay, impurities, pH of solution, endotoxins and microbial analysis. All tested parameters were within the specifications at both storage conditions. The data are comparable for both active substance manufacturers.

The analytical methods used were the same as for release. A stress study was performed to evaluate the stability indicating properties of the HPLC purity method. Peramivir was stressed under acidic)

alkaline ,and oxidizing conditions. The impact of light, heat ,and humidity on the stability of the active substance was also investigated. Major degradation was observed under alkaline conditions. Some degradation was also detected upon exposure to acidic and oxidizing treatment. The samples from light and humidity stress studies showed no degradation

The photostability study performed in line with ICH Q1B showed that peramivir is not photo-labile. Mass balance was observed between % peak area for peramivir and % peak area for degradants. The method was therefore considered to be stability-indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container .

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product, Alpivab, is a clear, colourless, sterile, isotonic concentrate for solution for intravenous administration. Each vial contains 200 mg (10 mg/mL) of active peramivir in 0.9% (w/w) sodium chloride solution.

The product is presented as a multipack 3 x 200 mg vials. According to the applicant this presentation was developed to allow flexibility in dosing to patients with renal impairment and paediatric patients, who would require lower doses; and patients with normal renal function for whom the recommended dose is 600 mg. This raised concerns during the evaluation regarding the potential for contamination, confusion for users, prescription errors and the risk of overdose/underdose. For example, where a 600 mg dose is required, there is a potential increased risk of contamination (as 3 x 200 mg vials need to be combined) or underdosing (if the vials are not combined correctly) and where a lower dose is required there could be wastage (if not all vials in the multipack are used). According to the applicant, these risks are mitigated by the fact that peramivir is only prepared by HCPs under aseptic conditions and administered by a HCP in a medical setting. To further reduce these risks the applicant revised the SmPC (Section 4.2 Posology and Method of Administration) and the Patient Information Leaflet (PIL) improving the instructions for use. Nevertheless, in order to further avoid unnecessary confusion the CHMP recommends the applicant to consider changing the package size to 1 vial of 20 mL or create a new strength of Alpivab 600 mg in one vial of 60 mL.

The components of the formulation, their function, quality standards and quantitative composition have been described.

Table 1. Composition of finished product.

Component	Function
Peramivir	Active ingredient
Sodium Chloride	Tonicity agent
Hydrochloric Acid	pH adjustment

Sodium Hydroxide	pH adjustment
Water for Injection	Solvent

[1]The amount of peramivir trihydrate corresponding to 10 mg peramivir is ~11.6 mg

The product contains the excipient sodium chloride at a concentration of 0.9 mg/mL to achieve an isotonic solution with an osmolality in a physiologically favourable range, and the solvent water for injections (WFI). It may also contain dilute hydrochloric acid (1%) and/or sodium hydroxide (1N) for pH control. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The finished product does not contain any overages. Each container of peramivir concentrate for solution for injection is filled with a volume in slight excess of the labelled volume to ensure that 20 mL can be withdrawn from the vial.

The active substance, peramivir, is a small molecule supplied as a trihydrate. Peramivir is sparingly soluble in the neutral pH range and freely soluble at pH below its pKa. Peramivir is most stable in aqueous solutions at neutral pH.The active substance is stable during the manufacturing process.

In order to develop the formulation, a pH solubility profile was generated.Peramivir dissolved in 0.9% sodium chloride solution results in a solution that is physiologically compatible.

A 10 mg/mL solution in 0.9% sodium chloride at neutral pH demonstrated the best stability and potential for a long shelf life.based on these results the pH range for the product was selected.

A 10 mg/mL solution of peramivir in 0.9% sodium chloride was selected as the initial formulation for peramivir injection. The composition of the formulation has not changed throughout the clinical program with the exception of the addition of a pH adjustment.Additional temperature studies were performed as part of the formulation development .

A summary of the manufacturing process development and major manufacturing changes for peramivir injection have been presented. Sterilisation by moist heat at 121°C was investigated. On the basis of this study, a terminal sterilization process was then developed and validated to ensure a sterile product in accordance with Ph. Eur. Requirements.The container closure system is a 20 mLvial of Type I glass with a bromobutyl stopper and analuminum overseal with a flip-off cap. The proposed vial complies with the applicable Ph.Eur. 3.2.1 “Glass containers for pharmaceutical use”. The elastomeric stopper component meets the requirements of Ph. Eur. 3.2.9 “Rubber closures for containers for aqueous parenteral preparations”. The choice of materials for the container closure system was based on their protective, performance and compatibility characteristics, and has been validated by stability data and is adequate for the intended use of the product.

Samples were tested for protection from light, solvent loss, extractables, leachables, and container closure integrity. The results were satisfactory.

Test for sterility is performed. The excipients are routinely tested for microbial contamination and/or bacterial endotoxins, except the pH adjusters sodium hydroxide and hydrochloric acid (diluted).

As indicated in section 6.6 of the SmPC, the required dose of Alpivab concentrate is to be diluted with sodium chloride 9 mg/mL (0.9 %) or 4.5 mg/mL (0.45 %) solution for infusion, 5 % dextrose or Ringer lactate solution to a volume of 100 mL. Physical and chemical compatibility of the product with these diluents was demonstrated. Samples were stored at 5°C and 25°C (exposed to light). There was no

observed degradation after 72 hours in any diluent under any of the storage conditions.There was also no observed microbial contamination (< 1 cfu/10 ml). The study demonstrates that peramivir injection is compatible with the commonly used diluents 0.9% Sodium Chloride, 5% Dextrose, and Lactated Ringer's Injection, and with the materials commonly used for administration such as polyvinylchloride bags and PVC free bags, polypropylene syringes, and polyethylene tubing.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: compounding, sterile filtration, filling and stoppering, and terminal sterilisation. The process is considered to be a standard manufacturing process. Two finished product manufacturers are proposed. The manufacturing process flow chart from each manufacturing site has been provided. Although there are slight differences between the two sites; the order of addition and in-process control tests are the same, with the same limits. Based on the information provided, it is concluded that the differences between the two sites are minor and not expected to impact finished product quality.

Process validation was carried out on six pilot scale registration batches from one site and three commercial scale batches from the other site. It covered all stages of the manufacturing process including the proposed holding times.

Filter validation was also conducted. Supporting data have been provided for extractables and filter compatibility. The terminal sterilisation process was validated at both manufacturing sites. Process elements that ensure a sterile product have been sufficiently validated. Container closure integrity was demonstrated by microbial challenge. Growth was not observed in any test unit.

Overall, it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (IR, HPLC), assay (HPLC), degradation products (HPLC), pH (Ph. Eur.), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.), subvisible particles (Ph. Eur.) , extractable volume (Ph. Eur.) , osmolality (Ph. Eur.) , arsenic (Ph. Eur.).

The omission of a test for extractables and leachables, uniformity of dosage units, enantiomeric purity and heavy metals has been adequately justified. In accordance with ICH Q3D, Guideline for Elemental Impurities, the applicant has performed a risk assessment on elemental impurities in the finished product Alpivab.

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

Batch analysis results are provided for a sufficient number of pilot and commercial scale batches manufactured at one site, and commercial scale batches manufactured at the other site confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from six commercial scale batches of finished product manufactured by one site and three commercial scale batches of finished product manufactured by the other manufacturer stored for up to 60 months under long term conditions (25ºC / 60% RH), and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The stability batches of Alpivab are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Vials were stored upright and inverted in order to maximise potential interaction of the finished product with the stopper.

The stability specification is the same as that at release, with the omission of testing for identification, extractable volume and osmolality, which have been justified.

There was no significant change in the stability data at long-term or accelerated storage conditions, and batches remained within the specification throughout the study, including bacterial endotoxins and sterility. Vial storage orientation, upright or inverted, did not have an effect on the results obtained . Overall, results from the two manufacturing sites were comparable.

A stress study and a freeze-thaw study were conducted on a batch of finished product manufactured at one of the manufacturing sites Stress testing under conditions of acidic, alkaline, and oxidizing, light, heat, and humidity were applied to demonstrate the stability-indicating nature of the method for testing of the active substance.

In addition, stress studies were conducted by the applicant to evaluate the stability of peramivir concentrate for solution for injection during shipping studies. The results demonstrated that the finished product is stable at the shipping conditions tested. A freeze-thaw study was conducted to assess the effects of exposure to temperature extremes. No significant changes were identified. Peramivir injection was shown to be stable under extreme temperature conditions and the freeze-thaw cycling further ensuring the stability of the finished product.

Based on available stability data, the proposed shelf-life of 5 years with no storage conditions as stated in the SmPC (section 6.3) are acceptable.

Chemical and physical in-use stability after dilution (sodium chloride injection 0.9%, dextrose injection 5% and lactated Ringer's Injection) has been demonstrated for 72 hours at 5°C and 25°C (see pharmaceutical development section). However, from a microbiological point of view, the product once diluted, should be used immediately as stated in the SmPC. If not used immediately in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2ºC to 8ºC, unless dilution has taken place in controlled and validated aseptic conditions. If refrigerated, the diluted solution has to be allowed to reach room temperature before administering.

Adventitious agents

No excipients 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. One of the proposed starting materials (SM1) was not considered acceptable in line with ICH Q11 principles. Given the risk-benefit of the product, the

applicant's commitment to re-define this starting material post-approval within 6 months of Commission decision is considered acceptable. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. Nevertheless, in order to further reduce the risk of medication errors (underdose/overdose) in patients with moderate to severe renal renal failure, i.e. patients with creatinine clearance (CrCL) <50 mL/min and children, and reduce the risk of contamination the applicant is recommended to consider changing the package size from the proposed multipack (3 x 200 mg) to a single vial of 20 mL or to create a new strength Alpivab 600 mg in one vial of 60 mL.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP notes that the applicant has agreed with the Committee's recommendation to re-define starting material 1(SM1)two steps further back in the synthesis post-approval within 6 months of Commission decision, and update the dossier via standard post-approval variation procedures.

In addition, the CHMP recommends the following points for investigation:

1. Consider changing the pack size from the proposed 3 x 200 mg (3 vials containing 20ml each) multipack to a 1 x 200 mg pack (containing one vial of 20 mL) or create a new strength of Alpivab 600 mg in one vial of 60 mL to avoid unnecessary confusion and further reduce the potential for contamination, prescription errors and the risk of overdose/underdose.

2.3. Non-clinical aspects

2.3.1. Introduction

Peramivir is an inhibitor of the influenza enzyme neuraminidase (NA) with activity against various influenza A virus subtypes and influenza B (encompassing the 2009 influenza A (H1N1) pandemic strain, as well as the H5N1 and H7N9 avian strains). The influenza enzyme NA is a surface glycoprotein that cleaves sialic acid residues from glycoproteins and glycolipids on the host cell. Neuraminidase is responsible for the release of new virus particles from infected cells and may also assist in the spreading of virus through the mucus within the respiratory tract.

GLP

All pivotal nonclinical toxicity studies were conducted consistent with International Conference on Harmonisation (ICH) Nonclinical Testing Guidelines and in compliance with the Good Laboratory Practice (GLP) Regulations.

2.3.2. Pharmacology

Primary pharmacodynamic studies

A full description of the primary pharmacology of peramivir, related to antiviral activity (inhibition assays, in-vitro studies of the activity of peramivir against various influenza strains, susceptibility IC50 and secondary pharmacology) is provided in clinical section of this report: section 2.4.3 Pharmacodynamics and Pharmacokinetics-Pharmacodynamics (PK/PD).

Peramivir was shown to be active in *in vitro* assays that measured the inhibition of NA enzymatic activity, as well as in cell culture assays that measure endpoints of antiviral activity. Activity against a number of influenza A viruses (including H5N1 strain, 2009 pandemic H1N1 strain, and avian influenza H7N9 strain) and influenza B viruses has been demonstrated *in vitro*. IC50 values of 0.4 and 1.4 nM (neuraminidase (NA) enzyme inhibition from Type A and Type B viruses) have been reported in the literature. Some studies included comparison with marketed NA inhibitors oseltamivir carboxylate (OSE-C) and/or zanamivir (ZVR), one such study showed peramivir, zanamivir, and oseltamivir carboxylate each displayed similar IC50 values for neuraminidase compared to hemagglutinin-neuraminidase. In this study, peramivir had approximately tenfold lower IC50 values than zanamivir and oseltamivir carboxylate.

A large number of *in vivo* pharmacology studies were conducted over the non-clinical development life-cycle of this product, in which (for most) survival was the only endpoint. Peramivir has been evaluated for *in vivo* efficacy in mice (IV, oral, IM, and intranasal routes of administration), ferrets (IV, oral, and IM administration), and cynomolgus monkeys (oral and IV administration).

The majority of studies (more than 40 reports and publications) used oral administration of peramivir. However, a considerable number of studies used the intravenous (IV) route of administration. Only these IV studies are discussed in this report. The mouse infection model with seasonal influenza A virus, influenza B virus or avian (H5N1) influenza virus was used and dosing of peramivir occurred prior to or immediately after the time of viral inoculation of the animal.

In most of these studies mortality, mean number of days to death, arterial oxygen saturation, lung consolidation scores (a measure of the severity of influenza pneumonia) and viral titres in lung tissues and nasal washings were improved. Peramivir was effective in mice when administered IV either before or at the time of viral inoculation or up to 72 hours after viral inoculation for seasonal and pandemic strains of influenza A and B and avian influenza.

Female ferrets inoculated intranasally with B/Kadoma/1/2005 virus showed improved viral titres, protein concentration, numbers of inflammatory cells (based on nasal wash), with treatment. Systemic signs of illness, including rise in body temperature, loss of body weight, and nasal clinical signs, were also improved in animals given peramivir. In other studies in which infected ferrets were given IV peramivir, increased survival was observed and peramivir also reduced virus-induced disease, based on the lower occurrence of encephalitis and paralysis compared to controls. In another ferret study virus titre in nasal washes from control animals was 75-fold higher (1 x 105 TCID50/g) than in animals given peramivir (1.3 x 103 TCID50/g). In animals given peramivir, the virus was undetectable in the lungs or brain on either Day 4 or Day 6 post-infection. In contrast, virus was detected in the brain of

control animals on Days 4 and 6 post-infection (average titres ranging from 3.4 x 105 to 2.6 x 106 TCID50/g) and on Day 6 in the lungs (average titre 2.5 x 104 TCID50/g).

In the non-human primate, an IV dose of 30 mg/kg peramivir was given once to animals, either immediately after virus inoculation on Day 0, or at 24 hours after inoculation (inoculated intra-nasally with B/SendaiH/1051/2007 virus). The maximum virus titre in nasal swab samples from the control animals was observed on Day 3 post-infection. Virus titres in nasal swab samples from animal given peramivir were significantly reduced on Days 2 and 3 compared with controls ($P < 0.01$). A reduction ($P < 0.05$) was also observed on Days 5 and 7 24 hours after inoculation. In the control group, body temperatures were increased on Days 1 to 4 compared with pre-inoculation values; peramivir administered on the day of inoculation or 24 hours later resulted in a lower body temperature compared with controls ($P < 0.05$) in all animals. Peramivir did not inhibit the production of serum anti-HA antibodies against the inoculated B/SendaiH/1051/2007 virus.

Secondary pharmacodynamic studies

When peramivir was tested in an *in vitro* screening assay at a concentration of 1 x 10-5 M, the inhibition ratio of peramivir for each receptor (e.g., adrenergic, muscarinic, opiate, histamine receptors), ion channel (e.g., potassium and calcium channels), or transporter (e.g., gamma amino butyric acid, serotonin transporters) tested in this study was generally very small. Binding inhibition greater than 20% was found for the human alpha-1Aadrenergic (25.46%) and human serotonin 5HT2B (40.42%) receptors. The Applicant provides further discussion of the 25.46% inhibition seen with the human alpha-1A adrenergic receptor and the 40.42% inhibition seen with the human serotonin 5HT2B (40.42%) receptor in the secondary pharmacodynamics *in vitro* screening assay (Study number: AL-4143-G). The consequences of these results have limited clinical relevance.

Safety pharmacology programme

In safety pharmacology studies, peramivir was tested for effects on the CNS in rats and mice; on the cardiovascular system both *in vitro* and *in vivo* (in anesthetised rats, guinea pigs, and dogs; and in conscious monkeys); on the respiratory system in conscious rats and anesthetised guinea pigs; on the gastrointestinal system in mice, and on the renal system in rats. None of the safety pharmacology studies showed adverse effects. *In vitro,* peramivir did not affect either the hERG channel current at the highest feasible concentration (300 μM), nor did it affect the action potential of isolated guinea pig cardiac papillary muscles in 2 assays. *In vivo*, peramivir did not affect general behaviour and neurobehavioral function at IV doses ≤ 100 mg/kg (mouse and rat); cardiovascular function at an intra-duodenal dose of 100 mg/kg (dog) or at IV doses ≤ 10 mg/kg (rat and guinea pig) or ≤ 60 mg/kg (monkey); respiratory function at IV doses ≤ 10 mg/kg (rat and guinea pig); intestinal locomotion at oral doses ≤ 300 mg/kg (mouse); or urinary function at oral doses ≤ 300 mg/kg (rat). The applicant has conducted a satisfactory TQT study with a 1200 mg IV peramivir dose which showed no effect on QTc or HR.

In anaesthetised, ventilated male Dunkin-Hartley guinea pigs (Study number: DS00321) a difference in lung compliance was seen at 10 mg/kg compared to controls at I.V doses of 10 mg/kg peramivir, however, this effect was not considered to be test article-related.

Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies with peramivir have not been performed.

2.3.3. Pharmacokinetics

The pharmacokinetics of peramivir have been evaluated following IV, IM, and oral administration in several animal species, including the mouse, rat, ferret, rabbit, dog, and cynomolgus monkey. Given that the proposed clinical dosing route is via intravenous infusion, the pharmacokinetics derived from oral and intramuscular routes are not discussed further.

In general, following intravenous administration of peramivir, exposure tended to increase dose-proportionally in all species and was similar in males and females, where assessed. The half-life obtained in the different species suggests a moderate rate of elimination. There was no accumulation observed following repeat intravenous dose administrations for 14 days. Based on the values for volume of distribution, peramivir was widely distributed in all species evaluated.

Following intravenous dose administration of [14C]-peramivir, the highest amounts of radioactivity, excluding the gastrointestinal (GI) tract, were observed in the kidney, urinary bladder, and liver.

Plasma protein binding of peramivir was low (<18%) when evaluated in a number of animals species, which reflects the low plasma protein binding observed in humans (<30%) and is therefore generally considered to be of little clinical significance. Tissue-to-plasma ratios were greater than one for GI tract and kidney; other tissues generally had ratios less than one. Similar patterns were observed in juvenile and adult rats and in rats given multiple doses.

Maximum concentrations of radioactivity were seen in rat tissues 5 minutes post intravenous dose at all doses tested, suggesting rapid tissue distribution following intravenous administration of [14C]-peramivir. There was no evidence of accumulation or persistence of radioactivity in any tissue of either mature or juvenile rats. In the juvenile rat brain, there was a time-dependent increase in tissue to plasma ratios up to 24 hr post-dose, with brain concentrations of approximately 6.5-7.5% of the maximum brain concentration still detected at 72 hours post-dose. Overall, there is no significant retention of radioactivity in the juvenile (or adult) brain following a single intravenous administration of peramivir.

In pregnant SD rats, the liver and kidney contained the highest amounts of radioactivity, with concentrations increasing in the uterus at later sampling times. Fetal exposure to [14C]-peramivir occurred between 1 and 24 hours post-dosing, indicating that peramivir readily crosses the placenta. This has been discussed in the proposed SmPC.

The metabolism of peramivir was evaluated *in vitro* and *in vivo* in the mouse, rat, rabbit, monkey and human. In the *in vitro* evaluation employing rat, dog, and human liver microsomes, peramivir was not extensively metabolised. The only detectable metabolite was M1 (oxo-peramivir), which was formed from the oxidation of the cyclopentyl ring in the rat (ca. 2%) and human (ca. 4%) but was not detected in the dog. In vivo, the results suggest that all species, including human, are poor metabolisers of peramivir following single and multiple intravenous administration, as unchanged peramivir was the only component identified in plasma and urine.

Following intravenous administration of peramivir, excretion is primarily via urine. Maximum concentrations of peramivir in the milk of lactating rats were below the plasma concentrations. However, overall exposure in the milk was approximately half of the overall exposure observed in the plasma, with a terminal half-life of approximately 6.5 hours, clearly demonstrating that peramivir is excreted in rat milk. This has been adequately addressed in the SmPC.

Peramivir did not inhibit or induce the P450 enzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 in in vitro studies and did not result in >50% inhibition of Pgp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 or MATE2-K. The package of in vitro studies has been updated

and further studies are not required, peramivir is unlikely to have any inhibition potential. Elimination of peramivir is not affected by the OAT1 and OAT3 inhibitor probenecid.

In vitro drug interaction studies with acetaminophen suggest that peramivir, at concentrations up to 10 mM, does not inhibit glucuronosyl transferase. Therefore, peramivir would not be expected to inhibit the glucuronidation of acetaminophen in vivo.

2.3.4. Toxicology

Peramivir has been evaluated in nonclinical studies following single and/or repeat-dose studies in the mouse, rat, guinea pig, rabbit, dog, and cynomolgus monkey by the intravenous and intramuscular routes of administration. Toxicology studies with daily administration up to 28-31 days duration were conducted by the IM and IV (both bolus and continuous infusion) routes of administration in the rat and monkey, as well as intravenous reproductive and developmental toxicity studies in the rat and rabbit. Chronic studies were conducted using weekly (monkeys) or biweekly (rats) IM dosing for 26 weeks in rats and 52 weeks in monkeys. In addition, studies evaluating genotoxicity and antigenicity have been conducted. Two-week oral toxicity studies were conducted in juvenile rats and rabbits, a four-week intravenous toxicity study was conducted in juvenile rats, and several intravenous nephrotoxicity studies were conducted in rabbits. As part of the oral development program (now cessed) carcinogenicity studies were initiated in the rat and mouse and dosed to completion; however only the rat study was fully evaluated with complete histopathology.

In the rat, IV (bolus) studies at doses up to 120 mg/kg/day for 28 days (mean AUC0–24 of 383,234 nhr/mL) and continuous infusions up to 1,440 mg/kg/day for one month (mean AUC0-24 up to 1,975 µghr/mL), were well tolerated. Similarly, in the monkey, bolus doses up to 90 mg/kg/day (AUC0–24 of 541,580 nghr/mL) and continuous infusion doses up to 720 mg/kg/day (AUC0–24 of 2,945 µghr/mL) for one month were well tolerated. Chronic studies conducted by the IM route using bi-weekly (rats) or weekly dosing (monkey) for 26 (rat) or 52 weeks (monkey) showed only injection site changes. There were no test-article related microscopic findings seen in these studies.

In the rabbit, at IV doses ≥200 mg/kg/day, following dosing from 1-9 days duration, the kidney was identified as the target organ for toxicity, with increased BUN and creatinine and increased ratios of excreted sodium and chloride compared to creatinine. Microscopically, mild to marked acute tubular necrosis was observed (in some studies “nephrosis”) which generally occurred at exposure (AUC) values of > 1,130,000 nghr/mL. Several additional nephrotoxicity studies were conducted to more thoroughly evaluate the renal changes and all such studies were consistent in the identification of a no-observed adverse-effect-level (NOAEL) of 100 mg/kg/day in the rabbit with respect to acute tubular necrosis (3.4x (Cmax) and 2.1x (AUC) exposure safety margin). This renal toxicity noted only in the rabbit may be related to the formation of the acyl glucuronide (DM98405; 14% – 33% of radioactivity) or other unidentified metabolite, which was not observed in other species or in humans (S-021812-PF-062-C).

The applicant points to the observation that peramivir in mice, rats, dogs and monkeys, is almost entirely excreted unchanged via urine, while in rabbits significant amounts of an acyl glucuronide of peramivir are excreted in the urine. Without providing any supporting data, the applicant claimed that acyl glucuronide likely causes the renal toxicity and that this is a species specific effect. However, renal effects were also noted in cynomolgus monkeys (increased kidney weight), and in adult (carcinogenicity study: renal tubular and pelvic mineralization, tubular dilatation, epithelial renal hyperplasia) and juvenile rats (drug-related minor renal cortical tubular changes), species that do not generate acyl glucuronide. The applicant has discussed this topic further, with a requirement for

updating sections 4.8 and 5.3 focus on the potential for renal toxicity and the possible clinical relevance.

As renal necrosis has been seen in rabbits, reports indicating any kind of nephrotoxicity should be closely monitored and therefore included as an important potential safety concern in the Safety specification in the RMP.

Peramivir was not antigenic, mutagenic or clastogenic. The UV/vis spectrum of peramivir does not show any absorbance at wavelengths above 250 nm.

Peramivir has been studied in embryo-fetal developmental intravenous toxicity studies in both rats and rabbits and in a fertility and early embryonic development study in rats. A pre- and post-natal study in rats was conducted during the development of peramivir, in addition to juvenile toxicity studies (oral and intravenous) in rats and rabbits. Peramivir was not teratogenic, and did not show effects on other reproductive parameters in these studies.

Table 2. Interspecies comparison

Species	Route	Duration of dosing	NOEL / NOAEL (mg/kg/day)	Cmax[a] (ng/mL)	AUC[a] $_{0-24}$	Safe Margin[b] based on:	
						Cmax	AUC_{0-24}
Rat	IM	2 weeks	75	184917	173692	4x	1.7x
	IM	26 weeks	75	170833	215460	3.7x	2.1x
	IV bolus	7 days	200[d]	C0[e] 913140	308616	19.8x	3.1x
	IV continuous Infusion	2 weeks	1152	692774	NC	1.51x	NC
	IV bolus	4 weeks	120[g]	675125	383234	14.8x	3.8x
	IV continuous Infusion	30-31 days	1440	NC	1975000	14.8x	3.8x
Rabbit	IV bolus	7 day	100	C0[e] 159000	219000	3.4x	2.1x
	IV bolus	7 day	100	C0[e] 454159	337718	9.9x	3.3x
Monkey	IM	2 weeks	54	197875	287193	4.3x	2.8x
		52 weeks	54	206917	239176	4.5x	2.3x
	IV bolus	2 weeks	45	375000	249000	8.2x	2.4x
		4 weeks	90	485000	541580	10.6x	2.5x
	IV continuous Infusion	30-31 days	720	123000[l]	2945000[l]	2.6x	5.3x
Human[g]	IV	1 day	600 mg/kg	45700	100800		

[a] At the end of the study. Mean male and female
[b] Based on600 mg/kg human dose
[c] Dosed every 2 weeks
[d] doses tested were 20, 50 and 200 mg/kg/day
[e] C0 Plasma concentration immediately post-dose
[f] dosed once a week
[g] Based on 600 mg human dose
[h] Css Steady state plasma concentration
[l] Day 14
NC Not calculated

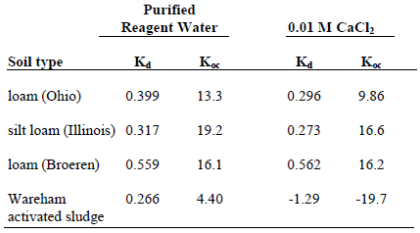
2.3.5. Ecotoxicity / environmental risk assessment

The log Kow values (-1.2 to -1.1) are <4.5 at all environmentally relevant pH values, and therefore peramivir does not meet the criteria for classification as a PBT compound and therefore screening for PBT is not required.

The calculation of the Predicted Environmental Concentration in surface water (PECsw) is based on the default value of Fpen (0.01) and given that the proposed dose is a single dose/year, a DOSEai value of 600 mg/365 for the calculation was used, which is acceptable. The calculated PECsw value (0.008 µg/L) is below the action limit of 0.01 µg/L and therefore a Phase II environmental fate and effects analysis is not required. However, further Phase II studies have been presented to further demonstrate that peramivir will not have an impact on the environment.

The outcome of the Phase IIA analysis indicated that peramivir is expected to be mobile in soil and not predicted to adsorb to solids during wastewater treatment; is not readily biodegradable; and is likely to have a low acute toxic effect to aquatic organisms. It can be concluded that peramivir will not have an impact on the environment.

Table 3. Summary of main study results

Substance (INN / Invented Name):Peramivir			
CAS-number (if available): 1041434-82-5 (trihydrate)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	FDA 3.02	-1.2 to -1.1 (pH 5 to pH 9)	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-1.2 to -1.1 (pH 5 to pH 9)	Not B
	BCF	N/A	N/A
Persistence	DT50 or ready biodegradability	N/A	N/A
Toxicity	NOEC or CMR	N/A	N/A
PBT-statement :	The log K_{ow} values for peramivir are < 4.5 at all environmentally relevant pHs, therefore the compound is not considered as PBT nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	0.008	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	FDA 3.08		Peramivir is expected to be mobile in soil (K_{oc} <100) and not predicted to adsorb to solids during wastewater treatment. **>10000 L/Kg threshold N.**

Soil type	Purified Reagent Water K_d	Purified Reagent Water K_{oc}	0.01 M $CaCl_2$ K_d	0.01 M $CaCl_2$ K_{oc}
loam (Ohio)	0.399	13.3	0.296	9.86
silt loam (Illinois)	0.317	19.2	0.273	16.6
loam (Broeren)	0.559	16.1	0.562	16.2
Wareham activated sludge	0.266	4.40	-1.29	-19.7

		Purified Reagent Water / 0.01 M $CaCl_2$ Soil type — % adsorbed — % adsorbed loam (Ohio) — 7.4 — 5.8 silt loam (Illinois) — 5.9 — 5.2 loam (Broeren) — 10.1 — 10.1 Wareham activated sludge — 0.3 — -1.7	
Ready Biodegradability Test	FDA 3.11	Parent drug remaining = 96.4% <3.6% degradation after 28 days	Not readily biodegradable

Phase IIa Effect studies

Study type	Test protocol	Endpoint	value	Unit	Remarks
Daphnia magna. Acute toxicity	FDA 4.08	EC_{50} (48h) NOEC	>990 990	mg/L mg/L	Low acute toxic effects
Fathead Minnow Acute Toxicity	FDA 4.11	LC_{50} (96h) NOEC	>990 990	mg/L mg/L	*Pimephales promelas* Low acute toxic effects
Activated Sludge, Respiration Inhibition Test	FDA 4.02	MIC	>1000	mg/L	*Aspergillus niger: Trichoderma viride, Clostridium perfringens,Bacillus subtilis, and Nostoc sp.* Considered to be non-toxic to species that would occur in sludge

2.3.6. Discussion on non-clinical aspects

Peramivir is an inhibitor of influenza virus neuraminidase, an enzyme that releases viral particles from the plasma membrane of infected cells and is also important for viral entry into uninfected cells, which causes further spread of infectious virus in the body. Peramivir as an inhibitor of the influenza NA enzyme has been evaluated in numerous *in vitro* and *in vivo* studies.

In mice, intravenously administration of peramivir was effective when given either before or at the time of viral inoculation or up to 72 hours after viral inoculation for seasonal and pandemic strains of influenza A and B and avian influenza. Ferrets were also infected with an influenza B strain (B/Kadoma/1/2005). The efficacy of peramivir (60 mg/kg, i.v.) was generally comparable to or exceeded that resulting from multiple doses of oseltamivir (30 or 60 mg/kg/day, p.o.) or peramivir (30 mg/kg, i.v.), based on nasal wash viral titre, protein concentration, and number of inflammatory cells.

Safety pharmacology studies were conducted to evaluate the effects of peramivir on the central nervous system (CNS), cardiovascular, respiratory, gastrointestinal, and renal systems. None of the safety pharmacology studies showed adverse effects of peramivir. Pharmacokinetic properties have not been investigated in the safety pharmacology studies, and safety margins based on exposure data from these studies can therefore not be calculated. However, when using exposure values from the toxicology studies, it can be estimated that the safety margins are adequate.

Peramivir was not teratogenic in embryo-fetal development studies in rats and rabbits and had no effects on mating or fertility in rats up to 600 mg/kg/day, at which exposures were approximately

8-fold of those in humans at the clinically recommended dose. However, in an embryo-fetal development study in rats, in which dams received continuous infusions of peramivir from day 6-17 of gestation at does of 50, 400 or 1000 mg/kg/day, dose related increases in the incidences of reduction of the renal papillae and dilatation of the ureters were observed. The teratological importance of these findings is unclear.

Peramivir was not mutagenic or clastogenic in a battery of *in-vitro* and *in-vivo* assays. Carcinogenicity studies by intravenous injection of peramivir were not performed.

Acute renal necrosis was found in rabbits at doses ≥ 200 mg/kg with a clear NOAEL established in multiple studies at 100 mg/kg/day. Two-week oral toxicity studies were conducted in juvenile rats and rabbits, and a four-week IV toxicity study was conducted in juvenile rats. In general, nephrotoxicity was observed in rabbits, no unexpected toxicity was observed, and no other target organ toxicity was identified in juvenile animals.

2.3.7. Conclusion on the non-clinical aspects

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity. Peramivir was thoroughly investigated and found to be devoid of genotoxic potential in a standard battery of *in vitro* and *in vivo* genotoxicity studies. Carcinogenic potential by intravenous injection has not been evaluated and is not warranted in view of recommended single administration.

However, renal necrosis has been seen in rabbits, but no clear mechanistic explanation has been provided. Thus, reports indicating any kind of nephrotoxicity should be closely monitored and therefore included as an important potential safety concern in the "Safety specification" of the RMP. An appropriate statement has been added to SmPC, section 5.3 (Preclinical safety data).

For Alpivab, a Marketing Authorisation can be granted from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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.

A request for routine GCP inspection was adopted for the pivotal study (0722T0621).

GCP inspections took place at two investigator sites in Japan between 4-7 July 2017 and 10-13 July 2017.

The outcome of the inspection carried out was issued on 14 September 2017.

Tabular overview of clinical studies

Table 4. Phase I studies included in the peramivir clinical developmental programme

Study	Design	Objectives	Peramivir dose&adm	Subjects	PKdata/popPK /matrices
IV administration					
BCX1812-101 (2006)	Double-blind, placebo-controlled dose-escalating	Safety, PK	Single IV dose 0.5 mg/kg IV over 15 minutes	Healthy subjects (US) N=8*	Plasma, urine
BCX1812-102 (2006)	Double-blind, placebo-controlled dose-escalating	Safety, PK	0.5, 1, 2, 4, 8 mg/kg IV BID for 1 or 10 days over 15 minutes	Healthy subjects (US) N=8*	Plasma, urine
BCX1812-103 (2006)	Double-blind, randomised, placebo-controlled dose-escalating	Safety, PK	Single IV dose 1, 2, 4, 8 mg/kg Multiple IV dose 2, 4 mg/kg BID for 1 or 10 days over 15 minutes	Healthy subjects (US) N=68	Plasma, urine popPK (CB-137-C)
0712T0611 (2007)	Placebo-controlled dose-escalating	Safety, PK	100, 200, 400 mg IV for 8 days over 15 minutes	Healthy males (Japan) N=32	Plasma, urine, nasal wash, throat gargle popPK (PPK-1, CB-077-C, CB-137-C)
0714T0612 (2007)	Placebo-controlled high-dose	Safety, PK	Single and multiple doses of 800 mg IV over 15 minutes	Healthy males (Japan) N=16	Plasma, urine, nasal wash, throat gargle popPK (PPK-1, CB-077-C, CB-137-C)
BCX1812-104 (2006)	Double-blind, multiple dose. randomised, placebo-controlled	Safety and PK in elderly	4 mg/kg IV over 15 minutes BID for 1, 5 or 10 days	Healthy subjects ≥ 65 years old (US) N=20	Plasma, urine popPK (CB-137-C)
BCX1812-105 (2006/2007)	Open-label, five cohort	Renal impairment	2 mg/kg IV single dose over 15 minutes	Healthy subjects w/normal renal function, healthy subjects w/renal impairment (US) N=30	Plasma, urine popPK (CB-137-C)
BCX1812-106 (2009)	Randomised, double-blind, placebo-and positive controlled, cross-over	Thorough QT study	Single IV doses of 600 mg or 1200 mg over 30 minutes	Healthy subjects (US) N=52	Plasma
BCX1812-108 (2009)	Open-label, randomised, three-period cross-over	DDI oral 100 mg rimantadine 100	Single dose 600 mg IV over 15 minutes	Healthy subjects (US) N=21	Plasma
BCX1812-109 (2009)	Open-label, randomised, three-period cross-over	DDI oral oseltamivir	Single dose 600 mg IV over 15 minutes	Healthy subjects (US) N=21	Plasma
BCX1812-110 (2011/2012)	Blinded, randomised, placebo-controlled, two-period cross-over	DDI oral contraceptive	Single dose 600 mg IV over 15 minutes	Healthy females (US) N=34	Plasma
IM administration/relative bioavailability IM vs. IV					
BCX1812-111	Open-label,	IM	75, 150, 300mg	Healthy subjects	Plasma, urine,

(2006)	single dose, three cohort	bioavailability PK after IM and IV dosing DDI probenecid	single dose IV over 15 minutes, IM or IM+prob. at Day 1, 8, 15.	(US) N=27	nasal wash, throat gargle
BCX1812-112 (2006)	Double-blind, placebo-controlled, repeat-dose	PK, safety	75, 150, 300 mg IM injections once daily for two days	Healthy subjects (US) N=24	Plasma, urine
BCX1812-113 (2010)	Open-label, randomised, cross-over	Relative bioavailability IM and IV dosing	600 mg IV as 30 minutes infusion and 600 mg IM (two bilateral injections)	Healthy subjects (US) N=24	Plasma, nasal wash, throat gargle Included in popPK (PPK-1)
BCX1812-116 (2008)	Open-label, randomised, two-period, cross-over	Relative bioavailability and PK of two IM formulations, safety	300, 600, 900mg IM injection	Healthy subjects (US) N=60	Plasma
BCX1812-117 (2007)	Open-label, parallel-group	Effect of needle length and BMI on PK	300, 450, 600mg single dose IM dorsogluteal vs. ventrogluteal	Healthy subjects (US) N=79	Plasma
SC administration					
BCX1812-118 (2007)	Open-label, single dose	PK and safety of SC injection	two bilateral gluteal 150 mg SC injections	Healthy subjects (US) BMI ≥ 30 kg/m^2 N=15 (6 males)	Plasma

***** Terminated early due to sponsor decision. In each study, doses of 0.3 mg/kg peramivir or placebo were administered to six and two healthy subjects, respectively. Peramivir C_{max} 1925.8 ng/mL, AUC_{0-inf} 4975.2 ng*h/mL, mean $t_{1/2}$ 2.9 h, mean Vd 426.6 mL/kg, CL 101.7 mL/h/kg (101). Mean values after 1st and 2nd dosing were C_{max} 2589.2 ng/mL and 2549.2 ng/mL, AUC_{0-12} 5954.7 and 6035.9 h*ng/mL. After 2nd dose $t_{1/2}$ was 2.9 h, 335.1 mL/kg, CL 81.2 mL/kg/h.

Table 5. Phase II and III studies investigating peramivir in acute uncomplicated influenza and hospitalised influenza

Study	Design	Objectives	Dose&adm	Subjects	PK data
Acute uncomplicated influenza – outpatient setting					
0722T0621 (pivotal study)	Phase II, randomised, multi-center, double-blind, placebo-controlled	Efficacy, dose-response, safety	300 or 600 mg IV (30 minutes) single dose	Influenza patients (Japan) N=298	Plasma Limited PK data, included in popPK (PPK-1, CB-137-C)
BCX1812-211 (supportive)	Phase II, randomised, multi-center, double-blind, placebo-controlled	Efficacy, safety	150 or 300 mg IM single dose (two bilateral IM gluteal injections)	Influenza patients (US) N=342	No PK data
BCX1812-212 (supportive)	Phase II, randomised, multi-center, double-blind, placebo-controlled	Efficay, safety	600 mg IM single dose (two bilateral 300 mg IM injections)	Influenza patients (US, South-Africa, Australia, NZ) N=402	Plasma Limited PK data, included in popPK (PPK-1)
BCX1812-311 (supportive)	Phase III, 2:1 randomised, double-blind, placebo-controlled	Efficacy, safety	300 mg IM single dose (two bilateral 150 mg IM gluteal injections)	Influenza patients (US) N=82*****	Plasma Limited PK data, included in popPK (PPK-1)
0722T0631 (0815T0631)	Phase III, multi-national,	Efficacy, safety vs. oseltamivir	300 or 600 mg IV single dose	Influenza patients	Plasma Limited PK data,

	double-blind, positive-control, parallel-group	phosphate 75mg BID for 5 days	over 15-60 min	(Japan, Korea, Tawan) N=1093	included in popPK (PPK-1, CB-139-C)
0722T0632 (0815T0632)	Phase III, multi-center, non-controlled, double-blind	Efficacy, safety, PK	300 or 600 mg IV for 1-5 days	Influenza patients with high risk factors (Japan) N=42	Plasma Limited PK data
0815T0633	Phase III, multi-center, open label	Pediatric efficacy, safety, PK	10 mg/kg or 600 mg for subjects ≥ 60 kg IV for 1-5 days	Influenza patients (Japan) N=117	Plasma Limited PK data
Influenza – hospital setting					
BXC1812-201	Phase II, multi-national, randomised, double-blind, positive-control	Oseltamivir BID for 5 days	200 or 400 mg IV for 5 days	Acute serious/life-threatening influenza (US, Canada, HK, NZ, UK, SA, Singaprore) N=137	Plasma Limited PK data
BXC1812-301	Phase III, multi-national, double-blind, placebo-controlled	+/- Standard of care(STC)	600 mg IV for five days (Adolescents:10 mg/kg, children 12 mg/kg)	Hospitalised influenza patients (America, Europe, India, Israel) N=230	Plasma Limited PK data
BXC1812-303	Phase III, randomised, multi-national, open label		300 or 600 mg IV for 5-10 days (Adolescents: 5 or 10 mg/kg)	Hospitalised influenza patients (US, Canada, Mexico, NZ, Australia) N=230	Plasma Limited PK data

***** Terminated early due to a sponsor decision (*i.e.* more concentrated formulation chosen for further studies).

2.4.2. Pharmacokinetics

Adults

The applicant conducted 17 Phase 1 studies in healthy volunteers (single and multiple-dose studies):

- There were 5 escalating single and multiple dose tolerance studies (**BCX1812-101, BCX1812-102, BCX1812-103)** plus two studies in Japanese subjects [**0712T0611 and 0714T0612**]) with IV doses ranging from 0.5 mg/kg to 8 mg/kg and from 100 to 800 mg daily on a fixed-dose basis.
- One special population study was conducted in subjects with renal impairment (**BCX1812-105**).
- One special population study was conducted in elderly subjects (**BCX1812-104**).
- Three drug-drug interaction studies were conducted with rimantadine (**BCX1812-108**), oseltamivir (**BCX1812-109**), and the oral contraceptive ethinyl oestradiol/levonorgestrel (**BCX1812-110**).
- A thorough QT (TQT) study was conducted (**BCX1812-106**) in healthy subjects using single IV doses of 600 mg (clinical dose) and 1200 mg (supra-therapeutic dose). See under Pharmacodynamics for details.

In addition to these 11 studies with IV dosing the applicant conducted several studies with intramuscular (IM) dosing and one with sub-cutaneous dosing.

Children

During the procedure, the applicant provided data from an ongoing study (**BCX1812-305**) in children with uncomplicated influenza and proposed use of peramivir from the age of 2 years.

Peramivir in human plasma was measured using SPE and LC/MS/MS with a range of 1.0-50,000 ng/mL or 2.5 to 50,000 ng/mL. Peramivir in human urine, nasal wash and throat gargles was measured using ultrafiltration and LC/MS/MS with a range from 10-50,000 ng/mL.

The composition of the formulation has not changed throughout the clinical programme, except for addition of a pH adjustment by either 1 N sodium hydroxide or dilute hydrochloric acid (1%) to pH 5.5 - 8.5. The pH range of the commercial solution is 4.5 to 7.0 as used in later studies.

Studies with IV peramivir

After initial studies that evaluated single and BID dosing with 0.5 mg/kg infused over 15 min, **BCX1812-103** evaluated single doses of 1, 2, 4 and 8 mg/kg and then additional cohorts received two doses of 4 mg/kg on the same day or 2 mg/kg or 4 mg/kg BID for 10 days. Subjects were Caucasian, African American or Hispanic. Tmax occurred at the end of the infusion, after which plasma concentrations declined rapidly in a multi-exponential fashion. Cmax and AUC increased with dose after single and multiple doses.

Table 6

Table 23: Mean (SD) Peramivir PK Parameters by Dose Group Following Single intravenous Administration on Day 1 (Cohorts 1-4)

Parameter	1 mg/kg (N=6)	2 mg/kg (N=6)	4 mg/kg (N=6)	8 mg/kg (N=6)
C_{max} (ng/mL)	5,552 (1,324)	11,350 (1,121)	20,490 (3,908)	44,910 (10,750)
T_{max}[1] (h)	0.25 (0.25-0.25)	0.25 (0.25-0.25)	0.25 (0.25-0.25)	0.25 (0.23-0.30)
AUC_{0-12} (ng*h/mL)	11,400 (1,660)	21,000 (2,870)	46,200 (4,460)	84,500 (21,600)
AUC_{0-last} (ng*h/mL)	11,700 (1,730)	21,600 (3,030)	47,700 (4,720)	86,900 (22,100)
$AUC_{0-\infty}$ (ng*h/mL)	11,700 (1,720)	21,600 (3,020)	47,800 (4,690)	87,000 (22,100)
$t_{½}$ (h)	7.94 (2.64)	15.5 (6.68)	19.9 (6.81)	20.7 (2.62)
CL (mL/min)	107 (24.2)	118 (9.37)	106 (6.77)	122 (18.0)
V_{ss} (L)	17.0 (3.77)	20.1 (1.29)	20.9 (2.88)	21.7 (5.62)
CL_R[1] (mL/min)	87.7 (72.5-110)	93.7 (35.3-115)	88.5 (59.5-104)	102 (36.3-122)
f_e[1] (%)	90.6 (58.5-97.0)	82.7 (30.4-86.5)	88.2 (59.1-93.3)	90.6 (24.9-94.9)

[1] Presented as Median (Range).

Trough values suggested that steady state was reached by day 3 of BID dosing. Comparison of AUCs on Days 1 and 10 of 2 and 4 mg/kg BID dosing showed negligible accumulation.

Table 7

Table 24: Statistical Assessment of Peramivir Accumulation Following Multiple BID Administration (Cohort 6 vs Cohorts 2-3)

Parameter	Dose Group	Treatment Day	N	GLS Mean[1]	Pair	Ratio[2] (%)	90% CI[3] (%)
C_{max} (ng/mL)	2 mg/kg	Day 1 Day 10	6 9	11,300 12,610	10/1	111.60	(91.96 – 135.42)
	4 mg/kg	Day 1 Day 10	6 9	20,140 24,470	10/1	121.50	(102.18 – 144.49)
AUC_{0-12} (ng*h/mL)	2 mg/kg	Day 1 Day 10	6 9	20,900 22,900	10/1	109.98	(97.79 – 123.68)
	4 mg/kg	Day 1 Day 10	6 9	46,000 43,100	10/1	93.77	(82.83 – 106.16)

[1] Geometric least-squares mean.
[2] Ratio of GLS means.
[3] 90% confidence interval around the ratio of GLS means.
Ln-transformed PK parameters were fitted on an ANOVA model with treatment day as fixed effect.
Source: BCX1812-103-PK

Table 8

Table 25: Mean (SD) Peramivir PK Parameters by Dose Group Following Multiple Twice-Daily Intravenous Administration on Day 10 (Cohort 6)

Parameter	2 mg/kg (N=9)	4 mg/kg (N=9)
C_{max} (ng/mL)	12,960 (3,121)	24,750 (3,742)
T_{max}[1] (h)	0.24 (0.23-0.25)	0.25 (0.23-0.27)
AUC_{0-12} (ng*h/mL)	23,100 (2,550)	43,600 (6,390)
$t_{½}$ (h)	22.8 (2.12)	22.6 (1.91)
CL (mL/min)	108 (4.53)	109 (12.3)
V_{ss} (L)	20.6 (2.64)	20.1 (3.08)
CL_R[1] (mL/min)	81.3 (25.8-105)	90.3 (13.2-124)
f_e[1] (%)	81.2 (22.2-98.2)	86.0 (12.8-103.3)

[1] Presented as Median (Range)
Source: BCX1812-103-PK

0712T0611 investigated once daily dosing of 100 mg, 200 mg and 400 mg and then 400 mg BID dosing for 8 days in healthy adult Japanese males using 15-minute infusions. Plasma concentrations increased with dose and with low CV% values. Simple linear regression of the Cmax, AUC_{0-t} and AUC_{inf} at the initial dosing and Cmax and AUCτ at the final dosing indicated that there was dose-proportionality in Cmax and AUC at dose levels up to 400 mg.

Table 9

Table 11: Dose-proportionality of C_{max} and AUC (simple linear regression analysis)

Day	Parameters	Slope of ln (Dose)	95% C. I.	
			Lower	Upper
Day 1	C_{max}	1.050	0.888	1.211
	AUC_{0-t}	0.926	0.824	1.029
	AUC_{inf}	0.926	0.824	1.029
Day 8	C_{max}	1.026	0.878	1.174
	AUC_{t}	0.992	0.888	1.097

Table 10

Table 8: Overview of the pharmacokinetic parameters after intravenous dosing: At the initial dosing

Dose (mg)		100	200	400	400
Number of Dose per Day*		1	1	1	2
C_{max} (ng/mL)	Mean	11200	21100	46800	50500
	SD	2900	1600	7000	3800
	CV(%)	26.1	7.8	14.9	[illegible]
	GeoMean	10800	21000	46300	50400
	GeoCV(%)	28.3	7.7	14.8	7.4
T_{max} (hr)	Mean	0.25	0.25	0.25	0.25
	SD	0.00	0.00	0.00	0.00
	Minimum	0.25	0.25	[illegible]	0.25
	Median	0.25	0.25	0.25	0.25
	Maximum	0.25	0.25	0.25	0.25
AUC_{0-t} (ng hr/mL)	Mean	17498	33671	63354	68743
	SD	2003	3621	8621	6178
	CV(%)	11.4	10.8	13.6	9.0
	GeoMean	17407	33508	62855	68506
	GeoCV(%)	11.0	10.8	13.9	9.2
AUC_{inf} (ng hr/mL)	Mean	17513	33695	63403	68784
	SD	2001	3622	8620	6187
	CV(%)	11.4	10.8	13.6	9.0
	GeoMean	17423	33532	62904	68547
	GeoCV(%)	11.0	10.8	13.9	9.2
CL (L/hr))	Mean	5.77	5.99	6.41	5.86
	SD	0.61	0.65	0.90	0.55
	CV(%)	10.6	10.9	14.0	9.3
	GeoMean	5.74	5.96	6.36	5.84
	GeoCV(%)	11.0	10.9	13.9	9.2
$T_{1/2}$ (hr)	Mean	6.7	4.0	5.4	3.8
	SD	4.6	0.2	3.8	0.1
	CV(%)	68.5	4.1	71.2	3.1
	GeoMean	5.6	4.0	4.7	3.8
	GeoCV(%)	69.6	4.1	54.2	3.0
MRT (hr)	Mean	2.64	2.65	2.44	2.58
	SD	0.33	0.27	0.28	0.23
	CV(%)	12.6	10.0	11.3	9.0
	GeoMean	2.62	2.63	2.43	2.57
	GeoCV(%)	12.4	10.4	11.0	9.0
Vss (L)	Mean	15.16	15.77	15.53	15.00
	SD	2.14	1.35	1.71	0.82
	CV(%)	14.1	8.6	11.0	5.4
	GeoMean	15.04	15.72	15.45	14.98
	GeoCV(%)	13.7	8.5	11.7	5.5

Steady state was estimated to occur within 3 days after the start of repeated dosing. The trough concentration during dosing with 400 mg BID was ~ 13 times higher than that during 400 mg QD

dosing. However, based on AUCs, almost no accumulation was observed as a result of repeated dosing. The difference in $t_{1/2}$, z following initial and final dosing reflected the use of 48 and 72 h final measurement time points.

The urea-corrected drug concentrations in throat secretions increased in a dose dependent manner up to 400 mg. Concentrations remained > 2 ng/mL up to 24 hours after dosing with 200 mg or more. The Cmax and AUC in throat secretions were low with geometric mean values that were <10% of the plasma values after BID dosing. The pre-dose geometric mean concentration on Day 8 was ~ 6 x higher with BID vs. QD dosing. Similar findings applied to nasal secretions.

LC/MS/MS applied to plasma and urine did not detect the acyl-glucuronic acid conjugate, enantiomers or other unknown metabolites of peramivir.

0712T0612 investigated a single dose of 800 mg and then dosing with 800 mg once daily or placebo in 16 (4 placebo) healthy adult Japanese males using 15-minute infusions. The mean accumulation ratio for Cmax and AUC at the initial and final dosing was close to 1 (Cmax: 0.943, AUC: 0.968), indicating that there was almost no accumulation on repeated dosing.

Table 11

Table 9: Pharmacokinetic parameters in the plasma and urine after intravenous dosing of S-021812

Step Day Dose (mg)		Step I Day 1 800	Step II Day 1 800	Step II Day 6 800
C_{max} (ng/mL)	Mean	86200	90400	85500
	SD	15400	9200	13100
	CV (%)	17.8	10.2	15.3
	GeoMean	85200	89900	84700
	GeoCV (%)	17.1	10.5	14.7
T_{max} (hr)	Mean	0.25	0.25	0.25
	SD	0.00	0.00	0.00
	Minimum	0.25	0.25	0.25
	Median	0.25	0.25	0.25
	Maximum	0.25	0.25	0.25
AUC_{0-t} (ng hr/mL)	Mean	133566	135775	—
	SD	19914	13211	—
	CV (%)	14.9	9.7	—
	GeoMean	132286	135237	—
	GeoCV (%)	15.5	9.8	—
AUC_t (ng hr/mL)	Mean	—	—	131385
	SD	—	—	12871
	CV (%)	—	—	9.8
	GeoMean	—	—	130876
	GeoCV (%)	—	—	9.6
AUC_{inf} (ng hr/mL)	Mean	133795	136058	—
	SD	19972	13248	—
	CV (%)	14.9	9.7	—
	GeoMean	132510	135518	—
	GeoCV (%)	15.5	9.8	—

The mean of the ratio of AUC_t at the final dosing in relation to the AUC_{inf} at the initial dosing was close to 1 (0.966), indicating that there was almost no change in the pharmacokinetics on repeated dosing. Based on data obtained in the previous study (above) at lower doses, there was dose-proportionality in Cmax and AUC during intravenous dosing up to 800 mg. The concentrations of peramivir in throat and nasal secretions were low compared to plasma after 800 mg QD dosing.

Table 12

Table 12: Dose-proportionality of the C_{max} and AUC of S-021812

Dose	Parameters	Slope of ln(Dose)	95% C.I.	
			Lower	Upper
First Dose	C_{max}	1.007	0.910	1.104
	AUC_{0-t}	0.969	0.900	1.038
	AUC_{inf}	0.969	0.900	1.038
Last Dose	C_{max}	1.011	0.924	1.098
	AUC_t	1.010	0.949	1.070

IV vs. IM peramivir

BCX1812-111 compared single IV and IM doses of 75 mg, 150 mg or 300 mg in 3 separate dose cohorts. Each cohort received 3 treatments – IV, IM and IM with 1 g oral probenecid. The absolute bioavailability of the IM formulation was 92% to 99% based on ratios of geometric LS means).

Table 13

Table 12: Statistical Assessment of Peramivir Intramuscular Absolute Bioavailability

Parameter	Dose Group	Treatment Group[a]	N	GLS Mean[b]	Pair	Ratio[c] (%)	90% CI[d] (%)
$AUC_{0-\infty}$ (ng*h/mL)	75 mg	A	7	10,900			
		B	9	10,800	B/A	98.6	(95.6 – 101.6)
	150 mg	A	9	24,400			
		B	8	22,500	B/A	92.3	(85.1 – 100.1)
	300 mg	A	9	47,800			
		B	9	47,100	B/A	98.5	(94.9 – 102.2)

[a] Treatment A = IV infusion; Treatment B = IM injection.
[b] Geometric least squares mean.
[c] Ratio of GLS means.
[d] 90% confidence interval around the ratio of GLS means
Ln-transformed PK parameters were fitted on an ANOVA model with sequence, period, and treatment as fixed effects and subject nested within sequence as random effect.

Exposure to peramivir increased in proportion with IM or IV dose over the 75 to 300 mg dosing range with 90% CI for the slope estimates within the predefined limits for proportionality (0.84, 1.16). For Cmax the 90% CIs did not entirely fall within (0.84, 1.16) but slope estimates were close to 1 (0.919 and 0.912 for IV and IM administration, respectively). Probenecid had no significant effect on maximum and overall peramivir exposure with geometric LSMs close to 100% (range: 95% to 106%) and 90% CIs within 80-125% for all comparisons.

Table 14

Table 8: Mean (SD) Peramivir PK Parameters by Treatment and Dose Group

Parameter	Dose Group	Treatment Group A IV N=9	Treatment Group B IM N=9	Treatment Group C IM + Probenecid N=8
C_{max}[a] (ng/mL)	75 mg	5,740 (817)[e]	4,300 (760)	4,550 (975)
	150 mg	11,100 (2,680)	7,610 (884)[e]	7,530 (1,420)
	300 mg	20,400 (1,730)	15,200 (2,370)	15,600 (2,210)
T_{max}[b] (h)	75 mg	0.25 (0.25-0.27)[e]	0.50 (0.50-0.50)	0.50 (0.50-1.00)
	150 mg	0.25 (0.23-0.28)	0.56 (0.50-1.00)[e]	0.50 (0.50-0.50)
	300 mg	0.25 (0.23-0.28)	0.50 (0.50-0.50)	0.50 (0.50-1.00)
$AUC_{0\text{-last}}$ (ng*h/mL)	75 mg	11,000 (1,650)[e]	10,800 (1,190)	11,100 (1,350)
	150 mg	24,600 (4,000)	22,700 (3,600)[e]	21,400 (2,480)
	300 mg	47,900 (5,100)	47,200 (5,370)	50,000 (6,310)
$AUC_{0-\infty}$ (ng*h/mL)	75 mg	11,000 (1,750)[f]	10,800 (1,170)	11,000 (1,380)[f]
	150 mg	24,700 (4,010)	22,800 (3,610)[e]	21,500 (2,460)
	300 mg	48,000 (5,130)	47,300 (5,390)	50,100 (6,370)
$t_{½}$ (h)	75 mg	13.8 (2.52)[f]	25.2 (19.9)	16.5 (5.45)[f]
	150 mg	26.0 (6.33)	24.8 (3.07)[e]	25.2 (3.32)
	300 mg	21.7 (2.12)	22.8 (2.45)	21.5 (1.98)
CL[c] (mL/min)	75 mg	116 (18.1)[f]	117 (12.5)	115 (14.5)[f]
	150 mg	104 (15.6)	112 (17.2)[e]	118 (11.9)
	300 mg	105 (11.3)	107 (11.3)	101 (12.3)
V_d[d] (L)	75 mg	20.0 (2.59)[f]	265 (247)	160 (36.1)[f]
	150 mg	20.2 (3.78)	242 (53.6)[e]	257 (45.8)
	300 mg	22.4 (2.21)	211 (36.6)	187 (11.7)
CL_R (mL/min)	75 mg	105 (20.6)[g]	111 (14.1)[e]	107 (13.9)[f]
	150 mg	98.4 (29.6)[e]	101 (13.1)[e]	105 (10.4)
	300 mg	94.9 (23.5)[f]	96.5 (12.0)	93.7 (12.4)[g]
f_e (%)	75 mg	89.5 (5.7)[f]	94.9 (6.8)[e]	91.4 (6.6)
	150 mg	94.1 (18.8)[e]	90.7 (6.1)[e]	89.7 (8.0)
	300 mg	91.4 (17.3)[f]	90.4 (7.2)	94.5 (2.9)[g]

[a] Represents a back-extrapolated, rather than observed, maximum concentration for Treatment A.
[b] Presented as Median (Range)
[c] Represents CL/F for Treatment B (IM) and Treatment C (IM + Probenecid)
[d] Represents V_{ss} for Treatment A (IV) and V_z/F for Treatment B (IM) and Treatment C (IM + Probenecid).
NOTE: Vz/F overestimates the volume of distribution.
[e] N=8
[f] N=7
[g] N=6

As a percentage of the time-matched corresponding concentration in plasma, the concentrations of peramivir in nasal washes and throat gargles generally increased over time, suggesting a slightly delayed clearance of peramivir from these anatomic sites vs. clearance from plasma.

BCX1812-113 was specifically designed to evaluate the relative bioavailability of IM (DG; 2 x 2 mL volumes) and IV (30-minute infusion) 600 mg doses in white and black adults with BMI ≤ 29.9 kg/m^2. Bioequivalence was shown for AUC_{0-24} and AUC_{0-inf} between IM and IV routes but not for Cmax.

Table 15

Table 8: C_{max}, $C_{24\,hr}$ and AUC_{0-24}– Pharmacokinetic Population

	Peramivir 600 mg	
	IV (N =24)	IM (N =23)
AUC_{0-24} (ng*hr/mL)		
Mean (SD)	102500 (18790)	102400 (19120)
Geometric Mean	100800	100700
Median	99170	96950
Min, Max	66410, 153600	65910, 153300
Coefficient of Variation	18.34	18.68
Least Square Means (90%) CI)	100800 (94430, 107700)	101400 (94900, 108200)
Ratio of geometric means of IM Peramivir to IV Peramivir (90% CI) [1]	100.5% (97.6%, 103.5%)[a]	
F-test value for Sequence Effect (p-value)	<0.01 (0.9766)	
F-test value for Period Effect (p-value)	1.36 (0.2560)	
$C_{24\,hr}$ (ng/mL)		
Mean (SD)	52.9 (21.1)	52.6 (19.6)
Geometric Mean	49.3	49.8
Median	48.4	46.1
Min, Max	23.7, 117	29.2, 116
Coefficient of Variation	39.9	37.2
Least Square Means (90%) CI)	49.3 (43.5, 56.0)	50.7 (44.7, 57.5)
Ratio of geometric means of IM Peramivir to IV Peramivir (90% CI) [a]		102.7% (99.5%, 106.1%) [a]
F-test value for Sequence Effect (p-value)	0.19 (0.6686)	
F-test value for Period Effect (p-value)	13.66 (0.0013)	
C_{max} (ng/mL)		
Mean (SD)	46300 (10100)	36500 (8420)
Geometric Mean	45700	35700
Median	46200	32900
Min, Max	28200, 68200	26100, 55100
Coefficient of Variation	21.5	23.1
Least Square Means (90%) CI)	45700 (42300, 49400)	35700 (33000, 38700)
Ratio of geometric means of IM Peramivir to IV Peramivir (90% CI) [a]		78.2% (73.3%, 83.3%)
F-test value for Sequence Effect (p-value)	0.06 (0.8104)	
F-test value for Period Effect (p-value)	0.45 (0.5106)	

Mean values for t1/2 (3.3 and 3.6 h), clearance (CL/F 6034, 6035 mL/h) and Vz/F (28520 and 31400 mL) were similar following IV and IM administration of peramivir. There were no notable differences between IV and IM administrations for peramivir concentrations in throat-gargle or nasal-wash samples except for throat-gargle samples at 24-hours post-dose for which the difference was not thought likely to be clinically significant due to the high variability of the results.

1. Distribution

The extent of binding of ^{14}C-peramivir to plasma proteins was <18% when determined in human plasma by equilibrium dialysis at concentrations from 10-1,000 ng/mL. In a further study, fresh heparinised human plasma was spiked with peramivir to achieve concentrations from 1-1,000 ng/mL. Plasma protein binding was determined to be < 30% using equilibrium dialysis followed by a validated LC-MS/MS assay. There were no conclusive trends in the extent of plasma protein binding over a wide concentration range and no apparent gender differences.

2. Excretion

Following IV administration the plasma concentrations of peramivir decline multi-exponentially with a major decline over the first 24 h and an average terminal $t_{1/2}$ ~15-30 hours when PK sampling is carried out over 48-72 hours. The POPPK analysis indicates that peramivir undergoes extensive renal elimination as intact drug such that total CL correlated well with CrCL and renal CL accounted for >90% of drug recovered in the urine.

3. Metabolism

Using peramivir (100µg/mL) in human liver 9000 x g (S9) homogenates and MS, one metabolite of peramivir oxidized at the cyclopentyl ring was identified at low concentrations (<4% of added substrate). No other metabolites were found.

A clinical metabolite profiling study was not conducted. The metabolism of peramivir was assessed by LC-MS/MS analysis of plasma and urine after single or repeated IV dosing in healthy adult Japanese male subjects. Peramivir was excreted unchanged in urine. Unchanged peramivir was the only component identified in plasma and urine after single and multiple intravenous administrations. No enantiomer of peramivir was detected in plasma after single and repeated intravenous administrations.

Pharmacokinetics in target population

After single IV doses of 300 mg or 600 mg in Asian patients with influenza the CV% values were small.

Table 16

Table 12: Mean (CV%) Peramivir PK Parameters Estimated from Sparse Sampling with PK Model after Single IV Dose in Patients with Uncomplicated Influenza (Study 0815T0631)

PK Parameter	Peramivir Administered IV		
Nominal Dose	300 mg	600 mg	300 and 600 mg groups combined
Estimated Actual Dose	267 mg	535 mg	
	(N=364)	(N=362)	(N=726)
C_{max} (µg/mL)	24.4 (15)	48.4 (16)	-
AUC (h*µg/mL)	41.02 (17.3)	82.13 (15.9)	-
CL (L/h)	-	-	6.66 (14.0)
V_{ss} (L)	-	-	15.3 (10.0)

BCX1812-PPK-1 used data from non-Japanese Phase 2/3 studies (BCX1812-113, 212 and 311) and from the Japanese studies 0712T0611, 0714T0612 (Phase 1), 0722T0621 (Phase 2) and 0815T0631 (Phase 3). The peramivir PK data were best described by a simple 2-compartment model with linear elimination. The peramivir Vd was demonstrated to be dependent on weight and Asian race. The weight adjusted Vd was <2% lower in Asian vs. non-Asian subjects. The rate of peramivir elimination was dependent on CrCL.

During the procedure, a further POPPK model was developed to include additional datasets from the Phase 1 renal impairment study BCX1812-105, the Phase 1 elderly study BCX1812-104 and the Phase 3 paediatric study BCX-1812-305. This model was used to derive the dose adjustment schema for

subjects with renal impairment (see below) and to confirm that weight did not *per se* merit dose adjustment.

Special populations

4. Impaired renal function

BCX1812-105 evaluated IV peramivir in subjects with normal renal function (cohort 1) or with mild, moderate or severe impairment (cohorts 2-4) or ESRD on haemodialysis (cohort 5). Cohorts 1 - 4 received a single dose of 2 mg/kg over 15 minutes and cohort 5 received 2 mg/kg at 2 hours before the start of dialysis and again at 1 hour after completion of dialysis. Cmax was generally similar across all cohorts following a single IV dose but $AUC_{0\text{-last}}$ and $AUC_{0-\infty}$ increased with the severity of renal impairment.

Note that $AUC_{0\text{-last}}$ cannot be compared between the ESRD and other groups as this parameter is truncated to 48 and 72 hours after the first and second doses, respectively. The $AUC_{0-\infty}$ increased vs. controls by 28%, 302% and 412% in mild, moderate and severe renal impairment, respectively. In ESRD haemodialysis reduced systemic exposure by 73% to 81%.

Table 17

Table 9 Mean (SD) Peramivir PK Parameters by Renal Group and Dose

Parameter	Renal Function Group					
	Normal (N=6)	Mild (N=5)[4]	Moderate (N=6)	Severe (N=5)[4]	ESRD	
					Dose 1 (N=6)	Dose 2 (N=6)
C_{max} (ng/mL)	12,800 (2,860)	12,500 (3,590)	13,700 (3,780)	13,200 (2,910)	11,000 (3,000)	15,500 (3,610)
T_{max}[1] (h)	0.25 (0.25-0.30)	0.25 (0.23-1.00)	0.25 (0.23-0.32)	0.25 (0.25-0.28)	0.25 (0.25-2.25)	0.25 (0.25-1.25)
$AUC_{0\text{-last}}$ (ng*h/mL)	26,000 (3,200)	33,900 (7,870)	108,000 (31,200)	136,000 (40,600)	107,000[2] (20,300)	470,000[3] (81,200)
$AUC_{0-\infty}$ (ng*h/mL)	26,000 (3,180)	33,900 (7,880)	108,000 (31,200)	137,000 (41,100)	ND	ND
$t_{½}$ (h)	20.7 (4.78)	23.7 (2.84)	28.7 (3.21)	30.7 (2.75)	70.6[2] (33.9)	93.1[3] (53.3)
CL (mL/min)	108 (9.90)	77.9 (21.4)	26.8 (5.35)	21.1 (4.68)	ND	ND
V_{ss} (L)	22.0 (4.35)	20.6 (6.07)	21.9 (3.40)	23.5 (2.80)	ND	ND
CL_{CR} (mL/min)	97.1 (9.23)	66.3 (15.8)	23.2 (5.59)	14.7 (3.27)	ND	ND
f_e (%)	90.4 (7.5)	86.0 (8.5)	85.9 (5.5)	71.6 (16.4)	ND	ND

[1] Presented as Median (Range)
[2] Parameter is truncated to 48 hours post-infusion.
[3] Parameter is truncated to 72 hours post-infusion.
[4] Subjects 1001 (mild renal impairment) and 1002 (severe renal impairment) are excluded as the actual duration of infusion was longer than 15 minutes due to pump malfunction.

Peramivir was recovered unchanged in the urine, with the majority of the recovery complete by 12 hours post-dose in subjects with normal renal function or mild renal impairment and by 24 to 36 hours in subjects with moderate or severe renal impairment. Urine samples were not collected from the ESRD group. On average, renal clearance accounted for 89.9%, 85.1%, 86.6% and 69.6% of total clearance in subjects with normal renal function and subjects with mild, moderate, and severe renal

impairment, respectively. However, CLr may be underestimated in the severe renal impairment group. Peramivir clearance (CL and CLr) correlated well with CrCL with coefficients of determination of 0.877 and 0.912, respectively. The slope of the relationship was nearly equal to 1 (1.15) and the 90% CI included 1 (0.982, 1.31), suggesting that peramivir is primarily eliminated through glomerular filtration and is not subject to active tubular secretion or reabsorption.

The applicant proposed dose adjustments when CrCL fell below 50 mL/min based on three simulated regimens. Based on the comparison of AUC_{0-24} between adults with normal renal function/mild impairment and those with moderate or severe impairment, and considering the safety profile of peramivir at 300 mg. 600 mg and 1200 mg single doses, the regimen chosen (and reflected in the revised SmPC) was considered to provide exposures in moderate (300 mg dose) and severe (200 mg dose) impairment that were likely to be effective without exceeding typical exposures at 600 mg by more than 2-fold. This conclusion was supported by simulations of exposures that could be expected at the extremes of each renal function category.

Additional simulations failed to identify suitable dose adjustment recommendations for subjects of <13 years and < 50 kg body weight. Therefore, the adjustment schema in the SmPC is age and weight restricted.

5. Elderly

BCX1812-104 evaluated IV dosing in 20 subjects aged ≥ 65 years who received 2 infusions 12 h apart of 4 mg/kg over 15 min, after which 16 subjects were randomised to receive 4 mg/kg or placebo twice daily (3:1 ratio) for 5 days (Group A) or 10 days (Group B). The 20 subjects (10 male; 19 Caucasian) were aged from 65 to 79 years (mean 70.1 years). CrCL ranged from 82.8 mL/min to 197.9 mL/min. Cmax of peramivir was similar after the first dose of treatment and after the last dose following BID dosing. There was no meaningful difference in AUC0-12 after the first and last doses on Days 5 or 10. The mean percent recovery of peramivir in urine over 48 hours post-dose 1 was 81.2% with a mean of 494.2 mg recovered compared with the mean total daily dose of 626.6 mg. The applicant compared the results with those obtained from younger subjects in study 103. Cmax values after a single 4 mg/kg IV dose were ~10% higher in elderly subjects when compared to young adults (22,647 vs. 20,490 ng/mL) and AUC0-12 at steady state was ~34% higher (61,572 vs. 43,600 ng•h/mL).

Table 18

Table 14: Single-dose and Steady-state Exposure (Mean ± SD) with 4 mg/mL Peramivir in Nonelderly and Elderly Healthy Volunteers

	Single dose		Steady-state (after 10 days)	
	BCX1812-103	BCX1812-104	BCX1812-103	BCX1812-104
	Nonelderly	Elderly	Nonelderly	Elderly
C_{max} (ng/mL)	20,490 ± 3,908	22,647 ± 4824	24,750 ± 3,742	22,933 ± 2951
AUC_{0-12} (ng•h/mL)	46,200 ± 4,460	61,334 ± 8793	43,600 ± 6,390	61,572 ± 8584

There were only 22 subjects aged ≥ 65 years included in PPK-1 and a further 7 were enrolled in the renal impairment study (above). The data were insufficient to determine whether age *per se* affects peramivir PK.

Paediatric patients with uncomplicated influenza

BCX1812-305 commenced in March 2015 at 16 US sites. The primary objective was to evaluate the safety of IV peramivir compared with oral oseltamivir in paediatric subjects with uncomplicated influenza. In a staged cohort design the study will eventually enrol children aged from 28 days to 17

years of age with uncomplicated influenza and presenting no more than 48 hours after symptom onset. Subjects were randomised 4:1 to IV peramivir or oral oseltamivir as follows:

1. A single dose of IV peramivir 600 mg IV if ≥ 13 years of age or 12 mg/kg IV if ≤ 12 years of age, diluted to 100 mL and infused over 15 min

2. Oral oseltamivir dosed BID for 5 days as capsules or as an oral suspension

As of the March 31, 2017 cut-off, a total of 122 subjects were enrolled (99 peramivir and 23 oseltamivir).

Table 19

Table 1: Summary of Study BCX1812-305 Enrolment Status as of March 31, 2017

Age Group		Target Number of Subjects for Enrolment	Number of Subjects Enrolled as of 30 Apr 2016	Number of Subjects Enrolled Between 01 May 2016 and 31 Mar 2017	Total Number of Subjects Enrolled
1	Birth to < 28 days	10	N/A	0	0
2	≥ 28 days to < 2 years	20	4	3	7
3	≥ 2 to < 7 years	40	26	11	37
4	≥ 7 to < 13 years	40	48	N/A	48
5	≥ 13 to < 18 years	30	30	N/A	30
Total		140	108	14	122

N/A = not applicable

In the age cohort from 2 to < 7 years 6 subjects were < 3 years old at the time of enrolment, ranging from 2.2 to 2.9 years. Up to 4 samples were collected per subject. PK data and numbers contributing to the PK analysis are shown below by age cohort.

Table 20. Updated Cumulative Summary PK Parameters for BCX1812-305

Age Group		N	C_{max} (ng/mL)	T_{max} (h)	T_{last} (h)	AUC_{last} (ng.h/mL)
28 days-<2 years	Mean (SD)	4	40100 (8780)	0.48 [0.37, 1.1]	3.4 [3.4, 4.2]	60900 (6970)
	Geometric Mean		39400	NA	NA	60600
	%CV		21.9	NA	NA	11.4
2 years - < 7 years	Mean (SD)	28	53600 (26200)	0.48 [0.32, 3.5]	3.5 [0.48, 4.4]	74000 (30000)
	Geometric Mean		47400	NA	NA	68100
	%CV		48.9	NA	NA	40.6
2 years - < 4 years	Mean (SD)	6	54100 (28000)	0.48 [0.38, 1.6]	3.5 [0.48, 4.4]	66700 (15600)
	Geometric Mean		48900	NA	NA	65400
	%CV		51.8	NA	NA	23.4
4 years - < 7 years	Mean (SD)	22	53500 (26400)	0.48 [0.32, 3.5]	3.5 [3.3, 4.3]	75600 (32500)
	Geometric Mean		47000	NA	NA	68700
	%CV		49.4	NA	NA	43.0
7 years - < 13 years	Mean (SD)	39	66800 (35400)	0.47 [0.25 – 3.5]	3.5 [3.3 – 3.8]	87000 (40800)

	Geometric Mean		61200	NA	NA	81000
	%CV		53.0	NA	NA	46.8
13 years - <18	Mean (SD)	20	54300 (17900)	0.39 [0.28-0.63]	3.4 [3.3 – 4.2]	72400 (20000)
	Geometric Mean		51500	NA	NA	69500
	%CV		33.0	NA	NA	27.6
2 years - < 13 years	Mean (SD)	67	61300 (32300)	0.47 [0.25, 3.5]	3.5 [0.48, 4.4]	81700 (37000)
	Geometric Mean		55000	NA	NA	75400
	%CV		52.8	NA	NA	45.3
2 years - < 18 years	Mean (SD)	87	59700 (29700)	0.45 [0.25, 3.5]	3.5 [0.48, 4.4]	79500 (34000)
	Geometric Mean		54200	NA	NA	74000
	%CV		49.8	NA	NA	42.7
All Subjects	Mean (SD)	91	58800 (29400)	0.45 [0.25-3.5]	3.5 [0.48-4.4]	78700 (33400)
	Geometric Mean		53400	NA	NA	73400
	%CV		49.9	NA	NA	42.5

Abbreviations: AUC_{last} = area under the plasma concentration versus time curve from time zero to the last measurable concentration; C_{max} = maximum observed plasma concentration; CV = coefficient of variation; NA = not applicable; T_{last} = time of last measurable plasma concentration; T_{max} = time to achieve C_{max}
T_{max}

It was concluded that the **12 mg/kg dose** (up to 50 kg) provided plasma exposures across age sub-categories with normal renal function that were comparable with those achieved with a 600 mg dose in subjects of ≥ 50 kg.

Pharmacokinetic interaction studies

In vitro

1. Peramivir is not a substrate of P-gp. In a Caco-2 cell model, peramivir at 300 µM did not significantly inhibit digoxin efflux.

2. At 3 to 450 µM peramivir did not result in >50% inhibition of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 or MATE2-K. Peramivir had an efflux ratio <2 for P-gp and BCRP and an uptake ratio <2 for OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K.

3. In primary cultures of human hepatocytes peramivir did not induce CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 at concentrations from 50-10,000 ng/mL.

4. In human liver microsomes peramivir did not inhibit CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 at concentrations up to 100 µM.

5. Peramivir (up to 10 mM) did not inhibit the biotransformation of paracetamol (at concentrations from 0.625 to 2 mM) by human liver glucuronosyl transferase.

In vivo

BCX1812-108 – IV peramivir (600 mg) plus oral rimantidine (100 mg)

In this US study using single doses given alone and together, the 90% CIs around the GMRs for Cmax, AUC_{0-24} and AUC_{0-inf} indicated no effect of rimantadine on peramivir PK or *vice versa*.

BCX1812-109 – IV peramivir (600 mg) plus oral oseltamivir (75 mg)

In this US study using single doses administered after a standard light breakfast, the 90% CIs around the GMRs for Cmax, AUC_{0-24} and AUC_{0-inf} indicated no effect of oseltamivir on peramivir PK. There was no effect of peramivir on the active molecule oseltamivir carboxylate. There was also no effect of peramivir on the AUC of the pro-drug oseltamivir but the oseltamivir Cmax was slightly higher on co-administration (ratio 120%; 90% CI 99, 144) and CV% values for oseltamivir Cmax were 69% when given alone vs. 43% following co-administration.

BCX1812-110 – IV peramivir (600 mg) single dose plus oral contraceptive

In this US study single IV doses of peramivir 600 mg and placebo were administered one week apart to adult female subjects who had been taking Levora (0.15 mg levonorgestrel [LNG] and 0.03 mg ethinyl oestradiol [EE]) for 7-14 days and for 14-20 days. Due to a misinterpretation of the protocol the pre-dose and 24-h sampling occurred after the subsequent OC dose (i.e. at ~ 0.5 and 24.5 hour) so trough levels were not measured but they were estimated by linear regression and extrapolation from data in the terminal portion of the PK curve. Due to this error, the primary endpoint was modified to $AUC_{0.5-12}$ and secondary and exploratory endpoints ($AUC_{0.5-24}$ and AUC_{0-24}) were added.

For EE the extrapolated C_{24} concentrations indicated that the 90% CIs for the GMR were 72.4%, 105.9% but those for $AUC_{0.5-12}$, $AUC_{0.5-24}$ and Cmax fell within 80% to 125%. The study was powered with the assumption that the EE CV% would be 23% but the actual CV% across all of the PK parameters ranged from 34 to 40%. For LNG all of the 90% CIs around the GMRs fell within 80-125%. The study was powered with the assumption that the LNG CV% would be 27% but the actual CV% across all of the PK parameters ranged from 38 to 57%. A cross-study comparison of plasma peramivir values indicated no effect of co-administration with EE and LNG.

2.4.3. Pharmacodynamics

Mechanism of action

Enzyme inhibition assays in cell culture indicated that peramivir is a selective inhibitor of the influenza neuraminidase (NA) enzyme. NA cleaves sialic acid residues from glycoproteins and glycolipids on the host cell and is responsible for the release of newly synthesised virus particles from infected cells. Inhibition of NA hinders spreading of virus within the respiratory tract.

Primary and Secondary pharmacology

Primary pharmacology

The primary pharmacology of peramivir relates to its antiviral activity. The table shows the peramivir IC_{50} (nM) values obtained from some of the studies that employed NA inhibition assays.

Table 21

Report Number	Influenza Virus Subtype[a]	Number of Virus Strains Tested	Range of Mean IC_{50} (nM)[b]		
			Peramivir	OSE-C	ZVR

P97-1812-001	H1N1	6[c]	0.09–0.81	0.69–2.24	0.30–0.80
	H1N9	1[c]	1.3	2.1	1.6
	H2N2	4	0.17–1.39	0.01–1.45	0.76–1.78
	H6N2	1	1.08	0.84	1.07
	H3N2	4	0.14–0.83	0.21–0.56	0.68–2.32
	B	8	0.60–10.78	5.00–24.3	1.53–17.0
EDMS-USRA-3424162	H1N1	4	0.09–0.37	0.69–2.24	0.30–0.80
	H2N2	2	0.17–0.18	0.21–0.25	0.76–0.99
	H3N2	3	0.14–0.29	0.21–0.24	0.68–2.32
	B	4	0.82–1.53	7.70–10.36	1.53–3.31
CDC 2009	pH1N1	13	0.06–0.26	0.28–1.41	0.30–1.34
	H1N1	1	0.16	0.61	0.56
	H1N1	1	13.87	200.73	0.8
PMV-EB-033-N	H1N1	1	0.50	1.40	Not done
	H2N2	1	0.94	0.70	Not done
	Avian H6N1	1	0.62	2.09	Not done
	Avian H9N2	1	1.12	0.86	Not done
	Avian H2N3	1	0.69	0.99	Not done
	Avian H5N3	1	0.90	1.03	Not done
	Avian H8N4	1	0.91	1.22	Not done
	Avian H10N4	1	0.51	1.22	Not done
	Avian H4N5	1	0.24	0.99	Not done
	Avian H12N5	1	0.30	1.02	Not done
	Avian H11N6	1	0.[illegible]	1.21	Not done
	Avian H13N6	1	0.69	1.19	Not done
	Avian H7N7	1	0.85	0.86	Not done
	Avian H10N7	1	1.18	2.46	Not done
	Avian H3N8	1	0.39	3.38	Not done
	Avian H6N8	1	0.35	2.19	Not done
	Avian H11N9	2	0.39–0.45	1.13–1.18	Not done

On-site dissociation studies were conducted to compare the binding affinities of peramivir, OSE-C, and/or ZVR to the NA enzyme from A/NWS/G70c (H1N9) influenza virus. The half-life was 1.25 hours for NA/ZVR and NA/OSE-C complex and > 17 hours for the NA/peramivir complex.

A laboratory-generated variant of influenza B/Yamagata/16/88 virus with reduced susceptibility to peramivir had 6 mutations in the HA gene plus an H274Y mutation in the NA gene. Peramivir bound 70-fold less tightly to this NA compared with the WT NA.

In-vitro studies of the activity of peramivir against various influenza strains, including some with mutational resistance to other NA inhibitors, are summarised in the table below.

Table 22

Table 1: Activity of Peramivir against Influenza A and B Viruses and Avian Influenza Viruses in Cell Culture Assays In Vitro

Report Number	Influenza Virus Subtype	No. of Virus Strains Tested	Endpoint	Range of Mean EC_{50} (nM)[a]		
				Peramivir	OSE-C	ZVR
S-021812-EB-115-N	H1N1	2	Plaque counts by neutral red staining	0.93-15	60-140	5.8-37
	H3N2	1		0.36	0.78	4.6
	B	2		25–26	31–42	21–29
S-021812-EB-108-N	H1N1	3	Plaque counts by neutral red staining	0.48-18	7.5–360	13–130
	H3N2	4		0.06–1.9	5.3–260	3.6–59
	B	3		4.8–120	30–720	7.9–150
P97-1812-001	H2N2	1	Plaque counts by crystal violet staining	< 1.0	< 1.0	< 1.0
	B	1		95.0	467	67
Smee, Huffman 2001	H1N1	5	Neutral red uptake	0.09–21	0.17– > 100	0.22– > 100
	H3N2	12		< 0.01–0.19	< 0.01–0.50	< 0.01–0.65
	B	5		0.06–3.2	0.11–3.0	0.03–1.3
	Avian H5N1	2		0.01–0.02	0.22–0.25	0.20–0.22
DD01037[b]	H1N1	9	Cytotoxicity by MTT[c]	3.1–> 100	Not tested	Not tested
	H2N2	1		1.4	Not tested	Not tested
	H3N2	10		0.5–28	Not tested	Not tested
	B	9		All > 100	Not tested	Not tested
	Avian H5N3	1		24.1	Not tested	Not tested
PMV-EB-034-N	H1N1	1	Cell viability by WST-8 reagent	> 100	> 100	Not tested
	H3N2	1		13	45	Not tested
	B	4		All > 100	All > 100	Not tested
PMV-EB-035-N[d]	H1N1	4	Cytopathic effect by visual light microscopy	13–> 100	All > 100	All > 100
	H3N2	2		72– > 100	81– > 100	Both > 1000
	B	4		110–490	280– > 1000	130–470
Boltz 2008	H5N1	1	Plaque size reduction assay	0.3	0.5	0.7

[a] Where data range was not provided in the report, the mean EC_{50} value alone is presented
[b] Comparator drug was ribavirin
[c] MTT = 3-(4,5-Dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium bromide
[d] Report PMV-EB-035-N only provided IC_{90} data

The plaque reduction assay in MDCK cells showed that recombinant H1N1 virus carrying the H275Y NA mutation had decreased susceptibility to peramivir and OSE-C but not to ZVR. The recombinant H1N1 virus carrying the E119Q NA mutation demonstrated decreased susceptibility only to OSE-C.

NA enzyme inhibition assays showed that a recombinant H1N1/09 virus carrying the N146S NA mutation had an approximate 2-fold decrease in susceptibility to ZVR and OSE but not for peramivir, while the D198G NA mutation conferred a 10-fold reduction in susceptibility to ZVR, OSE and peramivir. A recombinant H1N1/09 virus carrying the D198G and H275Y NA mutations was highly resistant to OSE and peramivir but not to ZVR. Studies with a human H1Nl influenza isolate A1/Hokkaido/15/02 showed that the NA Y155H mutation conferred reduced susceptibility in enzyme inhibition assays to peramivir (30-fold) as well as to OSE and ZVR (> 100-fold) compared with WT NA. Another mutant virus with NA Vl14I and HA D225N mutations affected susceptibility in the enzyme inhibition assay and receptor binding, respectively, but to lesser extents than the Y155H and D225G mutations.

Clinical isolates with reduced susceptibility to peramivir have been found among influenza A virus strains, including H1N1 and pH1N1 as well as among influenza B strains. Molecular markers of reduced susceptibility to peramivir were mapped to a single NA mutation in each virus; these mutations included Q136K and H275Y for viruses of the N1 NA subtypes, R292K for viruses of the N9 subtype and R152K and D198E for influenza B viruses.

For influenza A:

1. Depending on the virus genetic background, the H275Y mutation causes intermediate susceptibility or resistance to peramivir in N1 viruses, resistance to OSE-C but does not affect susceptibility to ZVR
2. The R292K substitution commonly observed in the N2 virus subtype gives intermediate susceptibility to peramivir and ZVR and resistance to OSE-C
3. Substitution at E119, as commonly observed in N2 viruses, generally does not affect susceptibility to peramivir and OSE-C but confers resistance to ZVR

For influenza B:

1. Substitution at R152 confers resistance to peramivir, OSE-C and ZVR
2. Substitution at D198 does not affect susceptibility to peramivir and ZVR but gives resistance to OSE-C
3. Substitution at H274Y gives resistance to peramivir and OSE but not to ZVR

Secondary pharmacology

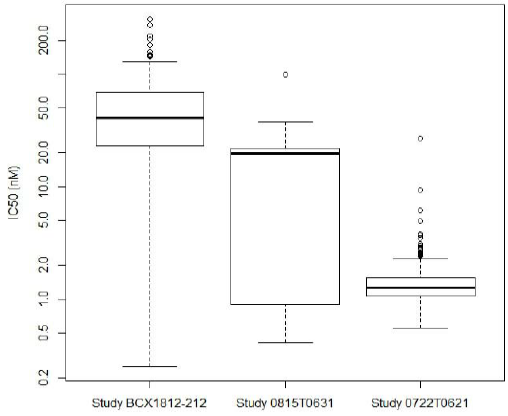
BCX1812-106 was a TQT study that evaluated two single doses of IV peramivir (600 mg and 1200 mg; administration over 30 minutes), IV placebo and oral moxifloxacin (400 mg). For both doses of peramivir, the QTcF did not increase by more than 10 msec with upper bounds of the 95% one-sided confidence intervals (CIs) that also did not exceed 10 msec. The maximum placebo-subtracted difference of QTcF was 1.71 msec at 510 minutes (4.5 hours) post dose and the maximum upper bound of QTcF was 3.94 msec at 510 minutes post dose during peramivir 600 mg treatment. Results from QTcI and QTcB analysis were confirmatory of the primary endpoint results. During peramivir treatment there were no values of QTcF > 450 msec, and a single value of QTcI > 450 msec. For changes from baseline, one QTcF outlier value > 30 msec was noted but there were no QTcI changes > 30 msec. There was no differential effect by gender on QTcF. Changes in heart rate were similar between treatments.

PK-PD analyses

In-vivo nonclinical studies have suggested that peramivir peak concentration, trough concentration and AUC significantly affected the time to death but overall AUC correlated best with in-vivo efficacy.

BCX1812-PPK-1 includes an analysis of PK-PD. In the PD model the time to alleviation of symptoms (TTAS) was described using a parametric hazard model. TTAS, PK and IC50 data were available from BCX1812-212, 0722T0621 and 0815T0631. The IC50 values were higher in the non-Japanese study BCX1812-212 in which all the A/H1N1 had the H275Y mutation and there was no difference in TTAS between a 600 mg IM dose of peramivir and placebo in this study. Furthermore, study 0815T0631 was conducted in a season in which A/H1N1 with the H275Y mutation predominated.

Boxplot of the distribution of IC_{50} in studies BCX1812-212, 0815T0631, and 0722T0621



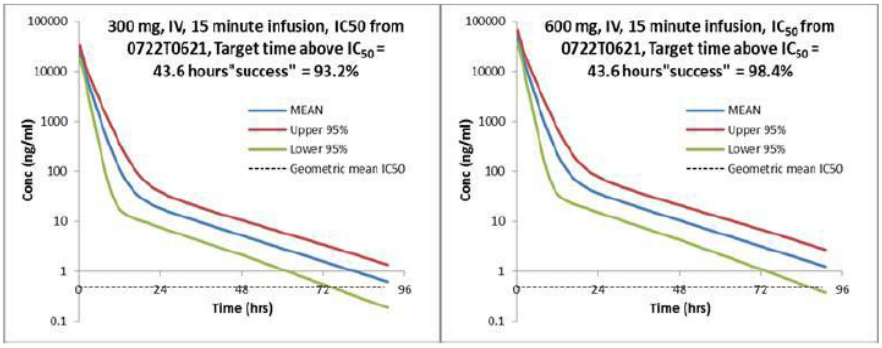
The effect of peramivir was found to be dependent on the duration that plasma drug concentration exceeds the IC_{50} for that patient's virus. In addition, it was found that the relationship between duration above IC_{50} and hazard was saturable. An Emax relationship was found, with the time above IC_{50} that resulted in 50% (ET_{50}) of the maximum possible effect being 21.8 hours.

A simulation study was conducted using the results of the PK model to determine the fraction of the population that would achieve 2 x ET_{50} with single IV doses of 300 mg and 600 mg. The value $2xET_{50}$ (43.6 hours) was chosen as being a practical clinical duration, given the typical duration of symptoms and the typical delay between onset of symptoms and start of treatment. This target duration would be predicted to achieve 75% of the maximum possible effect.

The results suggested that a dose of 600 mg will result in more patients exceeding the IC_{50} for the target duration in a typical influenza season and a low susceptibility influenza season. The majority of patients in a typical influenza season (as in 0722T0621) will reach target time above IC_{50} with 300 or 600 mg IV doses (93% and 98% respectively) but a higher fraction will achieve this after a 600 mg dose based on the target set at 75% of maximum effect. A smaller fraction of the population would reach target duration in typical seasons if the target were set to 90% of the maximum effect.

Figure 2.

Figure 8 Simulated PK profiles (with 95% CI) for 300 mg (left) and 600 mg (right) IV Dose (Study 0722T0621)

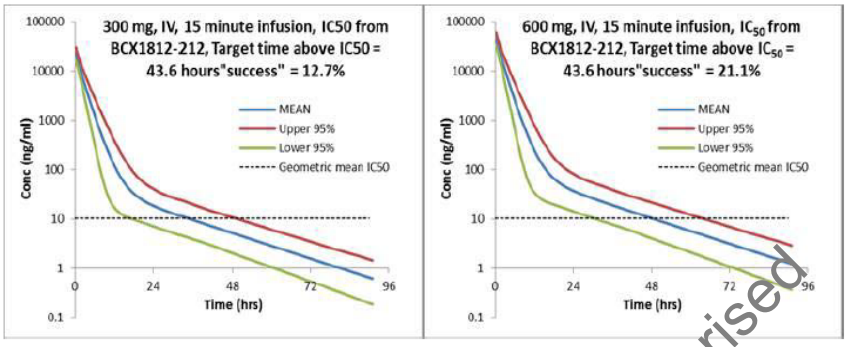


The simulation below suggested that the distribution of IC_{50} values (median=12.7 nM, range 0.06 nM – 208 nM) in the non-Japanese study BCX1812-212, which was conducted in a season when the

circulating influenza A/H1N1 strain carried the H275Y mutation, would result in 12.7% of patients achieving plasma concentrations greater than IC_{50} for 43.6 hours after a 300 mg dose, rising to 21.1% after a 600 mg dose.

Figure 3.

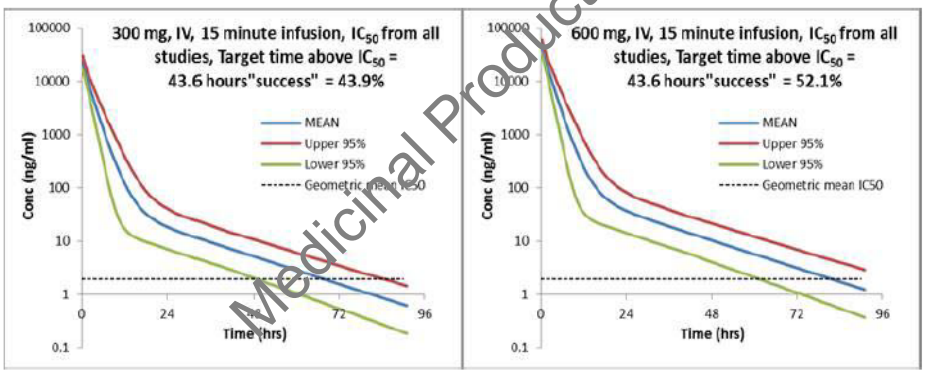
Figure 7: Simulated PK profiles (with 95% CI) for 300 mg (left) and 600 mg (right) IV Dose (Study BCX1812-212)



A similar simulation using all available IC_{50} values suggested that 300 mg or 600 mg IV over 15 minutes would result in 43.9% and 52.1% of patients, respectively, having concentrations greater than IC_{50} for at least 43.6 hours.

Figure 4.

Figure 6: Simulated PK profiles (with 95% CI) for 300 mg (left) and 600 mg (right) IV Dose (Studies 0722T0621, 0815T0631 and BCX1812-212)



2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The SmPC recommends that all doses of peramivir are administered in 100 mL volumes and infused over 15-30 minutes. This reflects the conditions under which it was administered IV to healthy subjects and patients (mostly 60-100 mL volume over 15-60 minutes).

The pharmacokinetics of peramivir appears to be simple. Following IV dosing there is dose linearity over a range of 50 to 1200 mg. Plasma levels decline in a multi-exponential fashion with an average distribution $t_{1/2}$ of ~3-8 hours (representing the major decline in peramivir concentrations over the initial 24 hours) and an average terminal $t_{1/2}$ of approximately ~15-30 hours when PK sampling is

carried out over 48-72 hours. The terminal-phase elimination $t_{1/2}$ following a 600 mg IV dose is ~20 hours. Mean clearance (CL) following IV administration ranged between 6.03 L/h and 6.78 L/h across IV doses of 300-1200 mg. After single IV doses the CV% values for Cmax, AUC and CL are < 20%.

Plasma protein binding of peramivir appears to be low (<30%). The POPPK estimated central volume of distribution (~12.5 L) indicates that it distributes into extracellular fluid spaces. Some studies reported urea-corrected drug concentrations in throat and nasal secretions, indicating relatively low levels compared to plasma after IV dosing. However, it is not possible to interpret these data in terms of any relationship to efficacy against influenza virus.

The applicant did not conduct a mass balance study. An *in-vitro* study using peramivir 100 µg/mL and human liver S9 homogenates detected one metabolite (oxidized at the cyclopentyl ring) at low concentrations (<4% of added substrate). In the Japanese study 0712T0611, LC/MS/MS applied to plasma and urine did not detect the acyl-glucuronic acid conjugate, enantiomers of peramivir or other unknown metabolites. Furthermore, Module 2.6.4 reports on S-021812-PF-02, in which plasma and urine were analysed by LC-MS/MS after single or repeated intravenous administration of peramivir (trihydrate) in adult Japanese male subjects. Unchanged peramivir was the only component identified in plasma and urine after single and multiple intravenous administrations. No peramivir acyl glucuronide was detected in plasma or urine and no enantiomer of peramivir [(+)-peramivir] was detected. Overall, the lack of a mass balance study can be accepted.

The results of several PK studies indicated that peramivir undergoes extensive renal elimination, with CL of parent drug being slightly higher than CLr. CL and CLr approximate to glomerular filtration rates. Elimination is not affected by the OAT1 and 3 inhibitor probenecid. It seems that peramivir is cleared by glomerular filtration and is not subject to tubular secretion or reabsorption.

The results of a renal impairment study using low doses (2 mg/kg) indicated no significant change in Cmax but the AUC of peramivir increased with declining renal function. There was a 3-fold increase in AUC and 3-fold drop in CL and CLr between the mild and moderate renal impairment groups. Patients with moderate or severe renal impairment were excluded from the major clinical studies of efficacy of single IV doses. The SmPC recommends dose reductions when CrCL is < 50 mL/min based on simulations using a final and updated POPPK model.

It is acceptable that the applicant has omitted a study in patients with hepatic impairment.

The results of several POPPK analyses performed at various stages of clinical development to investigate the effects of multiple demographic factors (e.g. age, weight, gender, CrCL and ethnicity) on the PK of peramivir revealed that weight had a notable effect on exposure but additional simulations that no dose adjustment based on weight *per se* was required.

After a 600 mg IV dose in Japanese patients in 0715T0621 the mean AUC was estimated to be ~80,000 ng.h/mL. In the pivotal bioequivalence study in non-Asian healthy subjects the mean $AUC_{0\text{-inf}}$ was ~103,000 ng.h/mL. Regarding differences between healthy subjects vs. patients with uncomplicated influenza, the cross-study comparisons made using Japanese data indicated that CL was 22% higher in patients. In these Japanese studies, the mean plasma AUC after a 600 mg dose in patients (~80,000 ng.h/mL) fell between the means after 400 mg (65,000 ng.h/mL) and 800 mg (130,000 ng.h/mL) in healthy subjects. Overall, it seems that plasma exposures in Asian and non-Asian patients with uncomplicated influenza are within the same range.

Data on the effect of gender on PK after a 600 mg IM dose indicated that Cmax was 6-25% higher and AUC was up to 31% higher in female subjects. The $t_{1/2}$ of peramivir in female subjects (21.1 ± 5.8

hours) was slightly longer than in male subjects (16.1 ± 4.0 hours) after subcutaneous injection. The difference is not likely to be of clinical relevance.

Whether there may be an effect of increasing age on peramivir PK that is independent of an age-related change in CrCL cannot be determined due to paucity of data from persons older than 64 years. A cross-study comparison of PK in healthy subjects aged >64 years and young adults found that AUC_{0-12} at steady state was ~34% higher in the older subjects although their estimated CrCL was 80-200 mL/min.

Peramivir did not inhibit or induce CYP isoenzymes in a routine battery of tests. Although oseltamivir has been reported to be a substrate and inhibitor of P-gp as well as being a substrate for OAT1, OAT3 and MRP4, the applicant reports studies suggesting that peramivir is not a good substrate or an inhibitor of these and other transporters.

The results of three drug interaction studies indicate that at therapeutic doses peramivir has no effect on the PK of rimantidine (extensively metabolised but exact mechanism unclear), oseltamivir or oral contraceptives. Therefore, peramivir can be used in combination with these drugs at therapeutic doses. The applicant has not conducted a clinical DDI study with paracetamol although this agent was allowed during clinical efficacy studies for management of severe symptoms. Paracetamol is mainly metabolised in the liver by sulphation and glucuronidation to form non-toxic metabolites whereas the toxic metabolite (NAPQI) is formed by the cytochrome system, especially CYP2D6. The completed in-vitro studies suggest that peramivir is not expected to influence the formation, onward metabolism or excretion of paracetamol and its metabolites.

Both studies that directly compared IV and IM doses showed a slightly lower Cmax with IM dosing but very similar AUC after 300 mg and 600 mg doses.

The data that were added from BCX1812-305 support use of 12 mg/kg from the age of 2 years up to 50 kg body weight and thereafter the 600 mg dose should be used. Further simulations led to a conclusion that dose adjustments cannot be derived with confidence for children with impaired renal function.

Pharmacodynamics

Peramivir acts as a neuraminidase inhibitor with IC_{50} values that are lowest for wild-type influenza A H1N1 and H3N2 viruses and the range is similar for a range of other N types regardless of the H type. As observed with oseltamivir and zanamivir, there is an upward shift in IC_{50} values for influenza B strains.

Because NA and HA surface proteins of the influenza virus have a close functional relationship, reduced susceptibility to NA inhibitor(s) by viruses can potentially arise through mutations in either the NA and/or HA gene. The mutation in N1 neuraminidase of human influenza virus which confers high-level resistance to oseltamivir is a single amino acid substitution of histidine (H) to tyrosine (Y) at position 275. Most of the early work on structure and inhibitor design is based on two other subtypes (N2 and N9) and the corresponding amino acid in these subtypes is at position 274. Consequently, some workers in the field use 'N2 numbering' (H274Y) and some use the actual 'N1 numbering' (H275Y) when describing the mutation in the N1 gene. The applicant has used both numberings interchangeably.

Reduced susceptibility to both oseltamivir and peramivir is most often associated with the H275Y mutation in the neuraminidase gene. This mutation does not affect susceptibility to zanamivir. The 2009 H1N1 pandemic strain was initially susceptible to oseltamivir and zanamivir but reduced

susceptibility to oseltamivir associated with the H275Y mutation occurred at higher rates in some regions as the pandemic and the subsequent season progressed. Despite this, 98% of US viruses tested by CDC from the 2013-4 season were reported susceptible to oseltamivir.

Studies in mice have indicated that the plasma peramivir AUC correlates best with in-vivo efficacy. The final (4^{th}) POPPK analysis investigated the relationship between dose (i.e. 300 or 600 mg) and likely metrics of efficacy, such as proportion of patients with plasma concentration above viral IC_{50} for a target duration of time (i.e. 2xET50). This analysis concluded that:

1) The majority of patients would achieve target exposure with either 600 mg dose (98%) or a 300 mg dose (93%) in a year when susceptible virus predominates;

2) A higher proportion of patients would achieve target exposure with the 600 mg dose compared with the 300 mg dose for a given strain of resistant influenza virus (21.1% vs. 12.7%) and for all viral IC_{50} values collectively (52.1% vs. 43.6);

3) Intravenous doses in the range of 300-600 mg are on the ascending part of the peramivir exposure-response curve with respect to target time above viral IC_{50};

4) Because of the timing of clinical presentation and the typical time course of the disease increasing the dose much beyond 600 mg would have only modest improvement in time above IC_{50}.

The licensed dose in Japan is 300 mg while the licensed dose in the US is 600 mg. The abovementioned PK-PD analysis was based on three studies. In one of these studies all the H1N1 strains had the H275Y mutation and the study failed to differentiate a 600 mg IM dose from placebo in terms of TTAS. The PK-PD analysis is based on the finding that the time above IC_{50} that resulted in 50% (ET_{50}) of the maximum possible effect was 21.8 hours. This value was then doubled. This appears to be a rather questionable target. In addition, the 600 mg dose was not consistently superior to the 300 mg dose in the two major Japanese single dose IV studies. Nevertheless, the safety profiles of the two doses were comparable. Overall, selection of the 600 mg dose over the 300 mg dose for the EU population was agreed since, in theory, it might provide a more secure basis for expectation of benefit against less susceptible strains (including influenza B).

The applicant conducted a satisfactory TQT study with a 1200 mg IV peramivir dose which showed no important effect on QTc or HR.

2.4.5. Conclusions on clinical pharmacology

Peramivir pharmacokinetics are simple. The PK-PD analyses proposed to support selection of the 600 mg dose over the 300 mg dose are not entirely convincing but there is some possibility that the higher dose might cover a larger proportion of isolates and there is no dose-limiting safety concern. Therefore, use of the same dose in the EU as was approved in the US is acceptable. It should be noted that almost all the post-approval safety data come from Japan, where the approved dose is 300 mg. Simulations support the dose adjustment schema in the SmPC for persons aged from 13 years and from 50 kg body weight.

2.5. Clinical efficacy

The dossier included 10 (4 Phase 2 and 6 Phase 3) clinical studies which evaluated the efficacy of peramivir in the treatment of influenza. Seven exclusively or predominantly enrolled patients with uncomplicated influenza. Study **0722T0621** was proposed by the applicant as pivotal**.**

Study Identifier	No. of Centers	Study Dates (Start–Completion)	No. of Subjects Randomized / Evaluated for efficacy/ Completed / Dropouts	Design / Control	Dose and Route	Sex Age Race (based on ITTI)	Primary Endpoint*
Pivotal Study							
Shionogi Study 0722T0621	75	13DEC2007-18APR2008	300 Randomized 296 ITTI 291 Completed 9 Discontinued	Randomized, double blind, parallel design/ Placebo controlled	Single dose of placebo or 300 or 600 mg peramivir, administered by IV infusion	150 male subjects (51%) 146 female subjects (49%) 20 to 62 years of age 296 Asian subjects (100%)	Time to alleviation of symptoms

Three non-Japanese studies (BCX1812-211, BCX1812-311 and BCX1812-212) in which single doses of IM peramivir were used were submitted to support use of single IV doses of peramivir.

Study number	*Intramuscular peramivir*
BCX1812-212	A phase 2, multicentre, randomized, placebo-controlled, study to evaluate the efficacy and safety of intramuscular peramivir 600 mg in subjects with uncomplicated influenza
BCX1812-211	A phase 2, multicentre, randomized, double-mask, placebo-controlled study to evaluate the efficacy and safety of intramuscular peramivir in subjects with uncomplicated influenza
BCX1812-311	A phase 3 multicentre, randomized, double blind, placebo-controlled study to evaluate the efficacy and safety of intramuscular peramivir in subjects with uncomplicated influenza
BCX1812-211/311 Combined Analysis	

0815T0631 in uncomplicated influenza in Japan compared single IV doses vs. oseltamivir.

Study Identifier	No. of Centers	Study Dates (Start–Completion)	No. of Subjects Randomized / Evaluated for efficacy/ Completed / Dropouts	Design / Control	Dose and Route	Sex Age Race (based on ITTI)	Primary Endpoint*
Additional Studies							
Shionogi Study 0815T0631	146	12NOV2008 – 15MAY2009	1099 Randomized 1091 ITTI 1038 Completed 61 Discontinued	Randomized, double blind, double dummy, parallel design/ Oseltamivir phosphate controlled	Single dose of 300 or 600 mg peramivir (IV) or twice-daily doses of 15 mg oseltamivir phosphate (PO) for 5 days	562 male subjects (52%) 529 female subjects (48%) ≥ 20 years of age 1091 Asian subjects (100%)	Time to alleviation of symptoms

The applicant supplied interim data from three cohorts in the paediatric study **BCX1812-305** during the procedure.

2.5.1. Dose response studies - Main study

Study 0722T0621: Phase II Clinical Study of Single-Dose Intravenous S-021812 in Patients with Influenza Virus Infection - A Double-Blind, Parallel Group, Comparative Dose-Finding Study –

This placebo-controlled, double-blind study was conducted in Japan between 2007 and 2008 at 75 centres. The primary objective was to compare the effectiveness of single intravenous doses of 300 mg and 600 mg peramivir with placebo using the duration of influenza as the indicator.

Methods

Study Participants

Male and non-pregnant or breastfeeding female in/outpatients aged 20-65 years were eligible if they had:

1. Fever ≥ 38.0°C (axillary temperature) and no clinical findings of bacterial infection or any other cause
2. At least two symptoms of moderate or greater severity among the following:
    1. Systemic symptoms (headache, aches and pains of the muscle or joints, feverishness or chills, fatigue)
    2. Respiratory tract symptoms (cough, sore throat, and nasal congestion)
3. A positive rapid antigen test (RAT) for influenza performed with a nasal or throat swab specimen.

The time elapsed between onset of illness (first temperature elevation by at least 1°C or onset of at least two symptoms of influenza) and enrolment was to be not more than 48 hours. Exclusions were intended to restrict the study to uncomplicated influenza in persons without known risks for complications.

Treatments

Patients received a single dose of 300 mg or 600 mg peramivir or saline placebo by IV infusion over 30 minutes using a fluid volume of 100 mL. Other antiviral drugs as well as drugs that could impact on symptom measurement or had a potential risk of inducing QTc prolongation were forbidden. If acetaminophen was taken, the temperature measurements and assessments of influenza symptoms were to be at least 4 hours after the acetaminophen use or immediately prior to administration of acetaminophen.

Objectives

The primary objective was to compare the effectiveness of single intravenous doses of 300 mg and 600 mg peramivir with placebo using the duration of influenza as the indicator.

Secondary objectives were:

- To compare effectiveness based on:
    - Amount of change from baseline in the composite influenza symptoms scores at 24, 36, 48 and 96 hours after the start of treatment
    - Time to recovery to normal temperature (37.0°C, axillary)
    - Virological efficacy (amount of change in influenza virus)
- To evaluate safety
- To confirm the pharmacokinetic profile and conduct PK-PD analyses

Outcomes / endpoints

Primary endpoint

The time to alleviation of the influenza symptoms (duration of influenza; TTAS) was the primary endpoint, which was defined as the time from the start of the investigational product dosing to the time to alleviation of the influenza symptoms. The time of alleviation of the influenza symptoms referred to the time point at which all of the seven influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, aches or pains of the muscle or joints, and fatigue) as recorded in the subjects' patient diary showed a score of "0: none" or "1: mild," and when this condition persists for at least 21.5 hours (24 hours - 10%).

Secondary endpoints

- Amount of change in composite influenza symptom scores at 24, 36, 48 and 96 hours
- Time to recovery to normal temperature (37.0°C, axillary)
- Amount of change in the influenza virus $TCID_{50}$ per unit time
- Time to resumption of daily activities
- Amount of change in the IL-6 and TNFα per unit time
- Change in drug sensitivity
- Amount of acetaminophen used
- Incidences of influenza related complications (sinusitis, otitis media, bronchitis and pneumonia)

Signs and symptoms were evaluation by the patients in diaries. Axillary temperature was measured using an electronic thermometer approximately every 12 hours up to Day 14. There was assessment of severity of 7 symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, aches and pains of the muscle or joints and fatigue) on a 4-grade scale: (0: none [normal condition]; 1: mild [mostly no concern]; 2: moderate [very uncomfortable]; or 3: severe [unbearable]). The assessment was performed twice daily from the time of screening to Day 9, and then once daily (at night) from Day 10 to Day 14.

A throat swab and a nasal swab (one-sided) were collected at the time of screening and at Visits 2, 3, 4 and 5. The following tests/assays were carried out at the laboratory conducting virological tests.

- At screening - virus subtype (A/H1/H3/H5, B)
- At screening and at the last virus-positive sampling point - NA inhibitory activity (IC_{50})
- At each scheduled visit - measurement of virus titre ($TCID_{50}$)

Specimens were also collected for measurement of the Type A and Type B influenza virus serum antibody titre at the laboratory conducting the laboratory tests.

Sample size

The aim was to recruit at least 240 patients (80 per group) with an upper limit of 300. The median value for duration of influenza in the placebo group was estimated to be 137 hours vs. 87 hours in the two active groups. It was assumed that the duration of influenza would follow an exponential distribution. Using log rank testing with a one-sided significance level of 0.025, a statistical power of 0.80 and a follow-up period after investigational product dosing of 336 hours (14 days), the required number of subjects would be 67 subjects per group. To account for proportions with unconfirmed influenza, it was proposed to recruit at least 80 per group.

Randomisation

Dynamic allocation was used for treatment allocation using a minimisation algorithm. The minimisation algorithm was designed to ensure balance between the treatment groups for the following factors:

- Existence of current tobacco use in the patient background at the time of screening: "Yes," or "No"
- Composite influenza symptoms (7 symptoms) score prior to the investigational product dosing: "14 points or less" or "15 points or more"

Blinding (masking)

The study was described as double blind. The investigational product for each of the three treatments arms was indistinguishable. The investigational product allocation manager was responsible for assigning patients to treatment groups and the CSR states that *the investigational product allocation manager will retain the investigational product allocation schedule until the breaking of the key code, ensuring the blinding of the study for all personnel involved with the study except the investigational product allocation manager.*

Statistical methods

1. The ITTI consisted of all treated patients confirmed to have an influenza virus infection from culture, PCR or a ≥4-fold increase in the antibody titre from screening to Visit 6. Patients were analysed according to their randomisation group. This population was used for the primary analysis.

2. The PPS consisted of all ITTI patients without violation of the protocol or insufficient observations.

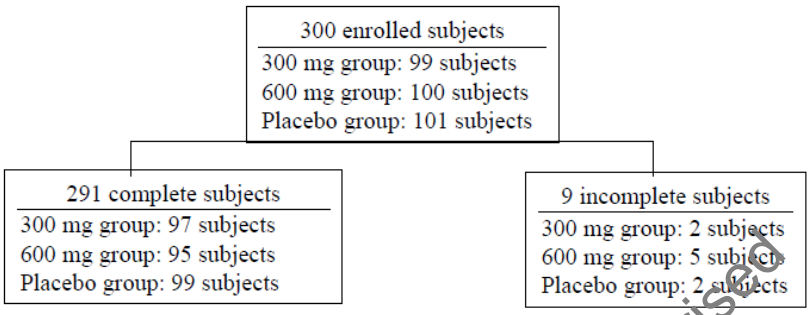
For the analysis of the primary endpoint (duration of influenza), the Cox proportional hazards model, using the existence of current tobacco use and the composite influenza symptoms (7 symptoms) score prior to dosing as the covariates, was to be applied using a one-sided significance level of 0.025. Patients with missing data were handled as if there had been no alleviation of symptoms at the missing data points. Any patients in whom the influenza symptoms did not disappear by the end of the study were treated as treatment failures and censored. The initial comparison was for the pooled peramivir groups vs. placebo. If a statistically significant difference was observed in this analysis, each treatment group was then to be compared separately with the placebo group in order to investigate the recommended dose level. The Hochberg procedure will be used to account for the multiplicity of comparing two doses to placebo. This means that an individual dose is considered significant if the associated test has 1-sided $p<0.0125$ or both doses will be considered significant if both tests have 1-sided $p<0.025$.

As a supportive analysis, stratified generalised Wilcoxon testing, with the existence of current tobacco use and the composite influenza symptoms (7 symptoms) score prior to dosing as the stratification factors, was to be used to compare each treatment group with the placebo group. Also, a Kaplan-Meier curve was to be drawn for each treatment group in order to calculate the median value and 95% confidence interval for the duration of influenza.

Results

Participant flow

There were 300 patients enrolled as shown below.



Nine patients discontinued from the study but six of the 9 were included in the ITTI population.

The protocol deviations mostly involved missing observations and use of prohibited concomitant medications.

Table 23

Table 8: List of Discontinued Subjects by Reason

	300 mg group N = 99	600 mg group N = 100	Placebo group N = 101
Complete subjects	97 (98.0%)	95 (95.0%)	99 (98.0%)
Discontinued subjects	2 (2.0%)	5 (5.0%)	2 (2.0%)
- Ineligible for inclusion	0 (0.0%)	1 (1.0%)	1 (1.0%)
- Failed to attend appointments	1 (1.0%)	0 (0.0%)	0 (0.0%)
- Request by the patient	1 (1.0%)	2 (2.0%)	0 (0.0%)
- Occurrence of adverse event	0 (0.0%)	0 (0.0%)	1 (1.0%)
- Insufficient efficacy / worsening	0 (0.0%)	0 (0.0%)	0 (0.0%)
- Other	0 (0.0%)	2 (2.0%)	0 (0.0%)

Conduct of the study

The protocol deviations mostly involved missing observations and use of prohibited concomitant medications.

Table 24

Table 10: List of protocol deviations

	300 mg	600 mg	Placebo	Total
Violation of the inclusion criteria and exclusion criteria	1	2	2	5
Patient with clinical findings believed to be caused by bacterial infection	0	1	0	1
Patient with more than 48 hours after onset	0	0	1	1
Patient with rapid influenza diagnosis (RAT) that was not confirmed to be positive within the time range stipulated in the protocol	1	0	1	2
Complications of chronic respiratory tract disease requiring drug therapy	0	1	0	1
Violation of the study method	2	1	1	4
Subcutaneous leakage of the investigational product	1	0	0	1
Intravenous infusion time was within 30 minutes	1	1	1	3
Violation of a prohibited concomitant drug (therapy)	3	8	5	16
Violation of a prohibited concomitant drug	3	8	5	16
Insufficient course observations	6	17	8	31
No testing performed, or exceeded the permissible range for the testing	4	6	5	15
Incomplete notation in the patient diary	0	1	0	1
Diary notation within four hours of the use of acetaminophen	2	10	3	15

Baseline data

Factors with a significant imbalance between treatments at screening were body temperature and IL-6.

Table 25

Table 13: Distribution of the primary patient background factors by treatment group (ITTI)

		300 mg group N = 99	600 mg group N = 97	Placebo group N = 100	p value
Gender	Male	46 (46.5%)	53 (54.6%)	51 (51.0%)	Pe=0.5246
	Female	53 (53.5%)	44 (45.4%)	49 (49.0%)	
Age (years)	Mean	34.2	33.9	34.4	Pa=0.9477
	SD	9.8	10.4	9.6	
	20 – 29	41 (41.4%)	42 (43.3%)	39 (39.0%)	Pk=0.9673
	30 – 39	28 (28.3%)	28 (28.6%)	33 (33.0%)	
	40 – 49	23 (23.2%)	16 (16.5%)	21 (21.0%)	
	50 – 59	6 (6.1%)	9 (9.3%)	5 (5.0%)	
	60 – 64	1 (1.0%)	2 (2.1%)	2 (2.0%)	
BMI (kg/m2)	Mean	22.81	23.06	22.51	Pa=0.6330
	SD	4.23	4.13	4.77	
Existence of current tobacco use*	No	65 (65.7%)	65 (67.0%)	66 (66.0%)	Pe=0.9877
	Yes	34 (34.3%)	32 (33.0%)	34 (34.0%)	
In-patient / Out-patient classification	In-patient	1 (1.0%)	0 (0.0%)	0 (0.0%)	Pe=0.6622
	Out-patient	98 (99.0%)	97 (100.0%)	100 (100.0%)	
Duration of influenza (hrs)	0 – 12	17 (17.2%)	10 (10.3%)	8 (8.0%)	Pk=0.1652
	12 – 24	42 (42.4%)	41 (42.3%)	40 (40.0%)	
	24 – 36	22 (22.2%)	31 (32.0%)	30 (30.0%)	
	36 – 48	18 (18.2%)	15 (15.5%)	22 (22.0%)	
Existence of influenza vaccination	No	76 (76.8%)	71 (73.2%)	76 (76.0%)	Pe=0.8362
	Yes	23 (23.2%)	26 (26.8%)	24 (24.0%)	
Composite influenza symptoms (7 symptoms) score (at enrollment)	Mean	11.5	11.8	12.0	Pa=0.3873
	SD	2.8	2.5	2.7	
	0 – 14	85 (85.9%)	83 (85.6%)	84 (84.0%)	Pe=0.9367
	15 - 21	14 (14.1%)	14 (14.4%)	16 (16.0%)	
Body temperature (°C)	Mean	38.44	38.64	38.50	Pa=0.0113
	SD	0.43	0.53	0.46	
IL-6	Mean	15.032	44.877	15.863	Pa=0.0119
	SD	11.793	196.796	14.201	
TNF-α	Mean	1.70	1.74	1.82	Pa=0.2930
	SD	0.47	0.59	0.61	

Pe: Determined by Fisher's exact test; Pa: Determined by one-way ANOVA; Pk: Determined by Kruskal-Wallis test
*: Allocation factor

All patients were PCR positive for influenza virus at baseline. There were no differences between groups in proportions with specific influenza A virus types/subtypes and IC_{50} values. Most (~70%) had A/H1 and ~ 25% had A/H3. Three patients had Type B influenza (2 in the 300 mg group and 1 in the 600 mg group).

Numbers analysed

Numbers in the ITTI and PP populations and reasons for exclusion are shown below.

Table 26

Table 11: Distribution of subjects for which the data was used and for which the data was not used in the effectiveness analysis sets

	300 mg group N = 99	600 mg group N = 100	Placebo group N = 101	p-value
ITTI	99 (100%)	97 (97%)	100 (99.0%)	0.2286
Subjects excluded from the ITTI	0 (0.0%)	3 (3.0%)	1 (1.0%)	
- Non-compliance with GCP	0 (0.0%)	0 (0.0%)	0 (0.0%)	
- Untreated subjects	0 (0.0%)	1 (1.0%)	1 (1.0%)	
- Missing effectiveness endpoint data	0 (0.0%)	1 (1.0%)	0 (0.0%)	
- Unidentifiable influenza virus infection	0 (0.0%)	1 (1.0%)	0 (0.0%)	
PPS	92 (92.9%)	89 (89.9%)	95 (95.9%)	0.6214
Subjects excluded from the PPS	7 (7.1%)	8 (8.0%)	5 (5.0%)	
- Ineligible subjects	4 (4.0%)	4 (4.0%)	2 (2.0%)	
- Study method violation	3 (3.0%)	3 (3.0%)	3 (3.0%)	
- Insufficient course observations	0 (0.0%)	1 (1.0%)	0 (0.0%)	

p-value: Determined by Fisher's exact test

Outcomes and estimation

Four patients were excluded from the ITTI population. In the ITTI population peramivir at either IV dose reduced the median duration of influenza symptoms by less than one day. The table below indicates that the differences for pooled peramivir patients vs. placebo and for each peramivir dose group vs. placebo reached statistical significance. The figure shows the Kaplan-Meier curves by treatment group. Similar findings applied in the analysis of the primary endpoint for the PPS population, although the magnitude of effect was smaller, especially in the 300 mg group (-17.4 h reduction vs. -21.0 h reduction for 600 mg).

Table 27

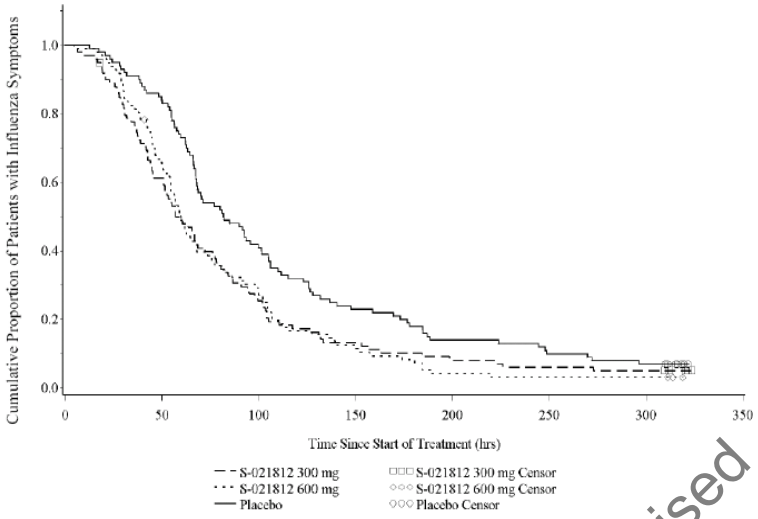
Table 15: Analysis results for the duration of influenza using the Cox proportional hazards model (ITTI)

	S-021812 consolidated group N = 196	300 mg group N = 99	600 mg group N = 97	Placebo group N = 100
Median (hrs)		59.1	59.9	81.8
(95% Confidence Interval)		(50.9, 72.4)	(54.4, 68.1)	(68.0, 101.5)
Improvement over Placebo (hrs)		-22.7	-21.9	—
Cox proportional hazards model				
Estimate		-0.3837	-0.4062	—
SE		0.1472	0.1479	—
Hazard ratio		0.681	0.666	—
(95% Confidence Interval)		(0.511, 0.909)	(0.499, 0.890)	—
Chi-square test statistic	9.5277	6.7916	7.5463	—
DF	1	1	1	—
p-value (one-sided	0.0010*	0.0046*	0.0030*	—
Adjusted p-value (one-sided)	---	0.0046*	0.0046*	—

Covariates: Current smoking behavior, Composite symptom scores at baseline
Adjusted p-value: Determined by Hochberg method
*: Statistical significance; p-value or Adjusted p-value (one-sided) <0.025

Figure 5.

Figure 3: Kaplan-Meier curves for the duration of influenza (ITTI)



The table below shows the change in composite symptom score during 5 days post-dose. The figure shows the change in scores over time graphically.

Table 28

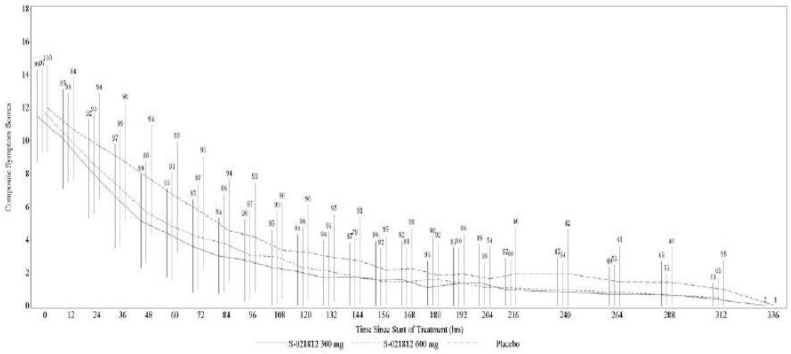
Table 16: Amount of change in the composite influenza symptom score by time point

Treatment group		Time after treatment (hrs)						
		12	24	36	48	72	96	120
300 mg group N = 99	N	85	92	87	89	85	90	81
	LS Mean	-1.6029	-3.4043	-5.1451	-6.7060	-8.2868	-9.0532	-9.8346
	Difference from placebo	-0.3308	-1.2433	-1.8394	-2.3455	-1.9364	-1.2599	-1.1095
	(95% confidence interval)	(-1.096, 0.434)	(-2.072, -0.423)	(-2.787, -0.0892)	(-3.201, -1.490)	(-2.851, -1.022)	(-2.062, -0.458)	(-1.856, -0.363)
	p-value	0.3953	0.0032*	0.0002*	<.0001*	<.0001*	0.0022*	0.0037*
600 mg group N = 97	N	86	93	89	86	87	87	86
	LS Mean	-1.8014	-3.3168	-4.7770	-6.2250	-7.8199	-8.8655	-9.6171
	Difference from placebo	-0.5293	-1.0696	-1.4714	-1.8645	-1.4695	-1.0722	-0.8921
	(95% confidence interval)	(-1.291, 0.232)	(-1.891, -0.248)	(-2.411, -0.531)	(-2.726, -1.003)	(-2.378, -0.561)	(-1.879, -0.265)	(-1.626, -0.158)
	p-value	0.1721	0.0109*	0.0023*	<0.0001*	<0.0016*	0.0094*	0.0174*
Placebo group N = 100	N	84	94	90	93	93	93	90
	LS Mean	-1.2721	-2.2472	-3.3056	-4.3605	-6.3503	-7.7933	-8.7250

Analysis method: Analysis of covariance, Covariates: Current smoking behavior, Composite symptom scores at baseline,
*: Statistical significance; p-value (two-sided) <0.05

Figure 6.

Figure 4: Change in the composite influenza symptoms score (mean value ± standard deviation; ITTI)



Ancillary analyses

The table shows the time to alleviation of each influenza symptom included in the composite score.

Table 29

Table 17: Time to alleviation of each influenza symptom (ITTI)

Influenza symptom		300 mg group N = 99	600 mg group N = 97	Placebo group N = 100
Cough	N[a)]	57	48	57
	Median (hrs)	27.9	48.4	81.9
	(95% confidence interval)	(21.0, 51.4)	(22.0, 59.6)	(55.5, 92.8)
	Improvement over Placebo (hrs)	-54.0	-33.5	—
	Cox proportional hazards model			
	Hazard ratio	0.629	0.617	—
	(95% confidence interval)	(0.432, 0.916)	(0.411, 0.926)	—
	p-value	**0.0158***	**0.0198***	—
Sore throat	N[a)]	46	43	46
	Median (hrs)	29.8	30.5	54.8
	(95% confidence interval)	(25.7, 37.2)	(14.4, 50.5)	(22.7, 58.9)
	Improvement over Placebo (hrs)	-25.0	-24.3	—
	Cox proportional hazards model			
	Hazard ratio	0.855	0.758	—
	(95% confidence interval)	(0.555, 1.317)	(0.497, 1.157)	—
	p-value	**0.4784**	**0.1993**	—
Headache	N[a)]	57	57	59
	Median (hrs)	30.7	22.2	40.9
	(95% confidence interval)	(26.8, 38.9)	(17.4, 30.9)	(21.2, 50.4)
	Improvement over Placebo (hrs)	-10.2	-18.8	—
	Cox proportional hazards model			
	Hazard ratio	0.681	0.628	—
	(95% confidence interval)	(0.468, 0.990)	(0.432, 0.915)	—
	p-value	**0.0441***	**0.0153***	—
Nasal Congestion	N[a)]	40	40	42
	Median (hrs)	28.7	31.3	38.1
	(95% confidence interval)	(19.3, 43.8)	(23.1, 42.2)	(29. 8, 59.5)
	Improvement over Placebo (hrs)	-9.4	-6.8	—
	Cox proportional hazards model			
	Hazard ratio	0.786	0.593	—
	(95% confidence interval)	(0.493, 1.253)	(0.374, 0.940)	—
	p-value	**0.3116**	**0.0262***	—

Influenza symptom		300 mg group N = 99	600 mg group N = 97	Placebo group N = 100
Feverishness or chills	N [a)]	90	92	91
	Median (hrs)	20.3	19.2	20.6
	(95% confidence interval)	(19.1, 21.6)	(16.9, 20.5)	(19. 2, 24.1)
	Improvement over Placebo (hrs)	-0.3	-1.5	—
	Cox proportional hazards model			
	Hazard ratio	0.722	0.742	—
	(95% confidence interval)	(0.530, 0.982)	(0.553, 0.997)	—
	p-value	**0.0381***	**0.0473***	—
Aches and pains of the muscles or joints	N [a)]	66	74	72
	Median (hrs)	20.9	29.9	35.9
	(95% confidence interval)	(18.7, 29.5)	(21.3, 34.1)	(28.5, 44.7)
	Improvement over Placebo (hrs)	-15.0	-6.0	—
	Cox proportional hazards model			
	Hazard ratio	0.701	0.765	—
	(95% confidence interval)	(0.497, 0.990)	(0.549, 1.064)	—
	p-value	**0.0435***	**0.1118**	—
Fatigue	N [a)]	76	76	87
	Median (hrs)	30.8	32.8	42.6
	(95% confidence interval)	(25.7, 42.5)	(27.9, 42.0)	(30.5, 47.9)
	Improvement over Placebo (hrs)	-11.8	-9.7	—
	Cox proportional hazards model			
	Hazard ratio	0.778	0.766	
	(95% confidence interval)	(0.567, 1.067)	(0.560, 1.048)	
	p-value	**0.1197**	**0.0951**	—

a) Subjects with a symptoms score prior to dosing of "0: none" or "1: mild" were excluded from the analysis.
Analysis method: Cox proportional hazards model
Covariates: Current smoking behavior, Composite symptom scores at baseline
*: Statistical significance; p-value (two-sided) <0.05

Overall, at least 40% of all patients and of ITTI patients were enrolled at 12 - 24 hours after the onset of influenza. A statistically significant shortening of the duration of influenza was observed in this category in both the 300 mg and 600 mg groups vs. placebo (one-sided p value: 0.0047, 0.0221). No statistically significant differences were observed in the other three time categories in the Cox proportional hazards model but the sample sizes were small and the associated confidence intervals wide. In the stratified generalised Wilcoxon test there was a statistically significant difference for peramivir vs. placebo in patients enrolled at 12 - 24 hours after the onset of influenza. Additionally, there was a statistically significant difference between the 600 mg group and the placebo group for patients enrolled at 24 - 36 hours after onset and between the 300 mg group and the placebo group for patients enrolled at 36 - 48 hours after onset.

The median value for the time to recovery to normal temperature was statistically significantly shorter in the two peramivir groups vs. the placebo group but in each case the observed difference was half a day (12-13 h). The proportion of patients recovering to normal temperature was statistically significantly higher in the 300 mg group at 24, 36, and 48 hours after dosing and in the 600 mg group at 36, 48 and 72 hours after dosing in comparison to placebo. In particular, 50.0% of the patients in the placebo had recovered to normal temperature at 36 hours after dosing compared to 80% or more in the peramivir groups.

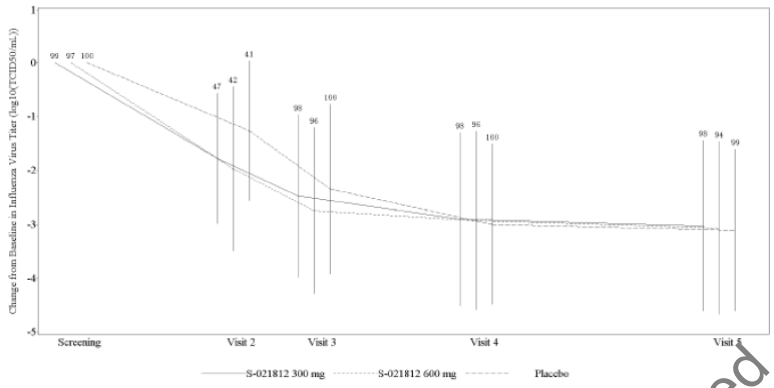
Time to resumption of daily activities [the time point at which the activity evaluation (IIWS) became 10] was statistically significantly shorter in the peramivir groups in comparison to the placebo group. The differences vs. placebo were about ~1.6 days for both peramivir doses.

The figure below shows the change in the influenza virus titre [log10 (TCID50)] from screening to each visit. The amount of change per unit time from screening up to Day 3 was statistically significantly larger in the 600 mg group vs. placebo (two-sided p value: 0.0027). No other comparisons reached statistical significance. The number of positive patients at Visit 3 (Day 3) was statistically significantly lower in both peramivir groups vs. the placebo group. Proportions positive at Visit 4 (Day 5) were just

under 10% in the peramivir groups and 13.4% in the placebo group. At Visit 9 only one patient tested was influenza positive (in the 600 mg group).

Figure 7.

Figure 6: Change in the amount of change in the influenza virus titer [log_{10} ($TCID_{50}$)] from the time of screening (mean value ± standard deviation) (ITTI)



The median ratios of NA inhibition activity (IC_{50}) against the last detected vs. screening virus were similar between the placebo group and the peramivir 300 mg group. Five patients in the 600 mg group had last detected virus that showed a ratio of >3. The virus titre was <LLD in these 5 patients at Visit 5 (Day 9). The duration of influenza ranged from 29.9 to 174.1 hours. Three had unusually long durations of symptoms or fever.

1. For IL-6, TNF-α and CRP, the amount of change per unit time vs. placebo was calculated from screening up to Visit 6. The amount of change in CRP at Visit 4 (Day 5) was statistically significantly larger in the 600 mg group (p-value: 0.0142).
2. The amount of change in the IL-6 was statistically significantly larger in the 300 mg group (p value: 0.0067) at Visit 3 (Day 3) and in the 600 mg group (p-values: <0.0001, 0.0443) at Visit 3 (Day 3) and Visit 4 (Day 5).
3. The amount of change in the TNF-α was statistically significantly larger at Visit 3 (Day 3) and Visit 4 (Day 5) in the 300 mg group (p-values: 0.0218, 0.0035).

Otitis media occurred in 1/97 (1.0%) in the 600 mg group, bronchitis occurred in 3/99 (3.0%) in the 300 mg group and in 3/100 (3.0%) in the placebo group but no patient had sinusitis or pneumonia. The mean amount of paracetamol used was 574.7 mg in the 300 mg group, 552.6 mg in the 600 mg group and 798 mg in the placebo group (not significant). The mean number of doses used was ~1.8 for peramivir groups and 2.7 for the placebo group (not significant).

Study 0815T0631: Phase III Clinical Study of Single-Dose Intravenous S-021812 in Patients with Influenza Virus Infection – A Double-Blind, Parallel Group, Comparative Study with Oseltamivir Phosphate

This was a Phase 3 double-blind and double dummy study conducted during 2008-2009 at 146 study sites in Japan (100), S. Korea (25) and Taiwan (21). The primary objective was to demonstrate non-inferiority of the peramivir 300 and 600 mg groups compared to the oseltamivir phosphate group for TTAS.

The patient selection criteria and the endpoints were as for study 0722T0621. Peramivir 300 mg or 600 mg and IV placebo were infused as a single dose in 60–100 mL over 15–60 minutes. Oseltamivir phosphate capsules (75 mg) and matching placebo were administered twice daily for 5 days. The investigator, sub-investigator or the CRC was to confirm eligibility and then access the Enrolment

Centre website, which checked the data against the selection criteria and then notified the drug number through the designated website. A person responsible for study drug allocation was designated to have a third party perform the drug allocation, considering maintenance of blinding and objective handling of cases. Hence patients were allocated to treatment groups by the minimization method to balance the distribution of the following factors:

- Composite symptom scores at screening: ≤14, ≥15
- Current smoking behaviour at screening: yes, no
- Countries (regions): Japan, South Korea, Taiwan
- Influenza virus type by RAT: A, B or A and B

It was planned to enrol 1050 patients (350 per group) with a cap of non-Japanese set at 735. In 0722T0621 the hazard ratio of peramivir to placebo was estimated to be 0.67 as to TTAS. The hazard ratio of oseltamivir phosphate to placebo was estimated to be 0.73 based on the results of the three placebo-controlled clinical trials that supported approval in Japan. The number of patients required per treatment group was calculated to be 339 supposing that TTAS is exponentially distributed, with a median of 73 hours for oseltamivir phosphate, a non-inferiority margin of 0.170 for the hazard ratio to oseltamivir phosphate, a two-sided significance level of 0.025, a power of 0.80, a follow-up period of 336 hours (14 days) and the log rank test for the statistical test. It was decided to accumulate 1050 patients to provide 350 ITTI patients per treatment group.

See 0722T0621 regarding the analysis populations. The Cox proportional hazards model, with composite symptom scores at baseline, was to be applied to the analysis of time to alleviation of symptoms. Patients who did not experience alleviation of symptoms were to be dealt with as censored cases. The 2-sided 97.5% confidence intervals of hazard ratios for the peramivir 300 mg and 600 mg groups against the oseltamivir phosphate group were to be calculated. If the upper limit of 97.5% confidence interval was not greater than 1.170, the peramivir group was considered to be non-inferior to the oseltamivir group.

The use of 97.5% rather than 95% confidence intervals was to account for the multiplicity of comparing two doses of peramivir to placebo.

Results

Overall, 1099 patients were enrolled (743 in Japan, 106 in South Korea and 250 in Taiwan). Six patients withdrew from the study before treatment with study drugs. More than 93% of patients per group completed the study. Host and influenza virus factors were balanced between groups.

Table 30

Table 11.2-1 Primary patient background factors by treatment groups (ITTI)

		S-021812 300 mg N=364	S-021812 600 mg N=362	Oseltamivir N=365	P-value
Region/country*	Japan	247 (67.9%)	249 (68.8%)	246 (67.4%)	P^e=0.9947
	Republic of Korea	36 (9.9%)	34 (9.4%)	35 (9.6%)	
	Taiwan	81 (22.3%)	79 (21.8%)	84 (23.0%)	
	Hong Kong	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Race	Asian	364 (100.0%)	362 (100.0%)	365 (100.0%)	
Sex	Male	180 (49.5%)	198 (54.7%)	184 (50.4%)	P^e=0.3209
	Female	184 (50.5%)	164 (45.3%)	181 (49.6%)	
Age (years)	Mean	34.9	35.9	34.6	P^a=0.2972
	SD	11.7	12.0	11.7	
	20 - 29	151 (41.5%)	135 (37.3%)	150 (41.1%)	
	30 - 39	99 (27.2%)	109 (30.1%)	110 (30.1%)	
	40 - 49	69 (19.0%)	65 (18.0%)	62 (17.0%)	
	50 - 59	30 (8.2%)	34 (9.4%)	30 (8.2%)	
	60 - 64	7 (1.9%)	11 (3.0%)	4 (1.1%)	
	65 -	8 (2.2%)	8 (2.2%)	9 (2.5%)	
BMI (kg/m^2)	Mean	22.59	22.78	22.54	P^a=0.6709
	SD	3.82	3.82	3.80	
Current smoking status*	No	251 (69.0%)	251 (69.3%)	253 (69.3%)	P^e=0.9929
	Yes	113 (31.0%)	111 (30.7%)	112 (30.7%)	
Inpatient/outpatient	Outpatient	361 (99.2%)	354 (97.8%)	359 (98.4%)	P^e=0.2978
	Inpatient	3 (0.8%)	8 (2.2%)	6 (1.6%)	
Duration of influenza (hours)	0 - 12	33 (9.1%)	24 (6.6%)	30 (8.2%)	P^k=0.3482
	12< - 24	129 (35.4%)	117 (32.3%)	131 (35.9%)	
	24< - 36	94 (25.8%)	114 (31.5%)	107 (29.3%)	
	36< - 48	108 (29.7%)	106 (29.3%)	95 (26.0%)	
	48< -	0 (0.0%)	1 (0.3%)	2 (0.5%)	
Result of rapid antigen test*	A	335 (92.0%)	333 (92.0%)	338 (92.6%)	P^e=0.7010
	B	27 (7.4%)	29 (8.0%)	25 (6.8%)	
	A and B	2 (0.5%)	0 (0.0%)	2 (0.5%)	
Influenza vaccination	No	300 (82.4%)	306 (84.5%)	302 (82.7%)	P^e=0.7188
	Yes	64 (17.6%)	56 (15.5%)	63 (17.3%)	
Composite symptom scores at baseline*	Mean	12.5	12.5	12.5	P^a=0.9712
	SD	3.4	3.3	3.2	
	0 - 14	260 (71.4%)	263 (72.7%)	261 (71.5%)	
	15 - 21	104 (28.6%)	99 (27.3%)	104 (28.5%)	
Body temperature (°C) at baseline	Mean	38.53	38.48	38.56	P^a=0.1292
	SD	0.49	0.49	0.52	

		S-021812 300 mg N=364	S-021812 600 mg N=362	Oseltamivir N=365	P-value
Influenza virus type	A	330 (90.7%)	323 (89.2%)	327 (89.6%)	P^e=0.9382
	B	21 (5.8%)	26 (7.2%)	23 (6.3%)	
	A and B	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	Unknown	13 (3.6%)	13 (3.6%)	15 (4.1%)	
Influenza virus subtype	A/H1	197 (54.1%)	200 (55.2%)	201 (55.1%)	P^e=0.9508
	A/H1 and A/H3	0 (0.0%)	0 (0.0%)	1 (0.3%)	
	A/H3	112 (30.8%)	108 (29.8%)	108 (29.6%)	
	A/H5	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	A/-	21 (5.8%)	15 (4.1%)	17 (4.7%)	
	B	21 (5.8%)	26 (7.2%)	23 (6.3%)	
	Unknown	13 (3.6%)	13 (3.6%)	15 (4.1%)	
Influenza virus titer (log_{10} [$TCID_{50}$/mL])	N	362	360	363	P^a=0.5958
	Mean	4.29	4.24	4.14	
	SD	1.97	1.85	1.92	
IC_{50} of S-021812 (nM)	N	350	353	349	P^a=0.9022
	Mean	13.8489	14.0264	13.6570	
	SD	10.3210	11.5516	10.4340	
	Min	0.5360	0.4140	0.5150	
	Median	19.7315	20.0170	19.6680	
	Max	37.8730	100.0000	36.9630	
IC_{50} of Oseltamivir (nM)	N	350	353	349	P^a=0.9758
	Mean	54.3613	54.1420	53.6514	
	SD	42.9356	43.6430	43.5275	
	Min	0.3310	0.2660	0.3420	
	Median	75.1430	75.2540	75.0620	
	Max	100.0000	100.0000	100.0000	

Pre-treatment virus isolates were sequenced from a total of 614 subjects that were determined to have an influenza A (H1 subtype) or mixed A (H1 and H3) subtype infection, of which 495 (80.6%) had a pre-existing H275(4)Y mutation in the NA gene.

In the ITTI each of the peramivir dose groups was non-inferior to the oseltamivir group for TTAS. The maximum difference in median times was 3.8 hours. Similar results applied in the PPS population.

Table 31

Table 11.4-1 Analysis of time to alleviation of symptoms using the Cox proportional hazards model (ITTI)

	S-021812 300 mg N=364	S-021812 600 mg N=362	Oseltamivir N=365
Median (hrs)	78.0	81.0	81.8
(95% Confidence Interval)	(68.4, 88.6)	(72.7, 91.5)	(73.2, 91.1)
Improvement over Oseltamivir (hrs)	-3.8	-0.8	---
Cox proportional hazards model			
_Estimate	-0.0552	-0.0301	---
_SE	0.0788	0.0786	---
_Hazard ratio	0.946	0.970	---
_(97.5% Confidence Interval)	(0.793, 1.129)	(0.814, 1.157)	---

Analysis method: Cox proportional hazards model
Covariates: Current smoking status, Composite symptom scores at baseline, Country /region, Influenza virus type, Sex, Complication, Previous drug

Cox proportional hazards model					
		Estimate	SE	P-value	Hazard ratio
Treatment group	Oseltamivir	---	---	---	---
	S-021812 300 mg	-0.0552	0.0788	0.4836	0.946
	S-021812 600 mg	-0.0301	0.0786	0.7015	0.970
Current smoking status	No	---	---	---	---
	Yes	-0.2606	0.0717	0.0003	0.771
Composite symptom scores at baseline		0.0699	0.0106	<.0001	1.072
Country /region	Japan	---	---	---	---
	Korea	-0.2610	0.1172	0.0260	0.770
	Taiwan	0.1019	0.0844	0.2274	1.107
Influenza virus type	Type A	---	---	---	---
	Type B	-0.0767	0.1292	0.5528	0.926
	Unknown	-0.2357	0.1694	0.1642	0.790
Sex	Male	---	---	---	---
	Female	0.2136	0.0667	0.0014	1.238
Complication	No	---	---	---	---
	Yes	0.1309	0.0678	0.0536	1.140
Previous drug	No	---	---	---	---
	Yes	0.1505	0.0661	0.0227	1.162

A sensitivity analysis conducted with 4 initial covariates (current smoking status, total score of 7 influenza symptoms prior to treatment, country/region and influenza virus type) were consistent with the primary analysis.

When the primary endpoint (Cox proportional hazards model) was analysed based on elapsed time between the onset of influenza and randomisation (0-12, 12-24, 24-36 and 36-48 hours) the groups appear generally similar. Apart from the 0-12 hours group where patient numbers are very small, the confidence interval upper bounds do not suggest inferiority for peramivir 600 mg compared to oseltamivir.

Table 32

Table 14.2-50 Analysis of Time to Alleviation of Symptoms using Cox Proportional Hazards Model in Patients whose Durations of Influenza are over 12 to 24 hours: ITTI

	S-021812 300 mg N=129	S-021812 600 mg N=117	Oseltamivir N=131
Median (hrs)	73.8	89.9	88.8
(95% Confidence Interval)	(66.3, 91.4)	(77.5, 115.3)	(71.0, 107.3)
Improvement over Oseltamivir (hrs)	-15.1	1.0	---
Cox proportional hazards model			
_Estimate	-0.0741	0.0647	---
_SE	0.1328	0.1367	---
_Hazard ratio	0.929	1.067	---
_(97.5% Confidence Interval)	(0.690, 1.250)	(0.785, 1.449)	---

Table 14.2-51 Analysis of Time to Alleviation of Symptoms using Cox Proportional Hazards Model in Patients whose Durations of Influenza are over 24 to 36 hours: ITTI

	S-021812 300 mg N=94	S-021812 600 mg N=114	Oseltamivir N=107
Median (hrs)	82.6	82.0	80.4
(95% Confidence Interval)	(65.7, 89.8)	(66.3, 102.3)	(68.6, 93.1)
Improvement over Oseltamivir (hrs)	2.2	1.6	---
Cox proportional hazards model			
_Estimate	0.0248	0.0146	
_SE	0.1572	0.1478	---
_Hazard ratio	1.025	1.015	---
_(97.5% Confidence Interval)	(0.721, 1.458)	(0.729, 1.413)	---

Table 14.2-52 Analysis of Time to Alleviation of Symptoms using Cox Proportional Hazards Model in Patients whose Durations of Influenza are over 36 to 48 hours: ITTI

	S-021812 300 mg N=108	S-021812 600 mg N=106	Oseltamivir N=95
Median (hrs)	81.8	69.4	87.6
(95% Confidence Interval)	(55.8, 103.2)	(54.0, 93.2)	(68.7, 113.5)
Improvement over Oseltamivir (hrs)	-5.8	-18.2	---
Cox proportional hazards model			
_Estimate	-0.0682	-0.2249	---
_SE	0.1506	0.1546	---
_Hazard ratio	0.934	0.799	---
_(97.5% Confidence Interval)	(0.667, 1.309)	(0.565, 1.129)	---

The point estimates for the changes in the composite symptom from screening to each evaluation point were all in favour of peramivir, and the upper bounds of the confidence intervals did not suggest that large inferiority of peramivir compared to oseltamivir was likely.

For time to alleviation of each of the 7 influenza symptoms there were no consistent trends for numerical values. Similarly, there were no important differences in the time to alleviation of general and respiratory symptoms, though the trends favoured peramivir.

The mean AUCs for the composite symptom scores were 790.2 for the 300 mg group, 826.5 for the 600 mg group and 833.9 for oseltamivir (two-sided *P* values = 0.2642, 0.6810). In respective groups, the median times to resolution of fever were 32.8, 33.7 and 37.3 hours. The proportions of patients reporting normal temperature 24 hours after the start of treatment were 59.3%, 57.9% and 49.7%, respectively. The doses and frequency of use of paracetamol showed higher doses taken and greater frequency of use in the oseltamivir group. The median times to resumption of normal activity were 151.7, 176.8 and 165.2 hours in respective groups.

There were no notable differences between treatment groups in the time-weighted changes in the influenza virus titre. Prior to study drug administration, the median IC_{50} value of peramivir was ~20 nM in all treatment groups, whereas the median IC_{50} for oseltamivir (carboxylic acid) was 75 nM. For

the 4 patients with the highest fold-changes in IC_{50} values, virus titres were <LLD by Visit 4 (Day 8) and TTAS was from 50.3 to 81.8 hours, with no clear relationship between susceptibility and clinical efficacy.

The incidence of sinusitis was 1/364 in the 300 mg group, 1/362 in the 600 mg group and 4/365 in the oseltamivir group. Otitis media occurred in on patient in the 300 mg group while bronchitis was reported in six patients in each group and pneumonia in 3, 1 and 2 patients in respective groups.

The median TTAS for patients with type A were 80.0, 80.7 and 81.8 hours and for type B (70 patients) the respective values were 55.3, 92.8 and 92.7 hours. For type A/H1 median TTAS values were 80.2, 83.6 and 88.8 hours and for type A/H3 the medians were 69.9, 70.6 and 75.1 hours. The proportion of patients with subtype A/H3 was significantly higher in Korea (62.9% to 75.0% per group) compared to 22.8% to 27.4% in Japan and Taiwan. At screening, the IC_{50} values for peramivir and oseltamivir for viruses obtained in Korea were low (reflecting low rates of A/H1N1 containing the H275Y mutation).

It is relevant to note that in Japan the median TTAS values were 78.0, 80.7 and 80.6 hours but in Korea they were 68.4, 49.7 and 63.4 hours. In Taiwan, median TTAS values were 80.0, 104.0 and 103.4 hours.

BCX1812-305: A Phase 3, randomized, open-label, active-controlled study to evaluate the safety, pharmacokinetics, and effectiveness of IV peramivir compared to oral oseltamivir in pediatric subjects with acute uncomplicated influenza

Refer to pharmacokinetics section (special populations) for the study design. Bilateral, mid-nasal swab specimens were collected for virologic analysis at baseline, Day 3, Day 7 and, where possible, Day 14. Virology laboratory tests included viral subtype determination from the baseline sample, culture and analysis by log_{10} $TCID_{50}$, RT-PCR assay, viral susceptibility to peramivir, oseltamivir and zanamivir, and genotypic analysis of primary virus isolates. Subjects or parents or caregivers were asked to provide an assessment of influenza symptoms on a 4-point severity scale (0, absent; 1, mild; 2, moderate; 3, severe) beginning before dosing on Day 1 until symptom resolution or through the last follow-up visit, whichever came first. Body temperature measurements were recorded once at screening and baseline by the site's normal method, and then via an electronic thermometer provided by the Sponsor BID until temperature normalized for 48 hours without the use of antipyretic medication.

There were 17/108 subjects with a negative rapid antigen test (RAT) at screening and 11/17 had a negative influenza PCR test at screening while 6 were positive. Most subjects (98 [91%]) completed the study. Study completion rates were 85% in the ≥ 2 - < 7-year-old cohort, 96% in the ≥ 7 - < 13-year-old cohort and 93% in the ≥ 13 - < 18-year-old cohort. Most of those enrolled (75 [69%] subjects) were included in the ITTI Population with 59 (69%) in the peramivir group and 16 (70%) in the oseltamivir group.

The mean age was 9.9 (SD 4.53) years with 54% female and 94% White (94%). The mean baseline Composite Symptom Score was 13 (SD 4.1). Overall and within each age cohort, the peramivir and oseltamivir groups were well balanced for demographic and baseline characteristics except for gender (61% female oseltamivir vs. 52% female peramivir).

There were 68 subjects with positive influenza virus titres ($log_{10}TCID_{50}$ > 0.5) at baseline and there was persistence at day 3 in 37/66 [56%] with available data but in only 2/66 (3%) by Day 7 and none at day 14. A lower percentage in the peramivir group (51% vs. 77%) had positive titres on day 3. There was no difference by day 7.

Proportions with detectable viral shedding on day 3 varied by virus subtype.

Table 33

Table 24: Summary of Positive Post-treatment Viral Cultures at Day 3 by Treatment Group and Virus Subtype

	Subjects with Positive Post-treatment Viral Culture at Day 3[1]		
Virus subtype	**Peramivir n (%)**	**Oseltamivir n (%)**	**Total n (%)**
Influenza A/H1N1	8/20 (40%)	5/ 7 (71%)	13/27 (48%)
Influenza A/H3N2	1/10 (10%)	1/ 2 (50%)	2/12 (17%)
B	18/22 (82%)	4/ 4 (100%)	22/26 (85%)

[1] Denominator represents subjects with available post-treatment sample for analysis.

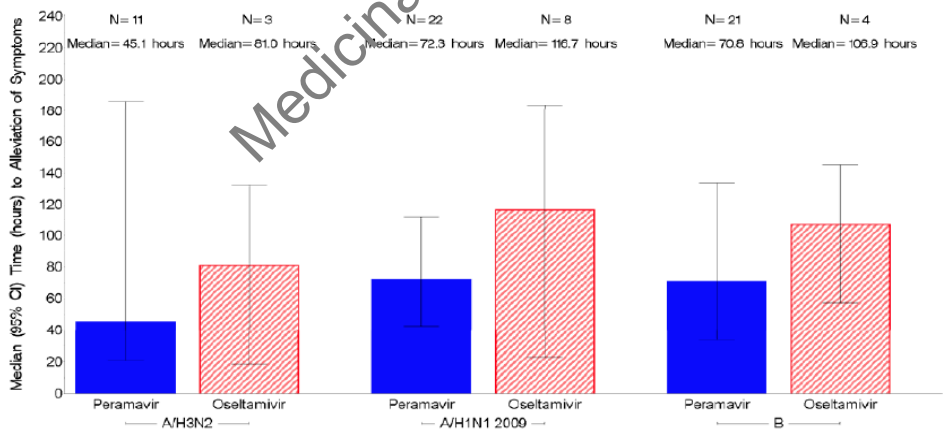
Overall, median $\log_{10}$ $TCID_{50}$/mL was 4.50 at baseline but was reduced in both groups by-3.25 on day 3 and -4 on day 7. There were no notable differences among the 3 older age cohorts in the reduction of influenza virus titres over time. Median values on day 3 were higher in subjects with influenza B virus (1.88) vs. 0.5 for each of A/H1N1 and A/H3N2.

Most (97%) of the 75 with a positive RT-PCR at baseline were still positive on Day 3 but rates dropped to 70% by Day 7 and 25% by Day 14. On day 7 the rates were 64% for peramivir and 93% for oseltamivir. There were no notable differences among the 3 older age cohorts or by viral subtype in the proportion with positive influenza results by RT-PCR results over time.

Influenza symptoms were alleviated after a median of 81.0 hours (range: 5.6 hours to 317.6 hours) after initial dosing among the subjects who were not censored (n = 64) with Kaplan-Meier estimations of 75.6 hours for peramivir vs. 99.8 h for oseltamivir. Among subjects who received peramivir, there were no notable differences among the age cohorts and no apparent age-related trends in the time to alleviation of symptoms. Influenza symptoms were alleviated more rapidly for subjects in the peramivir group compared with the oseltamivir group for each influenza subtype.

Figure 8.

Figure 4: Median (95% CI) Time to Alleviation of Symptoms by Viral Subtype – Intent-to-Treat Infected Population



Note: Figure based on Kaplan-Meier estimates. Time to alleviation of symptoms was the number of hours from initiation of study drug until the start of the 24-hour period in which all seven symptoms were either absent or present at a level no greater than mild for at least 21.5 (24 - 10%) hours. Subjects who did not achieve alleviation of symptoms were censored at the time of their last observed symptom assessment. Viral subtype groups A/H1N1 2009+B and A/Indeterminate only had 1 subject each and were omitted from this display.

Resolution of fever required oral temperature <37.4°C or axillary temperature <36.9°C and no antipyretic medications within 12 hours. There were no notable differences across the age cohorts in

temperature over time. Fever resolved more rapidly for subjects in the oseltamivir group than for subjects in the peramivir group (Kaplan-Meier estimations = 34.7 vs. 40.5 hours).

Summary of main study

The following tables summarise the efficacy results from the main study 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 pivotal trial 0722T0621

Title: A Phase 2 clinical study of single-dose intravenous peramivir in patients with influenza virus infection: a double-blind, parallel group, comparative dose-finding study			
Study identifier	0722T0621		
Design	This was a multicenter, placebo-controlled, double-blind, parallel-design study with dynamic allocation using the minimization method in patients with influenza virus infection. 300 mg and 600 mg treatment groups for peramivir were established, and each treatment group was given single intravenous administration of the investigational product. The injection volume was prepared to 100 mL, with intravenous infusion performed over a period of 30 minutes		
	Duration of main phase: 14 days Duration of Run-in phase: not applicable Duration of Extension phase: not applicable		
Hypothesis	Superiority		
Treatments groups	300mg		300mg. Single IV infusion, 99 randomized
	600mg		600mg. Single IV infusion, 100 randomized
	Placebo		Placebo. Single IV infusion, 101 randomized
Endpoints and definitions	Time to alleviation of the influenza symptoms (duration of influenza)	TTAS	Also referred to as: time to disappearance of influenza symptoms
	Time to recovery to normal temperature		Also referred to as time to resolution of fever
	Amount of change in virus titer per unit time		Also referred to as change in influenza virus titer by log_{10} $TCID_{50}$/mL and by RT-PCR
Database lock	Database transferred from Shionogi 16 June 2008		

Results and Analysis				
Analysis description	**Primary Analysis - Time to alleviation of the influenza symptoms**			
Analysis population and time point description	Intent to treat Infected Endpoint is time to event			
Descriptive statistics and estimate variability	Treatment group	300mg Peramivir	600mg Peramivir	Placebo
	Number of subjects	n=99	n=97	n=100
	Time to alleviation of the influenza symptoms (Median, hrs)	59.1	59.9	81.8

	95% Confidence Interval	50.9,72.4	54.4,68.1	68.0, 101.5

Effect estimate per comparison	Time to alleviation of the influenza symptoms (duration of influenza)	Comparison groups	S-021812 consolidated group vs. placebo
		Cox proportional hazards Chi-square test statistic	9.5277
		P-value (one-sided)	0.0010*
	Time to alleviation of the influenza symptoms (duration of influenza)	Comparison groups	300mg peramivir vs. placebo
		Cox proportional model hazards Chi-square test statistic	6.7916
		Adjusted p-value (one-sided)	0.0046*
	Time to alleviation of the influenza symptoms (duration of influenza)	Comparison groups	600mg peramivir vs. placebo
		Cox proportional model hazards Chi-square test statistic	7.5463
		Adjusted p-value (one-sided)	0.0046*
Notes	Refer to Table 15 of clinical study report 0722T0621 ((Module 5, Section 5.3.5.1)		

Covariates: Current smoking behavior, Composite symptom scores at baseline
Adjusted p-value: Determined by Hochberg method
*: Statistical significance; p-value or Adjusted p-value (one-sided) <0.025

Analysis description	**Secondary analysis - Time to recovery to normal temperature**		
Analysis population and time point description	Intent to treat Infected Endpoint is time to event		
Descriptive statistics and estimate variability	Treatment group	300mg Peramivir	600mg Peramivir	Placebo
	Number of subjects	n=99	n=97	n=100
	Time to recovery to normal temperature (Median, hrs)	29.3	30.2	42.4
	95% Confidence Interval	25.2, 33.3	25.9, 31.9	32.9, 46.5

Effect estimate per comparison	Time to recovery to normal temperature	Comparison groups	300mg peramivir vs. placebo
		Stratified log-rank test Chi-square test statistic	10.9107
		P-value	0.0010*
	Time to recovery to normal temperature	Comparison groups	600mg peramivir vs. placebo
		Stratified log-rank test Chi-square test statistic	12.0999
		P-value	0.0005*
Notes	Refer to Table 19 of clinical study report 0722T0621 (Module 5, Section 5.3.5.1)		

Analysis method: Stratified log rank test
Stratified factors: Current smoking behavior, Composite symptom scores at baseline
*: Statistical significance; p-value (two-sided) <0.05

Analysis description	**Secondary analysis - Amount of change in virus titer per unit time**			
Analysis population and time point description	Intent to treat Infected Endpoint is time to event			
Descriptive statistics and estimate variability	Treatment group	300mg Peramivir	600mg Peramivir	Placebo
	Number of subjects	n=95	n=93	n=97
	Amount of change in virus titer [log_{10} ($TCID_{50}$)] per unit time Day 1 to Day 3 (Mean)	-1.450	-1.563	-1.261
	SD	0.807	0.925	0.834
	Number of subjects	n=95	n=93	n=97
	Amount of change in virus titer [log_{10} ($TCID_{50}$)] per unit time Day 1 to Day 5 (Mean)	-2.154	-2.276	-2.012
	SD	1.146	1.206	1.107
	Number of subjects	n=95	n=91	n=96
	Amount of change in virus titer [log_{10} ($TCID_{50}$)] per unit time Day 1 to Day 9 (Mean)	-2.585	-2.671	-2.578
	SD	1.306	1.324	1.187
Effect estimate per comparison Day 1 to Day 3	Amount of change in virus titer [log_{10} ($TCID_{50}$)] per unit time Day 1 to Day 3	Comparison groups	300mg peramivir vs. placebo	
		Van Elteren Test Chi-square test statistic	2.7583	
		P-value	0.0968	
	Amount of change in virus titer [log_{10} ($TCID_{50}$)] per unit time Day 1 to Day 3	Comparison groups	600mg peramivir vs. placebo	
		Van Elteren Test Chi-square test statistic	8.9882	
		P-value	0.0027*	
Effect estimate per comparison Day 1 to Day 5	Amount of change in virus titer [log_{10} ($TCID_{50}$)] per unit time Day 1 to Day 5	Comparison groups	300mg peramivir vs. placebo	
		Van Elteren Test Chi-square test statistic	0.9504	
		P-value	0.3296	
	Amount of change in virus titer [log_{10} ($TCID_{50}$)] per unit time Day 1 to Day 5	Comparison groups	600mg peramivir vs. placebo	
		Van Elteren Test Chi-square test statistic	3.5683	
		P-value	0.0589	
Effect estimate per comparison Day 1 to Day 9	Amount of change in virus titer [log_{10} ($TCID_{50}$)] per unit time Day 1 to Day 9	Comparison groups	300mg peramivir vs. placebo	
		Chi-square test statistic	0.0074	
		P-value	0.9313	
	Amount of change in virus	Comparison groups	600mg peramivir vs. placebo	

	titer [log_{10} ($TCID_{50}$)] per unit time Day 1 to Day 9	Chi-square test statistic	0.3517
		P-value	0.5532
Notes	Refer to Table 23 of clinical study report 0722T0621 (Module 5, Section 5.3.5.1)		

Analysis method: van Elteren test
Stratified factors: Current smoking behavior, Composite symptom scores at baseline
Subset of patients who were positive for influenza virus titer at baseline
*: Statistical significance; p-value (two-sided) <0.05

Supportive studies

Three non-Japanese studies (BCX1812-211, BCX1812-311 and BCX1812-212) in which single IM doses of peramivir was used are proposed to provide supportive data for the use of single doses of IV peramivir. Study 311 was terminated early (82 patients randomised) due to the focus on IV dosing.

BCX1812-211/311 combined analysis

Patient selection criteria were similar to those in the Japanese Phase 2 study with single dose IV peramivir (0722T0621). Host and influenza characteristics are shown below.

Table 34

Table 11: Demographics and Baseline Characteristics in the Integrated Analyses: ITT Population

	Placebo (N = 141)	Peramivir 150 mg (N = 114)	Peramivir 300 mg (N = 172)
Age at Baseline (years)			
Mean (SD)	34 (11.5)	37 (15.5)	35 (13.1)
Median	32	32	32
Min, Max	18, 64	18, 92	18, 85
Gender			
Male	71 (50%)	47 (41%)	82 (48%)
Female	68 (48%)	67 (59%)	90 (52%)
Current Smoking Behavior at Randomization			
Smoker	30 (21%)	22 (19%)	39 (23%)
Nonsmoker	109 (77%)	91 (80%)	133 (77%)
Geographic Region			
North America	70 (50%)	45 (39%)	104 (60%)
Japan/Southeast Asia	3 (2%)	1 (1%)	1 (1%)
Rest of World	68 (48%)	68 (60%)	67 (39%)
Influenza Infection[1]			
Influenza A - H1N1, Wild Type	35 (25%)	32 (28%)	37 (22%)
Influenza A - H3N2	68 (48%)	50 (44%)	90 (52%)

Influenza B	28 (20%)	19 (17%)	31 (18%)
Indeterminate	3 (2%)	3 (3%)	5 (3%)
Duration of Illness at Randomization			
< 36 hours	98 (70%)	79 (69%)	114 (66%)
0 to 12 hours ago	2 (1%)	4 (4%)	8 (5%)
12 + to 24 hours ago	43 (30%)	32 (28%)	40 (23%)
24 + to 36 hours ago	53 (38%)	43 (38%)	66 (38%)
≥ 36 hours	41 (29%)	34 (30%)	58 (34%)
36 + to 48 hours ago	41 (29%)	34 (30%)	58 (34%)
Viral Culture at Baseline			
Positive	132 (94%)	100 (88%)	161 (94%)
Negative	9 (6%)	14 (12%)	11 (6%)

[1] Influenza type was determined from PCR and/or serology results where available. Subjects from studies where confirmation of influenza was by RAT test only had indeterminate influenza type.
[2] Severity of illness was assessed based on the sum of the seven symptoms of influenza from the first complete Subject Diary.

The results of the primary analysis of time to alleviation of influenza symptoms did not show a significant difference for peramivir vs. placebo. The actual differences in medians for peramivir groups vs. placebo were ~ 20 h with smaller differences for mean values. A borderline significant difference for 300 mg vs. placebo was found after controlling for factors as stated in footnote 2.

Table 35

Table 12: Time to Alleviation of Influenza Symptoms: ITTI Population

	Placebo (N = 134)	Peramivir 150 mg (N = 104)	Peramivir 300 mg (N = 163)
Kaplan-Meier Estimate (hrs)[1]			
N (Number Censored)	132 (22)	104 (17)	163 (29)
Mean (SD)	148.2 (7.25)	136.2 (8.15)	130.6 (6.89)
Median	134.8	114.1	113.2
95% CI	113.5, 163.8	95.2, 145.5	88.4, 130.4
25% - 75%	78.1 - 223.4	68.5 - 186.1	60.4 - 197.3
Primary Comparison			
P-Value[2]			0.161
HR (95% CI)[3]			0.838 (0.648, 1.085)
Secondary Comparison			
P-Value[4]			0.047
HR (95% CI)[5]			0.846 (0.657, 1.089)

[1] Time to alleviation of influenza symptoms was the number of hours from initiation of study drug until the start of the time period in which all seven symptoms of influenza were either absent or present at a level no greater than mild for at least 24 hours. Subjects who did not experience alleviation of influenza symptoms were censored at the last observed symptom assessment.
[2] P-value was based on the Wilcoxon-Gehan statistic for the comparison of peramivir 300 mg to placebo, controlling for smoking status, influenza season, and influenza type.
[3] The hazard ratio was based on the Cox Regression model, including parameters for treatment, current smoking behavior, influenza season, and influenza type.
[4] P-value was based on the Wilcoxon-Gehan statistic for the comparison of peramivir 300 mg to placebo.
[5] The hazard ratio was based on the Cox Regression model, which included treatment as a parameter.

Subgroup analyses of the primary endpoint suggested a benefit for active treatment in current smokers, in the 2007 Southern Hemisphere winter and in those with influenza A.

Table 36

Table 13: Time to Alleviation of Influenza Symptoms by Subgroup: ITTI Population

	Placebo (N = 134)	Peramivir 150 mg (N = 104)	Peramivir 300 mg (N = 163)
Kaplan-Meier Estimate (hrs)[1]			
Smoker			
N (Number Censored)	29 (5)	22 (3)	36 (3)
Mean (SD)	169.7 (15.79)	123.0 (13.83)	119.0 (13.48)
Median	168.4	98.7	106.9
95% CI	117.0, 226.0	78.0, 165.6	60.4, 138.0
25% - 75%	96.6 - 248.4	64.7 - 175.1	51.5 - 178.3
Nonsmoker			
N (Number Censored)	103 (17)	82 (14)	127 (26)
Mean (SD)	141.6 (8.02)	137.9 (9.37)	133.8 (7.98)
Median	123.7	115.7	114.3
95% CI	107.5, 160.5	92.2, 147.4	91.0, 131.3
25% - 75%	77.2 - 198.8	68.8 - 186.8	61.6 - 222.8
Northern Hemisphere (2006-2007)			
N (Number Censored)	43 (6)	41 (10)	42 (5)
Mean (SD)	134.5 (12.18)	142.9 (14.32)	128.6 (13.85)
Median	107.5	135.7	112.5
95% CI	87.0, 138.4	82.0, 163.6	63.7, 178.7
25% - 75%	73.8 - 185.7	64.7 - 273.5	50.3 - 199.7
Southern Hemisphere (2007)			
N (Number Censored)	62 (12)	62 (7)	63 (15)
Mean (SD)	160.2 (10.56)	130.2 (9.77)	134.4 (11.6)
Median	164.0	105.0	119.2
95% CI	127.9, 185.3	92.2, 138.6	7[illegible]37.9
25% - 75%	92.8 - 224.0	70.9 - 175.1	5[illegible]7 - 248.2
Northern Hemisphere (2007-2008)			
N (Number Censored)	27 (4)	1 (0)	58 (9)
Mean (SD)	140.7 (16.53)	225[illegible]	124.1 (10.08)
Median	118.2	2[illegible]	111.0
95% CI	88.4, 175.5	NA, NA	82.5, 129.1
25% - 75%	66.4 - 242.2	225.8 - 225.8	63.4 - 162.0
Influenza A Infection			
N (Number Censored)	104 (20)	85 (13)	129 (22)
Mean (SD)	152.3 (8.55)	136.1 (8.91)	128.3 (7.78)
Median	137.7	115.7	111.0
95% CI	117.0, 169.8	92.2, 145.5	86.6, 130.4
25% - 75%	74.8 - 248.4	70.9 - 181.9	55.3 - 195.9
Influenza B Infection			
N (Number Censored)	28 (2)	19 (4)	31 (5)
Mean (SD)	129.7 (11.38)	132.2 (19.05)	127.0 (14.11)
Median	114.5	100.8	125.5
95% CI	100.3, 143.8	68.2, 162.0	68.1, 162.0
25% - 75%	89.3 - 174.0	62.7 - 217.9	61.1 - 178.7

Other findings are summarised below.

Table 37

Table 24: Summary of Efficacy Findings

Efficacy Endpoints	Placebo	Peramivir 300 mg	P-value[1]	P-value[2]
Median time to alleviation of influenza symptoms (hrs)	134.8	113.2	0.161	0.047
Median time to resolution of fever (hrs)	66.8	42.8	0.004	< 0.001
Median time to resumption of usual daily activities (days)	10.0	10.0	0.065	0.102
Median time-weighted change from Baseline virus titer in log_{10} $TCID_{50}$/mL for Day 1 to Day 3	-1.38	-1.63	0.009	0.027
Subjects with viral shedding at Day 2	97/103 (94%)	83/101 (82%)	0.008	0.008
Subjects with viral shedding at Day 3	77/127 (61%)	68/154 (44%)	0.009	0.006
Subjects with any influenza-related complication	24 (18%)	18 (11%)	0.071	0.091

[1] Statistical analyses adjusted for smoking behavior, influenza season, and influenza type were performed for the primary comparison of peramivir 300 mg with placebo.
[2] Statistical analyses for the secondary comparison of peramivir 300 mg with placebo were conducted without adjustment for smoking behavior, influenza season, and influenza type.

BCX1812-212

Patient selection and dosing were similar to above. There were 402 adults enrolled and treated of which 282 were included in the ITTI influenza A (ITTI-A) population, which was designated primary. The mean age was 35 years (range 18 to 81 years) and 49% were male while 82% were non-smokers. Half had an estimated time of onset of influenza symptoms of 24 to 36 hours prior to screening and another 42% had symptom onset within 12 to 24 hours prior to screening. The mean initial composite symptom score was 14 in both groups (range 2 to 21).

Of the 334 with confirmed influenza 269 had a positive culture and 65 had only a positive PCR. Of these, 282 (84%) had influenza A, including 245 with an H1N1 subtype, 36 with an H3N2 subtype and 52 (16%) with influenza B. The CSR states that all the patients with influenza A/H1N1 infection had the H274Y mutation associated with oseltamivir resistance. Specifically, it is stated that 230/245 (94%) of influenza A/H1N1 contained this mutation and 15 had results that were indeterminate. In the ITTI-A population this mutation was present in 116/133 (87%) of A/H1N1 strains in the peramivir group and 129/149 (87%) in the placebo group.

The baseline IC_{50} values (nM) for influenza A/H1N1 were as shown below. In contrast the median peramivir IC_{50} for H3N2 was 1.0 nM and for influenza B it was 5.6 nM.

Viral Subtype/Assessment/Statistic		Peramivir	Oseltamivir	Zanamivir
Influenza A/H1N1		N = 203	N = 203	N = 202
	Mean (SD)	70 (71)	994 (1264)	1.4 (1.4)
	Median	51	488	1.0
	Min, Max	2.5, 634	0.9, 8927	<0.1, 9.7

For 279 ITTI-A patients for whom data were available, the median TTAS was 91.1 hours in the peramivir group and 106.9 hours in the placebo group (p = 0.222). An additional analysis in the ITTI-A population after excluding data from 29 patients enrolled at 2 sites (309 and 311; an explanation for this additional analysis was not found in the CSR) gave very similar results to the initial analysis. There were also no differences between groups for time to alleviation of the individual symptoms. In the ITTI-A population there were no differences in the primary endpoint in any of the sub-groups except

for females. In men the mean and median TTAS was longer in the peramivir group (e.g. median 118 vs. 104 h) but there was a significantly shorter TTAS in females (median 89 vs. 135 h; mean 110 vs. 144 h).

Table 38

Table 9: Time to Alleviation of Symptoms (ITTI-A Population)

Statistic		Placebo N = 147	Peramivir 600 mg N = 132
Kaplan-Meier Estimate (h)	Mean (SD)	125.0 (6.50)	114.7 (6.65)
	Median (95% CI)	106.9 (90.4, 127.4)	91.1 (77.7, 109.7)
	25% – 75%	57.6 – 184.8	56.6 – 170.9
P-value[a]			0.222
Hazard Ratio (95% CI)			0.927 (0.723, 1.188)

CI = confidence interval; h = hours; ITTI-A = Intent-To-Treat Infected Influenza A; SD = standard deviation

[a] P-values are from a Wilcoxon-Gehan test statistic controlling for smoking status and hemisphere of enrollment.

Note: Subjects at risk were the number at risk at the beginning of the interval. Cumulative events and Kaplan-Meier % were at the end of the interval. Time to alleviation of symptoms was the number of hours from initiation of study drug until the start of the time period in which all 7 symptoms of influenza were either absent or present at a level no greater than mild for at least 21.5 (24 - 10%) hours. Baseline was the time directly prior to initiation of study drug. Subjects who did not experience alleviation of symptoms were censored at the last observed symptom assessment. Three subjects, Subjects 311077, 311152, and 433004, were excluded due to missing diary data.

In the ITTI population the median time to alleviation of symptoms was 124 h for placebo and 121 h for peramivir.

Decreases in influenza virus shedding, measured by $TCID_{50}$, were similar between the peramivir and placebo groups at Days 3, 4 and 9. There were also no differences between active and placebo groups for the median severity of illness (AUC symptom score-hours 713.9 vs. 777.0) or median time to resolution of fever (44 vs. 45 h; the 4 h rule for measurements before or after antipyretic use was applied). The incidence of influenza-related complications was 22% in the peramivir group and 17% in the placebo group.

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

The applicant provided an analysis of the placebo-controlled single dose studies 0722T0621 (IV), BCX1812-211/311 and BCX1812-212 (all IM), in which 1032 adult patients with uncomplicated influenza were included in the ITTI population (408 placebo and 624 peramivir [doses of 150, 300 or 600 mg]). The number included 258 who received 600 mg IV (98) or IM (160). However, there was no pre-defined plan to conduct pooling. The data below are confined to the virological data.

Three studies were conducted during seasons in which A/H1N1 H275Y predominated. These include two for which the CSR mentions the occurrence of the mutation (BCX1812-212 and 0815T0631) and one other for which there is no mention in the CSR (0816T0632). It should be noted that the methods and range of investigations varied by study.

A total of 2886 patients across the studies had a laboratory-confirmed influenza infection. Baseline IC50 data were available for influenza from > 2300 patients. Over 1200 isolates were selected for sequence analysis, and partial or complete sequence data were available for 1122 of these. Paired genotypic data (baseline and post-treatment) were available for 182 patients.

Table 39

Table 12: TTAS by Treatment Group and Influenza Subtype, ITTI Population, 0722T0621 and BCX1812-211, -311 and -212 Pooled

Characteristic	Placebo N=408	Peramivir 150 mg N=104	Peramivir 300 mg N=262	Peramivir 600 mg N=258	Peramivir Overall N=624
Kaplan-Meier estimate (hours)					
Influenza A/H1N1, Wild Type					
N	110	32	111	80	223
Median	95.6	135.7	67.2	63.2	75.8
Bootstrap Method					
Difference in Medians [95% CI]	N/A	38.0 [-1.6, 72.1]	-28.5 [-47.9, -1.7]	-31.0 [-47.8, -6.1]	-19.8 [-38.5, 4.3]
Influenza A/H1N1, H275Y					
N	124	0	0	104	104
Median	108.9	N/A	N/A	92.1	92.1
Bootstrap Method					
Difference in Medians [95% CI]	N/A N/A	N/A N/A	N/A N/A	-15.9 [-35.7, 12.8]	-15.7 [-35.[illegible] 13.9]
Influenza A/H3N2					
N	110	50	111	41	202
Median	113.9	90.4	85.4	65.2	80.3
Bootstrap Method					
Difference in Medians [95% CI]	N/A N/A	-20.1 [-51.4, 43.0]	-27.7 [-54.1, 7.7]	[illegible] [-73.2, -21.5]	-31.2 [-56.2, -5.9]
Influenza B					
N	53	19	33	28	80
Median	113.1	100.8	117.[illegible]	133.0	124.3
Bootstrap Method					
Difference in Medians [95% CI]	N/A N/A	-12.1 [-50.7, 99.7]	[illegible].6 [-44.9, 47.3]	17.0 [-48.7, 98.8]	5.6 [-35.3, 41.6]

The table below summarises IC_{50} values at baseline.

Table 40

Table 21. Susceptibility of Baseline Virus Isolates to NAIs

	Susceptibility of Baseline isolates to NAIs: Median (range) IC_{50} – nM		
	Peramivir	Oseltamivir	Zanamivir
A/H1N1[a]	0.38 (0.01-108.66)	1.05 (0.03-1263.58)	1.08 (0.02-42.33)
A/H1N1 H275Y[b]	22.44 (0.41- 634.26)	100.00 (0.66-8926.74)	1.32 (0.03-9.67)
A/H3N2[c]	0.75 (0.01-28.47)	0.60 (0.01-311.49)	1.73 (0.01-7.80)
B[c]	3.41 (0.01-22.13)	18.24 (0.05-114.33)	5.05 (0.03-32.11)

a Viruses analyzed from studies conducted in seasons when influenza A/H1N1 H275Y was not predominant.
b Viruses analyzed from studies conducted in seasons when influenza A/H1N1 H275Y predominated.
c Viruses analyzed from studies conducted in seasons when influenza A/H1N1 H275Y was not predominant and when A/H1N1 H275Y predominated.

The only treatment-emergent mutation of significance associated with peramivir exposure was the H275Y mutation in A/H1N1. Sequence studies assessed treatment-emergent changes in NA and HA amino acids from baseline to post-baseline isolates in patients with no evidence of pre-existing substitutions associated with NAI resistance who had:

1) Delayed viral clearance following treatment

2) Virus demonstrating a defined increase in IC_{50} over the baseline mean IC_{50} for that viral subtype

3) In addition a small number of random samples were analysed.

There were 117 adult patients with paired baseline and post-baseline NA genotype data who received peramivir and were included in one of the three populations defined above. The amino acid substitution H275Y was identified in 12 cases, of which 11 had A/H1N1 and one was of indeterminate subtype.

Three other NA treatment-emergent substitutions that resulted in amino acid changes previously associated with NAI resistance were identified in single patients. One H3N2 virus showed a treatment-emergent N294N/S substitution and one H3N2 virus showed a treatment-emergent R292R/K substitution. The post-treatment peramivir IC_{50} values for these were close to the baseline median IC_{50} value for all H3N2 viruses isolated in the clinical studies. The third was an A/H1N1 virus with treatment-emergent V94I and R152K substitutions associated with a higher IC_{50} than the baseline median value for all H1N1 strains from the clinical programme.

Analysis of HA genotypic data identified a single treatment-emergent amino acid substitution that occurred in more than one patient. Five patients with H3N2 had a change in HA at position 173, which has been identified as a polymorphic site with multiple amino acids described previously. Three of the five had a mixture of I/L173 that resolved to L173 post-treatment, one had L173 at baseline and developed I173 post-treatment and one with L173 at baseline developed S173.

In patients who received peramivir in studies with fully sensitive pre-treatment isolates (0722T0621, BCX1812-211, 0918T0633, BCX1812-201, BCX1812-301 and BCX1812-303), fold changes in the post-treatment median IC_{50} values for peramivir compared to baseline ranged from 0.91 to 1.10. With the exception of the small number of isolates where genotypic changes were identified that correlated with IC_{50} changes, no other changes in susceptibility to peramivir were discernible.

A study that investigated the susceptibility of 233 influenza strains to peramivir after launch in Japan (2010) showed that 3.2% of A(H1N1)pdm09 and 0.5% of B viruses had reduced peramivir susceptibility. There was an increase in number of cases of A(H1N1)pdm09 with the H275Y NA mutation in 2011 (see the IC_{50} range).

Table 41

Table 17. Susceptibility of Virus Isolates to NAIs: 2010-2011 RAPIACTA Surveillance Program Japan

Influenza Subtype	N	NAI IC_{50} (nM)					
		Peramivir		Oseltamivir		Zanamivir	
		Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
A/H1N1pdm	102	0.11 (0.04)	0.05–68.62	2.01 (0.56)	0.90–628.74	0.81 (0.26)	0.39–3.42
A/H3N2	102	0.17 (0.05)	0.05–0.34	1.02 (0.23)	0.49–2.52	0.64 (0.25)	0.32–2.93
B	19	6.68 (2.40)	2.44–10.94	47.90 (9.90)	26.09–63.95	88.64 (30.49)	26.08–127.22

Mutations in 3 A/H1N1 isolates with peramivir IC_{50} values > 30 nM are shown below.

Table 42

Table 18. NA Sequencing Results and Amino acid Changes in Viruses with Reduced Susceptibility to Peramivir

Viral isolate	Timing of Specimen	NAI IC_{50} (nM)			Primary NA Mutations (N2 Numbering)
		Peramivir	Oseltamivir	Zanamivir	
A/Kyoto/10K124/2011	Before use of oseltamivir	34.19	428.78	0.92	H274Y, S62X, V176G, R419X
A/Hyogo/10K291/2011	Before use of zanamivir	68.62	628.74	1.49	H274Y, E51G
A/Kyoto/10K104(2)2011	3 days after start of oseltamivir use[a]	31.72	433.24	1.20	H274Y

a A pretreatment isolate from this patient showed a wild-type sequence at amino acid 274 (N2 numbering).

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical efficacy data can support an indication *for treatment of uncomplicated influenza.* The most important data come from the Japanese study that compared single doses of 300 mg and 600 mg with placebo (0722T0621). The PK data and final POPPK analysis are used to bridge the efficacy observed in this population to the general EU population. Furthermore, based on the safety and PK data presented in BCX1812-305 the applicant proposed that the indication may be applied from the age of 2 years. It can be agreed that an extrapolation of efficacy from adults to children could be accepted in case of uncomplicated influenza.

Following the prior approvals of two neuraminidase inhibitors (NAIs) in the EU, the peramivir studies focussed on the median TTAS as the primary endpoint. In the uncomplicated influenza setting the licensed NAIs were shown to shorten the median TTAS by ~24 h overall vs. placebo when treatment was commenced within 48 h of onset of the first recognisable symptoms. Based on these prior approvals and findings, as well as the acceptability of administering a placebo injection to adults with uncomplicated influenza and a low likelihood of progressing to more severe disease if such patients do not receive antiviral therapy (noting that the upper age limit was 65 years), it is appropriate that the applicant's designated pivotal study (0722T0621) compared single IV doses with placebo (normal saline).

The second study in which single IV doses were evaluated (0815T0631) in adults with uncomplicated influenza provided a direct comparison of the safety and efficacy of peramivir with the licensed oral treatment regimen for oral oseltamivir. There was no parallel randomised placebo group to put the results of the three NAI groups into context for the specific population studied. Therefore, interpretation of the study rests on the prior demonstrations of shortening the time to alleviation of symptoms (TTAS) by oseltamivir vs. placebo in adults.

Efficacy data and additional analyses

In 0722T0621 it was appropriate that the primary analysis was conducted in the ITTI population since no benefit could be expected in patients without influenza virus. Patients were enrolled based on rapid

antigen detection testing. All patients in the ITTI population had confirmed influenza virus infection from PCR and most met the viral titre threshold as well.

Dynamic allocation was used for treatment allocation using a minimization algorithm. A minimization procedure was employed as it was felt to be of critical importance that the treatment groups were balanced for tobacco use and screening influenza symptoms. The procedure as outlined is considered an acceptable approach to treatment allocation. In the case of borderline results an analysis using a re-randomisation test could be considered as the allocation was not fully randomised. However, the separation between the Kaplan-Meier curves seems clear, so this is not considered to be necessary. Handling of individual patients in terms of their inclusion in analysis populations was determined in a case review convened by the study sponsor and the medical expert (May 24, 2008) and in inspections performed by the medical expert (February 28, 2008 and April 26, 2008).

The applicant assumed for the purposes of the sample size calculation that the median values for the duration of influenza would be 50 h shorter in the two active groups vs. the placebo group, which seems unrealistic. The actual median TTAS were 59.1 hours in the 300 mg group and 59.9 hours in the 600 mg group vs. and 81.8 hours for placebo, representing differences of less than one day. This effect was obtained from a population in which ~85% had symptom scores <15 at baseline, >70% had wild-type influenza A/H1N1 and no virus had the H275(4)Y mutation.

The Cox proportional hazards model is appropriate for the analysis of time-to-event data. The outlined testing approach of first conducting a test using data from the combined peramivir groups and then testing the individual doses using the Hochberg procedure provides appropriate control of the type I error. The approach to handling missing data, where patients are assumed to not have had alleviation of symptoms at the missing time-point, is agreed.

Reflecting the primary analysis, there were statistically significant differences in change in the influenza symptoms at 24 hours onwards for the active vs. placebo groups. For individual symptoms, there was not always a statistically significant difference in time to alleviation between either of the active and the placebo groups. Active treatment shorted the time to recovery to normal temperature (< 37.0°C) by half a day. In contrast to the magnitude of effect on the primary endpoint, the median time to resumption of daily activities was 125.6 and 127.4 hours in the peramivir groups vs. 169.1 hours in the placebo group.

There was an early effect on viral shedding in the active groups but the self-limiting nature of the disease meant that the difference vs. placebo waned with time.

There were only 3 patients with influenza B. The difference for peramivir 600 mg vs. placebo for median TTAS was less for the sub-group with H1N1 (62.6 h vs. 81.4 h; ~19 h difference) compared to the smaller subgroup with H3N2 (50.5 h vs. 81.0 h; ~30 h difference). Since ~70% had H1N1 in the study this drives the overall difference vs. placebo in the primary analysis.

The single dose IM studies (BCX1812-211 and 311) were conducted in the same pre-pandemic season as 0722T0621, essentially in a non-Asian population in which H3N2 predominated and < 20% had influenza B. The median difference in TTAS for 300 mg peramivir vs. placebo was ~21 h but this showed no or borderline statistical significance depending on whether the factors smoking, influenza type and season were included in the analysis. Subgroup analyses of the primary endpoint suggested a benefit for active treatment in current smokers, in the 2007 Southern Hemisphere winter and in those with influenza A.

Specifically, in the subset with influenza B there was no benefit for peramivir (and no effect on shedding). There was no impact on time to resume normal daily activities in the ITTI or in various

subgroups of the population. These results do not provide strong support for a single 300 mg IV peramivir dose. The studies did not include an evaluation of the single 600 mg IV dose that is proposed for the SmPC.

In BCX1812-212, also a non-Asian study, the ITTI influenza A (ITTI-A) population was designated primary. In the ITTI-A population influenza A/H1N1 carrying the H274Y mutation was present in 116/133 (87%) in the peramivir group and 129/149 (87%) in the placebo group, resulting in a mean baseline IC_{50} value of 70 nM across all strains. Reflecting this distribution of viruses, the study failed to show a benefit for 600 mg peramivir over placebo overall or in various sub-groups except in female patients.

Integrated analyses of the single dose studies vs. placebo

Given that there was no plan to pool data across studies conducted in different seasons and populations, and the clear differences between the studies in terms of viruses and virus susceptibility, which seems to be the major driver of effect size, the overall comparisons for pooled peramivir data vs. pooled placebo data are not helpful. However, the overall picture does highlight the almost complete lack of any data in patients aged > 65 years and the lack of any convincing effect of peramivir on influenza B. Furthermore, the data support initiation of treatment only up to 36 h after onset of symptoms.

In 0815T0631 the approach of dividing the reference vs. placebo effect by two to obtain the non-inferiority margin is not acceptable. A justification based upon the lower bound of the confidence interval for reference vs. placebo and on considerations of clinical relevance would be expected. In the amended Statistical Analysis Plan a superiority test was planned if non-inferiority of peramivir was established. If non-inferiority was not established, the upper limit of the 97.5% CI for the hazard ratio was to be compared to 1.192. The value of 1.192 was calculated by taking the minimum value of the difference in the estimated effect between placebo and oseltamivir phosphate as the margin. The minimum effect of oseltamivir phosphate was calculated based on the upper limit of the 95% CI for the hazard ratio of oseltamivir phosphate to placebo. This “second non-inferiority test” using a more relaxed margin of 1.192 may actually use a margin based on a better statistical justification, as it is based upon the bounds of the historical confidence interval for oseltamivir vs. placebo. However, the data used as the basis for the calculation would need to be provided to confirm this. In the event, non-inferiority was shown using the original margin, so the test using a more relaxed margin was not required.

The magnitude of benefit for oseltamivir vs. placebo is modest and subject to variability between populations. Without a direct comparison with placebo it is not possible to deduce with certainty whether any active treatment was having a clinically important effect on TTAS.

It is of note that in the primary analysis all three active treatment groups had a median TTAS that was similar to that achieved with placebo in 0722T0621 (all ~ 80 h) but the differences between the two study populations in terms of virus and host characteristics make this cross-study comparison unreliable.

For example, the proportions presenting at 36-48 hours and with symptom scores at least 15 at baseline were larger than in 0722T0621. There were also differences vs. 0722T0621 in proportions with each influenza subtype (across the three countries ~55% had A/H1N1 and ~ 30% H3N2 but influenza B occurred in ~7%) and the mean peramivir IC_{50} at baseline was notably higher in this study, reflecting the emergence of H1N1 strains bearing the H275Y mutation. Pre-treatment virus isolates were sequenced from a total of 614 subjects that were determined to have influenza A (H1

subtype) or mixed A (H1 and H3) subtype infection. Of these viruses, 495 (80.6%) had the H275Y mutation at baseline.

TTAS by duration of symptoms before the first dose suggested that 300 mg peramivir was numerically better than the other groups if started before 24 h whereas the 600 mg dose was numerically better if started between 36 and 48 h post-onset. It seems there may have been other factors influencing these findings or they may have occurred by chance.

The median TTAS in patients with any influenza type A virus were 80.0, 80.7 and 81.8 hours for 300 and 600 mg peramivir and oseltamivir, respectively, but for the 70 patients across the three groups with type B the respective values were 55.3, 92.8 and 92.7 hours. Again, the result for 300 mg peramivir in this small sub-population (although statistically significant) may reflect a clustering of patients most likely to respond or may have arisen by chance.

In the relatively large numbers with A/H1 (598) or A/H3 (328) the median TTAS for the peramivir and oseltamivir groups were 80.2, 83.6 and 88.8 hours and 69.9, 70.6 and 75.1 hours for respective strains. Thus, although there was no placebo group, the difference for H3 vs. H1, taking into account that most of the H1 viruses were insusceptible to the NAIs, suggests that the two NAIs had comparable effects against susceptible H3N2 viruses.

Furthermore, the proportion of patients with subtype A/H3 was significantly higher in Korea (62.9% to 75.0% per group) compared to 22.8% to 27.4% in Japan and Taiwan. Rates for H1N1 were ~55% in Japan and ~66% in Taiwan but only 4-8 patients per group in Korea (11-22%). At screening, the median IC_{50} values for peramivir (and oseltamivir) for all viruses obtained in Korea were low (<1 nM; reflecting low rates of A/H1N1 containing the H275Y mutation) vs. 19 nM in Japan and 20 nM in Taiwan.

In Japan, the overall median TTAS values were 78.0, 80.7 and 80.6 hours for peramivir and oseltamivir dose groups, resembling those for H1N1 strains and for the overall study. The respective values in Taiwan, where H1N1 was even more prevalent, were 80.0, 104.0 and 103.4 hours. In contrast, the median TTAS values in Korea were 68.4, 49.7 and 63.4 hours. Although there was no placebo control, the data suggest generally comparable effects of peramivir and oseltamivir in subsets with NAI susceptible viruses.

Regarding other studies the study in high-risk patients was uncontrolled, small and the majority received multiple doses. The three studies in hospitalised patients involved multiple dosing. One of the three (BCX1812-301) compared QD peramivir (600 mg for adults; adjusted mg/kg for children) with a placebo plus standard of care control group. The ITTI-Non-NAI population (N=121) was used for primary analyses of efficacy. Time to resolution of fever drove the primary endpoint. The study failed to show superiority for addition of peramivir to SOC in the ITTI or ITTI-non-NAI populations and there were no differences for secondary or other endpoints analysed. A *post hoc* logistic regression identified prognostic factors, including gender and region but not age. Based on BCX1812-303 it cannot be ruled out that BID dosing with 300 mg or 600 mg might have shown a difference vs. placebo in the ITTI-Non-NAI subset. Overall, these studies do not really contribute to the evaluation of treatment effect of single IV doses of peramivir for the target patient population in the current application.

2.5.3. Conclusions on the clinical efficacy

The evidence for efficacy comes from a single placebo-controlled study in Japanese patients, ~70% of whom presented at 12-36 and mostly 12-24 h after symptom onset, Also, ~85% had symptom scores <15 at baseline and >70% had wild-type influenza A/H1N1. The primary analysis indicated a

statistically significant shortening of the median TTAS in the 600 mg group. The observed effect on median TTAS was 21.5 h. The greatest difference between peramivir and placebo occurred in those enrolled at 12-24 h.

This single pivotal study is not well supported by the two placebo-controlled studies in which a single 300 mg IM dose was given, although a benefit was demonstrated in some subgroups. The study that compared 600 mg IM with placebo showed no benefit of peramivir but this result was driven by the prevalence of the H275Y mutation in A/H1N1 in the season in which the study was conducted. The study that compared 300 mg and 600 mg IV doses of peramivir with oseltamivir showed similar TTAS values across the groups. However, in the absence of a placebo group it is not possible to draw clear conclusions on efficacy from this study.

Based on the extrapolation of efficacy in adults and the safety and PK analyses to support the dose regimen, the additional data from BCX1812-305 sanction the use from age 2 years onwards.

2.6. Clinical safety

Patient exposure

At the time of submitting the dossier, peramivir (IV or IM) had been given to 2,155 patients with influenza and to 596 subjects in Phase 1 studies. Single intravenous 600 mg doses for treatment of uncomplicated influenza were administered to 467 adults.

Table 43

Table 1: Table 9 Total Cumulative Exposure to Peramivir in Studies of Acute, Uncomplicated Influenza in Adults (Safety Population)

	Peramivir dose			
No. Subjects (%)	**<300 mg N = 113**	**300-<600 mg N = 655**	**≥600 mg N = 685**	**Overall N = 1453**
<300 mg	113 (100.0 %)	0	0	113 (7.8 %)
≥300-<600 mg	0	642 (98.0 %)	0	642 (44.2 %)
≥600-<1200 mg	0	12 (1.8 %)	667 (97.4 %)	679 (46.7 %)
≥1200-<2400 mg	0	1 (0.2 %)	17 (2.5 %)	18 (1.2 %)
≥2400-<3600 mg	0	0	1 (0.1 %)	1 (0.1 %)
≥3600 mg	0	0	0	0

Additional data from BCX1812-305 in children aged from 2 years were provided during the procedure.

Adverse events

In the adult uncomplicated influenza set 49.8% of peramivir patients vs. 51% of placebo patients and 48.8% of oseltamivir patients experienced at least 1 TEAE (see below). The most frequently observed TEAEs in all peramivir-treated patients were diarrhoea (7.4%), decreased neutrophil count (5.5%) and increased blood glucose (5.0%). A least one severe TEAE was reported for 5.0% of peramivir patients. Of all peramivir patients 0.8% had a severe AE of neutrophil count decreased, 1.1% had severe ECG QT prolonged, 0.6% had severe hyperglycaemia, 0.3% had severe hypophosphataemia and 0.3% had severe glycosuria.

TEAEs assessed by the Investigator as treatment related were observed in 22.2% of all peramivir patients. The most common were diarrhoea (4.5%), nausea (2.1%), neutrophil count decreased (1.8%), proteinuria and ALT increased (1.7%) and AST increased.

Table 44

Table 20: Overview of Adverse Events in Trials of Peramivir in Adult Acute Uncomplicated Influenza Set (Safety Population)

No. Subjects (%) with ≥1:			Peramivir			
	Placebo N = 441	Oseltamivir N = 365	< 300 mg N = 113	≥ 300- < 600 mg N = 655	≥ 600 mg N = 685	Overall Peramivir N = 1453
TEAE	225 (51.0%)	178 (48.8%)	43 (38.1%)	343 (52.4%)	337 (49.2%)	723 (49.8%)
Grade 3 or Grade 4 TEAE	27 (6.1%)	24 (6.6%)	4 (3.5%)	31 (4.7%)	38 (5.5%)	73 (5.0%)
Related TEAE	94 (21.3%)	73 (20.0%)	21 (18.6%)	140 (21.4%)	161 (23.5%)	322 (22.2%)
SAE	2 (0.5%)	2 (0.5%)	0	6 (0.9%)	1 (0.1%)	7 (0.5%)
TEAE Leading to Discontinuation of Study/Study Drug	0	5 (1.4%)	0	4 (0.6%)	6 (0.9%)	10 (0.7%)
TEAE Leading to Death	0	0	0	1 (0.2%)	0	1 (0.1%)

In **0722T0621** the overall ADR rates indicated no important differences between peramivir and placebo and in **0815T0631** the total ADR rates were similar between 600 mg IV peramivir and oseltamivir. An analysis of ADRs was conducted that was confined to 467 adults with uncomplicated influenza who received a single 600 mg IV dose. Those which occurred more often with peramivir compared to placebo are shown in the table below. Overall, 122/467 (26.1%) of patients treated with 600 mg IV peramivir experienced 229 reactions vs. 51/100 (51.0%) treated with IV placebo. Most individual reactions (49/90 [54.4%]) were reported by 1 to 3 patients. Most ADRs occurred in the Investigations SOC.

Table 45

Table 3: Treatment Emergent Adverse Events Related to Study Drug by System Organ Class and Preferred Term Occurring More Often in IV Peramivir Treated Subjects than IV Placebo Treated Subjects.

		Placebo				Peramivir 600 mg		
System Organ Class	Preferred Term	IM	IV	Overall		IM	IV	Overall
		(N=202)	(N=100)	(N=302)		(N=200)	(N=467)	(N=667)
Any Adverse Event Possibly, Probably, or Definitely Related to Study Drug		21 (10.4%)	51 (51.0%)	72 (23.8%)		31 (15.5%)	122 (26.1%)	153 (22.9%)
Investigations		3 (1.5%)	39 (39.0%)	42 (13.9%)		12 (6.0%)	76 (16.3%)	88 (13.2%)
	Neutrophil count decreased	0	0	0		0	15 (3.2%)	15 (2.2%)
	Blood creatine phosphokinase increased	0	0	0		4 (2.0%)	2 (0.4%)	6 (0.9%)
	Blood lactate dehydrogenase increased	0	0	0		0	6 (1.3%)	6 (0.9%)
	Blood alkaline phosphatase increased	1 (0.5%)	0	1 (0.3%)		0	3 (0.6%)	3 (0.4%)
	Blood urea increased	0	0	0		1 (0.5%)	2 (0.4%)	3 (0.4%)
	Blood albumin decreased	0	0	0		0	2 (0.4%)	2 (0.3%)
	Blood urine present	0	0	0		0	2 (0.4%)	2 (0.3%)
	Gamma-glutamyltransferase increased	0	0	0		0	2 (0.4%)	2 (0.3%)
	Blood chloride increased	0	0	0		0	1 (0.2%)	1 (0.1%)
	Blood creatinine increased	0	0	0		0	1 (0.2%)	1 (0.1%)

		Placebo				Peramivir 600 mg		
System Organ Class	Preferred Term	IM	IV	Overall		IM	IV	Overall
		(N=202)	(N=100)	(N=302)		(N=200)	(N=467)	(N=667)
	Blood glucose decreased	0	0	0		0	1 (0.2%)	1 (0.1%)
	Blood lactate dehydrogenase decreased	0	0	0		0	1 (0.2%)	1 (0.1%)
	Blood potassium increased	0	0	0		0	1 (0.2%)	1 (0.1%)
	Blood sodium increased	0	0	0		0	1 (0.2%)	1 (0.1%)
	Blood uric acid increased	0	0	0		0	1 (0.2%)	1 (0.1%)
	Electrocardiogram QT prolonged	0	0	0		0	1 (0.2%)	1 (0.1%)
	Protein total increased	0	0	0		0	1 (0.2%)	1 (0.1%)
	Urine ketone body present	0	0	0		0	1 (0.2%)	1 (0.1%)
Gastrointestinal disorders		8 (4.0%)	15 (15.0%)	23 (7.6%)		7 (3.5%)	45 (9.6%)	52 (7.8%)
	Nausea	5 (2.5%)	1 (1.0%)	6 (2.0%)		4 (2.0%)	11 (2.4%)	15 (2.2%)
	Vomiting	0	1 (1.0%)	1 (0.3%)		2 (1.0%)	6 (1.3%)	8 (1.2%)
	Abdominal pain upper	0	0	0		0	4 (0.9%)	4 (0.6%)
	Abdominal discomfort	0	0	0		0	2 (0.4%)	2 (0.3%)
	Gastritis	0	0	0		0	2 (0.4%)	2 (0.3%)
Nervous system disorders		4 (2.0%)	4 (4.0%)	8 (2.6%)		5 (2.5%)	5 (1.1%)	10 (1.5%)
	Hypoaesthesia	0	0	0		0	1 (0.2%)	1 (0.1%)
	Paraesthesia	0	0	0		0	1 (0.2%)	1 (0.1%)

		Placebo				Peramivir 600 mg		
System Organ Class	Preferred Term	IM	IV	Overall		IM	IV	Overall
		(N=202)	(N=100)	(N=302)		(N=200)	(N=467)	(N=667)
Skin and subcutaneous tissue disorders		2 (1.0%)	2 (2.0%)	4 (1.3%)		0	10 (2.1%)	10 (1.5%)
	Eczema	0	0	0		0	2 (0.4%)	2 (0.3%)
	Urticaria	0	0	0		0	2 (0.4%)	2 (0.3%)
	Dermatitis	0	0	0		0	1 (0.2%)	1 (0.1%)
	Drug eruption	0	0	0		0	1 (0.2%)	1 (0.1%)
General disorders and administration site conditions		3 (1.5%)	1 (1.0%)	4 (1.3%)		6 (3.0%)	3 (0.6%)	9 (1.3%)
	Chest discomfort	0	0	0		0	1 (0.2%)	1 (0.1%)
	Fatigue	0	0	0		0	1 (0.2%)	1 (0.1%)
Musculoskeletal and connective tissue disorders		2 (1.0%)	0	2 (0.7%)		1 (0.5%)	1 (0.2%)	2 (0.3%)
	Arthralgia	0	0	0		0	1 (0.2%)	1 (0.1%)
Psychiatric disorders		0	1 (1.0%)	1 (0.3%)		0	2 (0.4%)	2 (0.3%)
	Insomnia	0	0	0		0	2 (0.4%)	2 (0.3%)

Infections and infestations		0	1 (1.0%)	1 (0.3%)		0	1 (0.2%)	1 (0.1%)
	Herpes simplex	0	0	0		0	1 (0.2%)	1 (0.1%)
Eye disorders		0	0	0		0	1 (0.2%)	1 (0.1%)
	Vision blurred	0	0	0		0	1 (0.2%)	1 (0.1%)
Metabolism and nutrition disorders		0	0	0		0	1 (0.2%)	1 (0.1%)
	Decreased appetite	0	0	0		0	1 (0.2%)	1 (0.1%)

The data shown above were used as the basis of an analysis that identified ADRs to peramivir considered to be clinically relevant and medically plausible.

Adverse events of special interest in patients who received peramivir in the adult uncomplicated influenza set showed that:

1. Injection site pain (including IM injection) was reported for 9 (0.6%) patients compared to 4 (0.9%) in the placebo group.
2. Neuropsychiatric TEAEs comprised 3 (0.5%) patients with somnolence and 1 (0.07%) with depressed level of consciousness.
3. There were 5 (0.3%) patients with pre-syncope, 2 (0.1%) with syncope and one (0.1%) with hypersensitivity; rates were higher in the placebo group than any peramivir dose group.
4. Renal TEAEs comprised 54 (3.7%) with protein urine present, 18 (1.2%) with proteinuria, 8 (0.6%) with blood urea increased, 2 (0.1%) with blood creatinine increased and single cases of renal failure and renal impairment.
5. There were 80 (5.5%) patients with neutrophil count decreased, 26 (1.8%) with white blood cell count decreased, 6 (0.4%) with neutropenia and 3 (0.2%) with lymphocyte count decreased. Rates for these TEAEs were higher for peramivir compared to placebo but comparable to rates for oseltamivir.
6. Hepatic function TEAEs included 36 (2.5%) with ALT increased, 25 (1.7%) with AST increased, 17 (1.2%) with blood bilirubin increased, 8 (0.6%) with GGT increased, 3 (0.2%) with hepatic function abnormal and two patients (0.1%) with each of urobilinuria, bilirubin conjugated increased and hepatic enzyme abnormal. Rates were similar in the placebo group.
7. Haematochezia was reported in a 40-year-old man who received peramivir 600 mg with an event verbatim of bloody stools.
8. There were 21 (1.4%) with blood CPK increased, 8 (0.6%) with myalgia, 2 (0.1%) with blood creatinine increased and one (0.6%) with each of musculoskeletal pain, myalgia intercostal, renal failure, renal impairment and blood calcium decreased. Blood CPK increased was reported for a slightly higher incidence in the peramivir vs. placebo group (1.4% vs. 0.5%).

In **BCX1812-305** the second report included safety data from 92 children exposed to a single dose of peramivir. Overall, 21% experienced at least 1 TEAE. The most frequently reported TEAE was vomiting. A higher percentage in the oseltamivir group (4 [17%] subjects) compared with the peramivir group (8 [9%] subjects) experienced a study drug-related TEAE.

Summary of Treatment-Emergent Adverse Events
Safety Population

	Peramivir (N=92)	Oseltamivir (N=23)	Total (N=115)
Number of Subjects with			
Treatment-Emergent Adverse Events	19 (21%)	5 (22%)	24 (21%)
Severe or Life Threatening Treatment-Emergent Adverse Events	2 (2%)	0	2 (2%)
Treatment-Emergent Adverse Events Possibly, Probably, or Definitely Related to Study Drug	8 (9%)	4 (17%)	12 (10%)
Treatment-Emergent Serious Adverse Events	0	0	0
Treatment-Emergent Adverse Events Leading to Death	0	0	0
Treatment-Emergent Adverse Events Leading to Discontinuation of Study	0	1 (4%)	1 (< 1%)

Most TEAEs were moderate in intensity. Two children aged ≥ 13 - < 18 years had severe TEAEs. One had pyrexia that was considered possibly related to study drug and resolved during the study and the other had blood CK, AST and LDH increased, all considered possibly related to study drug and none resolved during the study. Overall, the safety profile of peramivir did not appear to be importantly different from that of oseltamivir. Further data will be provided when this study completes.

Serious adverse event / deaths / other significant events

AEs with an outcome of death were reported for one adult with uncomplicated influenza who received peramivir, 5 patients hospitalised for influenza in BCX1812-201 and -301 (2 peramivir) and 22 hospitalised patients in BCX1812-303 (16 peramivir). One other peramivir patient had an AE leading to death after the 28 day follow-up period. The peramivir patient with uncomplicated influenza who died was a 46-year-old white female with meningitis considered to be unrelated to treatment.

In adults with uncomplicated influenza SAEs were reported for 7 (0.5%) peramivir and 2 (0.5%) placebo patients. SAEs in the peramivir group included three with pneumonia (one specified as bacterial) and single cases of influenza, meningitis, myalgia and asthma. None of these SAEs was considered related to treatment. There were no SAEs reported in BCX1812-305.

There have been 4 pregnancies during clinical development in peramivir patients. One pregnancy was non-viable due to a hydatidiform mole. All 3 viable pregnancies ended in elective terminations for personal reasons. There were no suspected foetal anomalies.

Laboratory findings

In adults with uncomplicated influenza the graded shifts in laboratory values from baseline to final value showed no major differences between treatment groups.

Shifts for haemoglobin were shown for 2.5% peramivir and 1.6% placebo patients. In addition, shifts for neutrophils were shown for 2.1% peramivir vs. 0.9% placebo patients. The ISS provides further breakdowns by peramivir dose and vs. oseltamivir. The tables for haemoglobin and neutrophils are shown below.

Graded Laboratory Shifts from Baseline to Final Value by Treatment Group
Safety Population - Phase 2/3 Trials in Acute, Uncomplicated Influenza in Adults

LABORATORY PANEL Laboratory Parameter	Placebo (N=441)	Oseltamivir (N=365)	< 300 mg Peramivir (N=113)	300 -< 600 mg Peramivir (N=655)	≥600 mg Peramivir (N=685)	Overall Peramivir (N=1453)
Hemoglobin (g/dL)						
Any Baseline Grade	N = 431	N = 360	N = 110	N = 639	N = 676	N = 1425
No Shift	419 (97.2%)	355 (98.6%)	103 (93.6%)	619 (96.9%)	653 (96.6%)	1375 (96.5%)
Any Shift	7 (1.6%)	3 (0.8%)	6 (5.5%)	13 (2.0%)	16 (2.4%)	35 (2.5%)
Shift in 1 Grade	6 (1.4%)	3 (0.8%)	6 (5.5%)	13 (2.0%)	15 (2.2%)	34 (2.4%)
Shift in 2 Grades	1 (0.2%)	0	0	0	1 (0.1%)	1 (0.1%)
Shift in 3 Grades	0	0	0	0	0	0
Shift in 4 Grades	0	0	0	0	0	0

LABORATORY PANEL Laboratory Parameter	Placebo (N=441)	Oseltamivir (N=365)	< 300 mg Peramivir (N=113)	300 -< 600 mg Peramivir (N=655)	≥600 mg Peramivir (N=685)	Overall Peramivir (N=1453)
Neutrophils (10^3/uL)						
Any Baseline Grade	N = 326	N = 360	N = 110	N = 519	N = 554	N = 1183
No Shift	290 (89.0%)	349 (96.9%)	104 (94.5%)	504 (97.1%)	502 (90.6%)	1110 (93.8%)
Any Shift	3 (0.9%)	7 (1.9%)	0	6 (1.2%)	19 (3.4%)	25 (2.1%)
Shift in 1 Grade	3 (0.9%)	5 (1.4%)	0	6 (1.2%)	18 (3.2%)	24 (2.0%)
Shift in 2 Grades	0	2 (0.6%)	0	0	1 (0.2%)	1 (0.1%)
Shift in 3 Grades	0	0	0	0	0	0
Shift in 4 Grades	0	0	0	0	0	0

In the CSR for **0722T0621** the mean segmented neutrophil counts were lower in the peramivir groups vs. the placebo group on day 3 (Visit 3) and then increased to similar values at day 14 (Visit 6). In **0815T0631** similar numbers in the peramivir 600 mg and oseltamivir groups had decreases in neutrophils.

There were no remarkable differences between peramivir and placebo for urinalysis findings.

In **BCX1812-305** there were no mean changes of importance for clinical chemistry parameters from baseline to Day 7 and no apparent treatment group- or age cohort-related trends over time. In the peramivir group, one subject had Grade 4 high CK on Day 7 (20220 U/L; normal range: 49 - 397 U/L), along with other abnormalities, which was reported as a TEAE:

- Subject 009.019 (peramivir group, ≥ 13 - < 18-year-old cohort) experienced TEAEs of moderate ALT increased, severe AST increased, severe blood CK increased, and severe blood LDH increased, all on Day 7. On that day, the subject's ALT was Grade 1 high (125 U/L; normal range: 17 - 63 U/L), AST was Grade 4 high (508 U/L; normal range: 15 - 41 U/L), CK was Grade 4 high (20220 U/L; normal range: 49 - 397 U/L), and LDH was high (657 U/L, ungraded; normal range: 100 - 190 U/L). All 4 TEAEs were considered possibly related to study drug. The TEAE of ALT increased resolved on Day 14; on that date, the subject's ALT was within the reference range (44 U/L). The TEAEs of AST increased, blood CK increased, and blood LDH increased were not resolved during the study. However, by Day 14, the subject's AST had improved to high (not graded; 51 U/L), CK had improved to Grade 1 high (1989 U/L), and LDH had improved to high (not graded; 254 U/L).

Most haematology parameters did not demonstrate meaningful shifts in toxicity grade from baseline levels. The one exception was neutrophil count, which shifted to Grade 1 low in 2 subjects and to Grade 2 low in 1 subject, all in the peramivir group. None was considered clinically significant.

Safety in special populations

Limited information is available from BCX1812-305 in children (refer to above for safety findings).

Patients aged ≥ 65 years accounted for 2% of patients in the adult uncomplicated influenza studies. TEAE reporting rates were higher in patients aged ≥ 65 vs. < 65 years, reflecting the rates for those

aged ≥ 65 to < 75 years. Related TEAEs were reported for 21.9% aged < 65 and 30.2% aged ≥ 65 years.

Table 46

Table 57: TEAEs by Age Group in Subjects Treated with Peramivir, Adult Acute Uncomplicated Influenza Set (Safety Population,)

	18 to <65 years	≥65 years	≥ 65 to < 75 years	≥75 years
No. Subjects	**(N=1409)**	**(N=43)**	**(N=30)**	**(N=13)**
Any TEAE, n (%)	692 (49.1%)	31 (72.1%)	24 (80.0%)	7 (53.8%)
Severe/ potentially life-threatening TEAE	71 (5.0%) / 1 (0.1%)	1 (2.3%) / 0	1 (3.3%) / 0	0 / 0
Related TEAE	309 (21.9%)	13 (30.2%)	8 (26.7%)	5 (38.5%)
Frequently reported TEAEs				
Neutrophil count decreased	77 (5.5%)	3 (7.0%)	2 (6.7)	1 (7.7)
Diarrhoea	104 (7.4%)	3 (7.0%)	2 (6.7)	1 (7.7)
Blood glucose increased	67 (4.8)	5 (11.6%)	4 (13.3)	1 (7.7)
Blood phosphorus decreased	20 (1.4)	4 (9.3%)	2 (6.7)	2 (15.4)
Glucose urine present	18 (1.3)	3 (7.0%)	3 (10.0)	0
White blood cells urine positive	39 (2.8)	4 (9.3%)	2 (6.7)	2 (15.4)

Frequently reported: ≥5% preferred term for adult patients 18 to <65 years and ≥65 years

In the adult uncomplicated influenza set, female and male patients showed similar rates of TEAEs (52.3% vs. 47.2%, respectively) and related TEAEs (22.4% vs. 22.0%), whereas the rate for severe/life-threatening TEAEs was higher for women (5.9% vs. 4.1%). The majority of peramivir-treated patients were Asian and the highest rate of total TEAE reporting occurred in this ethnic group. Asians also had the highest rates for several individual TEAEs, including some of the commonest reported across groups.

Table 47

Table 58: TEAEs by Race in Subjects Treated with Peramivir, Adult Acute Uncomplicated Influenza Set (Safety Population,)

	White / Caucasian	Black / African American	Asian	Other
No. Subjects	**(N=305)**	**(N=100)**	**(N=996)**	**(N=52)**
Any TEAE, n (%)	121 (39.7%)	21 (21.0%)	558 (56.0%)	23 (44.2%)
Severe/ potentially life-threatening TEAE	11 (3.6%) / 1 (0.3%)	2 (2.0%) / 0	58 (5.8%) / 0	1 (1.9%) / 0
Related TEAE	56 (18.4%)	10 (10.0%)	243 (24.4%)	13 (25.0%)
Frequently reported TEAEs				
Nausea	24 (7.9%)	0	26 (2.6%)	3 (5.8%)
Diarrhoea	15 (4.9%)	3 (3.0%)	86 (8.6%)	3 (5.8%)
Neutrophil count decreased	1 (0.3%)	0	80 (8.0%)	0
Blood glucose increased	3 (1.0%)	0	69 (6.9%)	0
Protein urine present	1 (0.3%)	0	53 (5.3%)	0

The overall incidence rate of TEAEs was lower for Black/African American patients and higher for Asian than for White/Caucasians. However, within each racial group where there are data for comparators the rates were generally similar between the peramivir and placebo or oseltamivir groups.

The incidence of TEAEs in patients treated with peramivir or placebo was higher in Japanese/Southeast Asian patients than in North American patients but the severity of TEAEs was similar between

populations and generally consistent with underlying uncomplicated influenza. The most common TEAEs observed in North American peramivir patients were nausea (8.1%), diarrhoea (6.4%), dizziness (5.1%) and vomiting (4.7%). In Japanese/Southeast Asian peramivir patients the most common TEAEs were diarrhoea (8.9%), neutropenia (8.2%), increased blood glucose (7.1%) and proteinuria (5.5%). The difference in incidence of injection site pain and increased CK was due to IM injection, which was only used in N. American patients.

Immunological events

Across all clinical trials no individual exposed to peramivir experienced anaphylaxis or angioedema. One patient in BCX1812-303 experienced mild, non-serious erythema multiforme one day after completing 10 days of peramivir. Although the Investigator believed the event could be possibly related to peramivir, she had a history of HSV and polypharmacy.

Discontinuation due to adverse events

In the adult uncomplicated influenza set there were 10 peramivir patients and no placebo patients with TEAEs leading to discontinuation of therapy for reasons as shown below.

TEAEs that led to discontinuation and were considered to be at least possibly related to peramivir were the events of rashes, arthralgia, drug eruption, urticaria and abdominal pain upper.

Table 48

Table 32: TEAEs Leading to Discontinuation in Trials of Peramivir in Adult Acute Uncomplicated Influenza Set (Safety Population)

System Organ Class Preferred Term	Placebo N = 441	Oseltamivir N = 365	Peramivir			
			< 300 mg N = 113	≥ 300- < 600 mg N = 655	≥ 600 mg N = 685	Overall Peramivir N = 1453
Any	0	5 (1.4%)	0	4 (0.6%)	6 (0.9%)	10 (0.7%)
Infections and infestations	0	1 (0.3%)	0	2 (0.3%)	2 (0.3%)	4 (0.3%)
Pneumonia	0	1 (0.3%)	0	0	1 (0.1%)	1 (0.1%)
Bronchopneumonia	0	0	0	1 (0.2%)	0	1 (0.1%)
Meningitis	0	0	0	1 (0.2%)	0	1 (0.1%)
Nasopharyngitis	0	0	0	0	1 (0.1%)	1 (0.1%)
Gastrointestinal disorders	0	2 (0.5%)	0	1 (0.2%)	1 (0.1%)	2 (0.1%)
Vomiting	0	2 (0.5%)	0	0	0	0
Abdominal pain upper	0	0	0	0	1 (0.1%)	1 (0.1%)
Nausea	0	1 (0.3%)	0	0	0	0
Salivary gland pain	0	0	0	1 (0.2%)	0	1 (0.1%)
Skin and subcutaneous tissue disorders	0	0	0	1 (0.2%)	3 (0.4%)	4 (0.3%)
Rash	0	0	0	1 (0.2%)	1 (0.1%)	2 (0.1%)
Drug eruption	0	0	0	0	1 (0.1%)	1 (0.1%)
Urticaria	0	0	0	0	1 (0.1%)	1 (0.1%)
Musculoskeletal and connective tissue disorders	0	1 (0.3%)	0	0	1 (0.1%)	1 (0.1%)
Arthralgia	0	0	0	0	1 (0.1%)	1 (0.1%)
Back pain	0	1 (0.3%)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	1 (0.3%)	0	0	0	0
Upper respiratory tract inflammation	0	1 (0.3%)	0	0	0	0

Post marketing experience

Peramivir was first approved in Japan in JAN 2010 for the treatment of adults with influenza A and B, followed by use in children and infants in OCT 2010. It is estimated that ~3 million patients have been exposed to peramivir from JAN 2010 to MAR 20157 (shipped drug minus drug held in storage). Most of these patients were Japanese or Korean; use in the US is estimated at ~3,600.

Post-approval observational safety studies in Japan

1. In the first study 51/1309 patients experienced 78 AEs deemed related to peramivir by the prescribing physicians. All 78 were non-serious and 71 occurred within 3 days after the start of treatment. The most common were diarrhoea, vomiting and nausea.
2. In the second study in 1199 children there was no significant difference in the incidence of AEs or the types of AEs in infants and toddlers vs. older children. During this study, 27 patients reported 31 AEs of abnormal behaviour. Temperatures at the time of this AE ranged from 37° to 41°C, with a mean of 38.7°C and a median of 38.8°C. The duration of the abnormal behaviour was 5 minutes to 4 days. Three of 5 patients with an SAE of abnormal behaviour had influenza encephalopathy or febrile convulsion preceding the SAE.
3. In the third study 98 patients experienced 155 ADRs. None was fatal but there were 14 serious ADRs (9.0%), the most common of which were white blood cell count decreased (5) and neutrophil count decreased (4). The most common ADRs were AST increased (39) and ALT increased (29). In most cases, events such as ALT increased, eosinophil count increased, neutrophil count decreased and white blood cell count decreased occurred after 4 or more days. The incidence of ADRs was 12.3% in 71 patients treated for < 3 days and 16.9% in patients treated for ≥ 3 days.

Spontaneous and literature reports

Through 31 March 2017, there were 837 case reports comprising a total 1070 adverse reactions, of which 317 reactions were serious and 753 were non-serious. The most common are shown below.

Table 49

Table 5.1.1-1 Serious Adverse Reaction Frequency by System Organ Class: Global

System Organ Class	Serious Adverse Reactions	Percent Global Serious Adverse Reactions (N=317)	Percent Total Global Adverse Reactions (N=1070)
Investigations	48	15.14	1.42
Nervous system disorders	41	12.93	1.21
Hepatobiliary disorders	32	10.09	0.94
Immune system disorders	25	7.89	0.74
Gastrointestinal disorders	21	6.62	0.62
General disorders and administration site conditions	21	6.62	0.62
Vascular disorders	21	6.62	0.62
Renal and urinary disorders	20	6.31	0.59
Blood and lymphatic system disorders	18	5.68	0.53
Skin and subcutaneous tissue disorders	13	4.10	0.38
Cardiac disorders	10	3.15	0.29
Psychiatric disorders	9	2.84	0.27
Infections and infestations	9	2.84	0.27
Respiratory, thoracic and mediastinal disorders	8	2.52	0.24

Table 50

Table 5.1.1-2. Serious Adverse Reaction Frequency by Preferred Term: Global			
Preferred Term	**Serious**	**Percent Global Serious Adverse Reactions (N=317)**	**Percent Total Global Adverse Reactions (N=1070)**
Anaphylactic shock	18	5.68	1.68
Shock	16	5.05	1.50
Hepatic function abnormal	14	4.42	1.31
Liver disorder	12	3.79	1.12
Blood creatine phosphokinase increased	10	3.15	0.93
Acute kidney injury	9	2.84	0.84
Loss of consciousness	7	2.21	0.65
White blood cell count decreased	7	2.21	0.65
Neutropenia	7	2.21	0.65
Seizure	6	1.89	0.56
Altered state of consciousness	6	1.89	0.56
Rash	5	1.58	0.47
Abnormal behaviour	5	1.58	0.47
Blood pressure decreased	5	1.58	0.47
Death	5	1.58	0.47
Rhabdomyolysis	5	1.58	0.47
Diarrhoea	4	1.26	0.37
Platelet count decreased	4	1.26	0.37
Anaphylactic reaction	4	1.26	0.37
Cardiac failure	4	1.26	0.37
Enterocolitis haemorrhagic	4	1.26	0.37
Hepatitis acute	4	1.26	0.37

The tables below show cumulative global data for some ADRs of special interest.

Table 51

Table 6.1.3-1 Summary Tabulation Unsolicited Adverse Events and Adverse Reactions: Neutropenia and Leukopenia						
System Organ Class Preferred Term	**Adverse Event**			**Adverse Reaction**		
	Serious	**Non-Serious**	**Total**	**Serious**	**Non-Serious**	**Total**
Blood and lymphatic system disorders						
Agranulocytosis	1		1	1		1
Granulocytopenia	1		1	1		1
Leukopenia	2	2	4	2	2	4
Neutropenia	7	1	8	7	1	8
Blood and lymphatic system disorders Total	*11*	*3*	*14*	*11*	*3*	*14*
Investigations						
Granulocyte count decreased	1		1	1		1
Neutrophil count decreased	2	7	9	2	7	9
White blood cell count decreased	7	5	12	7	5	12
Investigations Total	*10*	*12*	*22*	*10*	*12*	*22*
Total	**21**	**15**	**36**	**21**	**15**	**36**

Table 52

Table 6.3.3-1 Summary Tabulation Unsolicited Adverse Events and Adverse Reactions: Hepatobiliary Effects						
System Organ Class Preferred Term	**Adverse Event**			**Adverse Reaction**		
	Serious	**Non-Serious**	**Total**	**Serious**	**Non-Serious**	**Total**
Hepatobiliary disorders						
Acute hepatic failure	1		1			
Drug-induced liver injury		1	1		1	1
Hepatic cirrhosis	1		1			
Hepatic function abnormal	15	12	27	14	10	24
Hepatitis acute	4		4	4		4
Hepatorenal syndrome	1		1			
Jaundice	2	1	3	2	1	3
Liver disorder	12	9	21	12	9	21
Hepatobiliary disorders Total	*36*	*23*	*59*	*32*	*21*	*53*
Infections and infestations						
Acute hepatitis B	1		1			
Infections and infestations Total	*1*		*1*			
Investigations						
Alanine aminotransferase increased	3	14	17	3	11	14
Aspartate aminotransferase increased	3	16	19	3	13	16
Blood bilirubin increased	1					
Hepatic enzyme abnormal	1		1	1		1
Hepatic enzyme increased		1	1		1	1
Liver function test abnormal			1		1	1
Transaminases increased		1	1		1	1
Investigations Total	*8*	*33*	*41*	*7*	*27*	*34*
Metabolism and nutrition disorders						
Hypoalbuminaemia	1		1	1		1
Metabolism and nutrition disorders Total	*1*		*1*	*1*		*1*
Skin and subcutaneous tissue disorders						
Yellow skin		1	1		1	1
Skin and subcutaneous tissue disorders Total		*1*	*1*		*1*	*1*
Total	**46**	**57**	**103**	**40**	**49**	**89**

Table 53

Table 6.5.3-1 Summary Tabulation Unsolicited Adverse Events and Adverse Reactions: Infusion Site Events						
System Organ Class **Preferred Term**	**Adverse Event**			**Adverse Reaction**		
	Serious	**Non-Serious**	**Total**	**Serious**	**Non-Serious**	**Total**
General disorders and administration site conditions						
Administration site swelling		1	1		1	1
Injection site discomfort		1	1		1	1
Injection site erosion	1		1	1		1
Injection site erythema		1	1		1	1
Injection site extravasation		3	3		3	3
Injection site necrosis	1		1	1		1
Injection site oedema	1		1	1		1
Injection site pain		5	5		5	5
Injection site ulcer	1		1	1		1
Instillation site pain		1	1		1	1
Peripheral swelling	1		1	1		1
General disorders and administration site conditions Total	*5*	*12*	*17*	*5*	*12*	*17*
Skin and subcutaneous tissue disorders						
Erythema		1	1		1	1
Skin exfoliation		1	1		1	1
Skin and subcutaneous tissue disorders Total		2	2		2	2
Vascular disorders						
Phlebitis		2	2		2	2
Vascular pain	1	11	12	1	11	12
Vascular disorders Total	*1*	*13*	*14*	*1*	*13*	*14*
Total	**6**	**27**	**33**	**6**	**27**	**33**

Table 54

Table 6.6.3-1 Summary Tabulation Unsolicited Adverse Events and Adverse Reactions: Muscle Effects						
System Organ Class **Preferred Term**	**Adverse Event**			**Adverse Reaction**		
	Serious	**Non-Serious**	**Total**	**Serious**	**Non-Serious**	**Total**
Investigations						
Blood bilirubin increased	1		1			
Blood creatine phosphokinase increased	13	5	18	10	4	14
Blood creatine phosphokinase MB increased	1		1	1		1
Investigations Total	*15*	*5*	*20*	*11*	*4*	*15*
Musculoskeletal and connective tissue disorders						
Muscle spasms		1	1			
Muscular weakness	1	2	3	1	2	3
Myalgia		3	3		2	2
Rhabdomyolysis	8		8	5		5
Musculoskeletal and connective tissue disorders Total	*9*	*6*	*15*	*6*	*4*	*10*
Total	**24**	**11**	**35**	**17**	**8**	**25**

Table 55

Table 6.7.3-1 Summary Tabulation Unsolicited Adverse Events and Adverse Reactions: Neuropsychiatric Events						
System Organ Class Preferred Term	**Adverse Event**			**Adverse Reaction**		
	Serious	**Non-Serious**	**Total**	**Serious**	**Non-Serious**	**Total**
Nervous system disorders						
Altered state of consciousness	6	3	9	6	2	8
Depressed level of consciousness	2	3	5	2	2	4
Encephalopathy	4		4	3		12
Febrile convulsion	1	2	3		1	1
Generalised tonic-clonic seizure	1		1	1		1
Hypoxic-ischaemic encephalopathy	1		1	1		2
Loss of consciousness	3	11	14	3	9	12
Memory impairment		1	1		1	1
Mental impairment	1		1	1		13
Seizure	6	3	9	6	3	9
Somnolence	1	2	3	1	1	2
Speech disorder		3	3		2	11
Tonic convulsion	3		3	3		3
Nervous system disorders Total	***29***	***28***	***57***	***21***	***48***	
Psychiatric disorders						
Abnormal behaviour	6	42	48	5	37	42
Delirium	4	5	9	2	5	7
Delirium febrile	1		1			1
Depression		1	1		1	1
Disorientation		1	1			1
Hallucination		11	11		9	9
Hallucination, auditory		2	2		2	2
Illusion		1	1		1	11
Psychiatric symptom	1		1	1		23
Psychiatric disorders Total	***12***	***63***	***75***	***8***	***55***	***63***
Total	**41**	**91**	**132**	**35**	**76**	**111**

A cumulative review of all available data within the Global Safety Database and scientific literature to evaluate the potential effects of administration of peramivir in pregnant and lactating women as well as AEs associated with infertility identified 34 reports, including 32 cases within the Global Safety Database and 2 within scientific literature involving 34 individual women. Of the 34 women, age was reported in 15 cases and ranged from 21-40 years of age. The following preferred terms (PTs) were reported from the 32 cases received within the Global Safety Database concerning exposure to peramivir during pregnancy and lactation: Maternal exposure during pregnancy (12), Maternal exposure timing unspecified (5), Exposure during breast feeding (6), Exposure during pregnancy (4), Pregnancy (3), Abortion spontaneous (1), Pregnancy test positive (1) and Benign hydatiform mole (1).

Of the 34 patients who were exposed to peramivir during pregnancy or lactation, 8 received peramivir between day 5 and week 9 of their first trimester, 3 received peramivir between week 17 and 21 of their second trimester, and 5 received peramivir between week 30 and 37 of their third trimester; in the remaining 14 patients, the timing of their pregnancy or post-partum state was not reported. Of the 34 patients, 10 patients received peramivir 300 mg; 2 received 300 mg intramuscularly (IM) and 8 received 300 mg IV; 7 patients received peramivir 600 mg IV either as a single dose or repeated dose

where peramivir was administered between 5-11 days, the dosage was not specified in 16, and in 1 patient, peramivir was administered as single 100 mg IV dose due to her creatinine clearance.

Five of the 34 patients electively terminated their pregnancy. Nine delivered healthy infants. Outcomes were not reported in 17 patients. One resulted in spontaneous abortion and one pregnant female died at 32 weeks of pregnancy due to progressive acute respiratory distress syndrome resulting in multi-organ failure.

2.6.1. Discussion on clinical safety

For the total patients exposed to peramivir the most frequently observed TEAEs were diarrhoea, decreased neutrophil count and increased blood glucose. Only hyperglycaemia reported as an AE occurred at a higher rate with peramivir than in the oseltamivir group and the difference for peramivir vs. placebo was minimal. In contrast, the rates for glycosuria reported as an AE were lower for peramivir vs. oseltamivir but higher for both actives vs. placebo.

Since oseltamivir is given orally for 5 days it is no surprise that it was associated with higher rates of upper gastrointestinal events compared to the single parenteral peramivir dose. In contrast, the rates for diarrhoea were similar across all active and placebo groups, which may be due to the impact of the background rates associated with influenza and/or with symptomatic treatments. Whereas no placebo patients had reduced neutrophils reported as an AE, the rate for peramivir (~5.5%) was slightly less than that for oseltamivir (8.8%) and did not increase with dose.

AEs of moderate or severe intensity did not occur at a higher rate with peramivir vs. oseltamivir or placebo. AEs considered drug-related mostly occurred at similar rates for peramivir vs. placebo or oseltamivir, especially when these comparisons are made only within single randomised studies. However, the pattern of differences for AE reports of reduced neutrophil counts was again apparent for the ADRs.

Within the clinical trial experience, 567 individual subjects (Peramivir: N=467; Placebo: N=100) were administered a single 600 mg IV dose of peramivir or placebo in one of the 3 completed clinical trials of uncomplicated influenza (0722T0621, 0815T0631 and 0815T0632). Within this dataset some degree of caution is required when making comparisons of total AEs and ADRs reported for patients treated with peramivir in different studies vs. the 100 who received an IV placebo in the Japanese pivotal study. A similar caution is needed when comparing peramivir with the oseltamivir group enrolled into a single study. In addition, the denominator for those who received peramivir is larger than those for the placebo and oseltamivir groups. Nevertheless, the overall picture is of no or small difference between active and placebo groups for individual AEs and ADRs, with a few exceptions of note. Also, for most AEs the rates were similar or lower for peramivir vs. oseltamivir. In this population, most relevant to the current application, there was no excess of deaths or SAEs with peramivir vs. placebo.

The laboratory data are probably best compared within the studies in which there was randomisation to peramivir or to placebo or oseltamivir. When viewed within studies there did not seem to be a difference between peramivir and placebo for effects on haemoglobin but there was an effect of peramivir with a reduction in neutrophils vs. placebo. Although the direct comparison with oseltamivir indicated that the two neuraminidase inhibitors gave very similar effects with an early decrease in neutrophil count followed by recovery to below baseline levels, neutrophil count decreased is listed as a common ADR in section 4.8 of the SmPC. Thrombocytopenia is listed as an ADR in the oseltamivir SmPC but the laboratory data currently do not suggest such an association with peramivir.

Review of clinical trial and post-marketing reports of reduced renal function indicated that although many of the cases had confounding issues a role for peramivir in triggering or exacerbating renal impairment cannot be ruled out and this has been reflected in the SmPC.

In the 2% of patients aged ≥ 65 years in the adult uncomplicated influenza studies the TEAE reporting rates were highest in those aged ≥65 years, reflecting the rates for those aged ≥ 65 to < 75 years. Related TEAEs were reported for 21.9% aged < 65 and 30.2% aged ≥ 65 years. However, the range of AEs reported was similar to that in younger subjects and there were no special concerns.

In the population of interest there were no major differences in AE rates between genders. The overall incidence rate of TEAEs was lower for Black/African American patients and higher for Asian than for White/Caucasians. The ISS tables indicate that within each racial group where there are data for comparators the rates were generally similar between the peramivir and placebo or oseltamivir groups.

The clinical trial and post-marketing data indicate that a range of hypersensitivity reactions may occur to peramivir, including serious systemic and skin reactions. These have been reflected in the SmPC.

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

There are no issues related to the safety profile of peramivir which preclude the granting of a Marketing Authorisation.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	1. Development of virus resistance to peramivir 2. Hypersensitivity reactions
Important potential risks	1. Severe cutaneous reactions 2. Neuropsychiatric events 3. Reduced renal function
Missing information	4. Use in immuno-compromised patients

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of final reports**
BCX1812-306: A Phase 3, multicenter, single-arm, open-label, study to evaluate the safety, pharmacokinetics and	Primary: To evaluate the safety and tolerability of peramivir administered intravenously (IV) in elderly subjects with	Elderly patients	Started and ongoing	31 December 2018

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of final reports
effectiveness of intravenous peramivir in elderly subjects with acute uncomplicated influenza infection and in subjects with acute uncomplicated influenza infection at higher risk for influenza complications Category 3	acute uncomplicated influenza infection and in subjects with acute uncomplicated influenza infection who are at higher risk for influenza complications.			

Risk minimisation measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Development of virus resistance to peramivir	Proposed SmPC sections: Section 5.1 and 4.4 Medical product only used in a medical setting and distribution of information to prescribers on resources where viral resistance can be monitored.	None
Hypersensitivity reactions	Proposed SmPC sections: 4.3 Contraindications 4.4 Special warnings and precautions for use 4.8 Undesirable events Medical product only used in a medical setting	None
Severe cutaneous reactions	Proposed SmPC sections: 4.3 Contraindications 4.4 Special warnings and precautions for use 4.8 Undesirable events Medical product only used in a medical setting	None
Neuropsychiatric events	Proposed SmPC sections: 4.4 Special warnings and precautions for use 4.8 Undesirable events Medical product only used in a medical setting	None
Reduced renal function	Proposed SmPc sections: 4.2 Posology 4.4 Special warnings and precautions for use	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	4.8 Undesirable events Medical product only used in a medical setting	
Use in immuno-compromised patients	Proposed SmPC sections: 4.4 Special warnings and precautions for use Medical product only used in a medical setting	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.3 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 19 December 2014. 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 peramivir 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 peramivir 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. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Alpivab (peramivir) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

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

Peramivir is proposed by the applicant for use as a single dose IV infusion for treatment of influenza in adults and children from 2 years of age.

Human influenza is due to A or B strains, both of which undergo antigenic drift over time. Influenza A strains can also undergo antigenic shift, resulting in major differences in antigenicity compared to prior circulating strains. Uncomplicated influenza occurs with a seasonal pattern in the EU and affects all age groups. In most previously healthy persons influenza is a self-limiting disease, although it has a significant economic burden due to impact on working hours lost and use of healthcare services resources. In influenza-naïve infants and young children, pregnant women, the elderly and those with certain underlying conditions, influenza can be severe and sometimes life-threatening. Some influenza-related deaths are due to secondary bacterial infections.

In pandemic years, the number of cases is much higher than usual due to a larger portion of the population lacking protective immunity against the pandemic influenza strain. Pandemics are usually accompanied by high rates of persons requiring contact with healthcare professionals and hospitalisation, increasing the seasonal burden on healthcare services. Some pandemics have been associated with large increases in mortality rates over the background seasonal rate.

Furthermore, in the last 20 years outbreaks of human infections with a variety of avian influenza strains have been well-documented. These outbreaks have tended to be associated with higher rates of severe infection and mortality. Thus far, these viruses have not acquired the ability to efficiently transfer between humans, which could lead to a pandemic.

3.1.2. Available therapies and unmet medical need

Oseltamivir (BID oral dosing for 5 days) and zanamivir (BID inhaled dosing for 5 days) are approved for the treatment of influenza A and B in the EU. These neuraminidase inhibitors (NAIs) have a modest effect on the duration of symptoms in subjects with uncomplicated influenza. Oseltamivir is also widely recommended and used for treatment of severe influenza although its efficacy in this setting has not been established. Reports of resistance to one or other of these NAIs exist but rates appear to be very variable and not yet problematical in the EU. The most common mutation associated with oseltamivir resistance (H275Y in N1 or H274Y in N2) does not confer resistance to zanamivir.

In some countries rimantidine is available for treatment of influenza A but resistance is more of a problem than for the NAIs such that circulating H3N2 and the last pandemic H1N1 strain are generally resistant. Generally, agents of the adamantane class are no longer recommended.

There remains an unmet need for antiviral agents that can be used to treat severe influenza infections due to a wide range of influenza A and B types that are not affected by resistance to NAIs or adamantanes.

3.1.3. Main clinical studies

This application rests on a single pivotal study (0722T0621), in which single IV doses of 300 mg and 600 mg peramivir were compared with placebo in Japanese adults with uncomplicated influenza.

Study 0815T0631 compared 300 mg and 600 mg single IV doses of peramivir with the licensed regimen of oseltamivir. There was no parallel randomised placebo group. Interpretation of the demonstration of non-inferiority for peramivir vs. oseltamivir for time to alleviation of symptoms (TTAS) in this study is based on the prior demonstration of superiority of oseltamivir vs. placebo for TTAS in adult populations.

The 300 mg peramivir single dose IM studies vs. placebo can be viewed as supportive based on PK studies that indicated similar AUCs of peramivir after IV and IM doses. The 600 mg IM dose study vs. placebo failed to show a benefit for peramivir due to the high proportion of cases due to H1N1 with the H275Y mutation in the season and region in which it was conducted.

An interim report is available from one ongoing study (BCX1812-305) of safety and PK in children with uncomplicated influenza in which there is 4:1 randomisation to peramivir or oseltamivir. Children from 2-<13 years received 12 mg/kg peramivir up to 49 kg (those 50kg and above received 600 mg); older children received 600 mg regardless of weight. These safety and PK data are proposed to support use from 2 years of age.

3.2. Favourable effects

In the pivotal study 0722T0621 conducted in 2008/9 in Japanese patients aged <65 years with confirmed influenza (ITTI population), the observed median TTAS were 59.1 h in the 300 mg group and 59.9 h in the 600 mg group vs. and 81.8 h for placebo, representing differences of ~22 h, i.e. less than one day. This treatment effect was obtained in a population in which ~70% of patients presented at 12-36 and mostly 12-24 h after symptom onset, noting that the greatest difference between peramivir and placebo occurred in those enrolled at 12-24 h. Also, ~85% had symptom scores <15 at baseline, >70% had wild-type influenza A/H1N1 and none had the H275Y mutation. The results of the primary analysis were supported by several other endpoints including the time to resumption of normal activities (125.6 and 127.4 hours in the peramivir groups vs. 169.1 hours in the placebo group, i.e. about a 40-h difference).

3.3. Uncertainties and limitations about favourable effects

In the pivotal study 0722T0621 there are limitations of the study population that have been mentioned in the SmPC. The data pertain to A/H1N1 or A/H3N2; only three patients had influenza B. Efficacy against influenza B cannot be substantiated and this has been stated in the SmPC.

In the 300 mg single dose IM studies, which were conducted in the same pre-pandemic season as 0722T0621, the population was mainly non-Asian and H3N2 predominated. The median difference in TTAS for 300 mg peramivir vs. placebo was ~21 h, which is very similar to the difference in the pivotal study, but the analyses showed no or borderline statistical significance depending on whether the factors smoking, influenza type and season were included. Subgroup analyses suggested a benefit for active treatment in current smokers, in the 2007 Southern Hemisphere winter and in those with influenza A. In the subset with influenza B there was no benefit for peramivir (and no effect on shedding). There was no impact on time to resume normal daily activities in the ITTI or in various subgroups of the population. The results do not provide strong support for a single 300 mg IV peramivir dose.

In BCX1812-212, also a non-Asian study, A/H1N1 carrying the H275Y mutation was present in 116/133 (87%) in the peramivir group and 129/149 (87%) in the placebo group in the primary analysis (ITTI-A) population, resulting in a mean baseline peramivir IC_{50} value of 70 nM across all strains. In the face of the high proportion of patients with these peramivir-resistant viruses, the study failed to show a benefit for 600 mg peramivir over placebo overall or in various sub-groups except in female patients.

Although the study failed to support the pivotal study, the results are very important for understanding the real clinical impact of the H275Y mutation on the clinical effect of peramivir. This limitation, noting that the same mutation gives resistance to oseltamivir, has been reflected in the SmPC.

Across the peramivir single dose studies vs. placebo there is an almost complete lack of any data in patients aged > 65 years and the number has now been stated in the SmPC. However, there is no major obstacle to the extrapolation of efficacy to those above > 65 years of age.

In 0815T0631, peramivir had a similar or slightly better effect on the various efficacy endpoints than did oseltamivir. The lack of a randomised placebo group means that a demonstration of non-inferiority based on the primary endpoint should be viewed with some degree of caution. The median TTAS for the peramivir 300 and 600 mg and oseltamivir groups were 80.2, 83.6 and 88.8 h, respectively, for A/H1 vs. 69.9, 70.6 and 75.1 h for A/H3. Most A/H1 viruses were insusceptible to the NAIs so the difference in effects for H3 vs. H1 could suggest that the two NAIs had comparable effects against susceptible H3N2 viruses. Furthermore, the proportion of patients with subtype A/H3 was significantly higher in Korea (62.9% to 75.0% per group), where the median TTAS values were lowest (68.4, 49.7 and 63.4 h) whereas in Japan, with H3N2 in only ~25% per group and H1N1 in ~55%, the median TTAS values were 78.0, 80.7 and 80.6 h for peramivir and oseltamivir dose groups.

3.4. Unfavourable effects

Some degree of caution is required when making comparisons between peramivir groups and the 441 patients who received placebo since this total number comes from 4 different studies and only 100 received an IV placebo. Caution is also needed when comparing peramivir with the oseltamivir group since the latter is confined to the population enrolled in a single study. In addition, the denominator for those who received a single 600 mg IV dose is 467 and the denominator for a single IV dose of placebo in these trials is 100. Nevertheless, the general overall picture suggests few differences between active and placebo groups for individual AEs and ADRs, with some exceptions of note. Also, a single intravenous infusion of peramivir 600 mg does not appear to cause major problems of local tolerance.

The most frequently observed TEAEs in all peramivir-treated patients were diarrhoea, decreased neutrophil count and increased blood glucose. Only hyperglycaemia reported as an AE occurred at a higher rate with peramivir than in the oseltamivir group and the difference for peramivir vs. placebo

was minimal. In contrast, the rates for glycosuria reported as an AE were lower for peramivir vs. oseltamivir but higher for both actives vs. placebo.

Since oseltamivir is given orally for 5 days it is no surprise that it was associated with higher rates of upper gastrointestinal events compared to the single parenteral peramivir dose. In contrast, the rates for diarrhoea were similar across all active and placebo groups, which may be due to the impact of the background rates associated with influenza and/or with symptomatic treatments. Whereas no placebo patients had reduced neutrophils reported as an AE, the rate for peramivir (~5.5%) was slightly less than that for oseltamivir (8.8%) and did not increase with dose.

AEs of moderate or severe intensity did not occur at a higher rate with peramivir vs. oseltamivir or placebo. AEs considered drug-related mostly occurred at similar rates for peramivir vs. placebo or oseltamivir, especially when these comparisons are made only within single randomised studies. However, the pattern of differences for AE reports of reduced neutrophil counts was again apparent for the ADRs.

In the population that is most relevant to the current application there was no excess of deaths or SAEs with peramivir vs. placebo.

When viewed within studies there did not seem to be differences between peramivir and placebo for effects on haemoglobin but there was an effect of peramivir with a reduction in neutrophils vs. placebo as mentioned above for AE rates. This has been reflected in the SmPC.

The range of hypersensitivity reactions to peramivir include anaphylaxis and severe skin reactions as well as non-severe rashes and urticaria. These have been reflected in the RMP and SmPC.

3.5. Uncertainties and limitations about unfavourable effects

Although many reports of impaired renal function came from patients with confounding factors, it cannot be ruled out that peramivir could exacerbate or contribute to renal impairment. This has been reflected in the SmPC.

Very few elderly patients were included in the single dose peramivir studies. In the 2% of patients aged ≥ 65 years in the adult uncomplicated influenza studies the TEAE reporting rates were highest in those aged ≥65 years, reflecting the rates for those aged ≥ 65 to < 75 years. Related TEAEs were reported for 21.9% aged < 65 and 30.2% aged ≥ 65 years. The range of AEs reported was similar to that in younger subjects and there were no special concerns but with so few patients treated it is not possible to derive a definitive safety profile in the elderly.

There were no new safety concerns arising from the study in children with uncomplicated influenza but the clinical trial data are limited. The post-marketing data do suggest that neuropsychiatric ADRs may occur especially in children but the relationship to peramivir remains unclear.

3.6. Effects Table

Table 56. Effects Table for peramivir for treatment of uncomplicated influenza.

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Median TTAS	Based on scores for 7 symptoms in the ITTI (co nfirmed influenza) population	Hour	Peramivir 600 mg IV 59.9h 300 mg IV 59.1h	Placebo 81.8h; Diff -21.9h and -22.7h	Study was limited to healthy Japanese adults aged < 65 years with total symptom scores at baseline mostly < 15 and 40% were enrolled 12-24h after symptom start with < 20% enrolled after 36 h. Also > 70% had H1N1.	0722 T0621
Median TTAS	same	Hour	Peramivir 600 mg IV 81h 300 mg IV 78h	Tamiflu 81.8h; NI demonstr ated	Study was limited to Asian adults, 97% aged < 65 years. Baseline scores were mostly <15 and 75% were enrolled < 36 h after symptom start. Also 55% had H1N1 and 30% H3N2 with different median TTAS by A type and by country reflecting prevalence of A types.	0815 T0631
Unfavourable Effects						
Decrease in the neutrophil count	Percentage with AE reported	%	~6% peramivir ~3% oseltamivir	Placebo 0%	Difference supported by the laboratory abnormalities not reported as AEs	
Hyperglyc aemia and/or glycosuria	Percentage with AE reported	%	5.3% and 1.5% peramivir 3.3% and 2.2% oseltamivir	Placebo 4.8% and 0.2%		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The evidence for efficacy comes from a single placebo-controlled study in mildly unwell Japanese adult patients aged <65 years, most of whom had influenza A/H1N1. The primary analysis indicated a statistically significant shortening of the median TTAS in the 600-mg group. The observed effect on median TTAS was 21.5 h. The greatest difference between peramivir and placebo occurred in those

enrolled at 12-24 h. There was a greater effect (40 h reduction) of peramivir on time to resumption of normal activity. This study can support an indication for *treatment of uncomplicated influenza*.

This single pivotal study is not strongly supported by the two placebo-controlled studies in which a single 300 mg IM dose was given, although a benefit was demonstrated in some subgroups. The study that compared 600 mg IM with placebo showed no benefit of peramivir but this result was driven by the prevalence of the H275Y mutation in A/H1N1 in the season in which the study was conducted. The study that compared 300 mg and 600 mg IV doses of peramivir with oseltamivir showed similar TTAS values across the groups.

3.7.2. Balance of benefits and risks

The magnitude of benefit of a neuraminidase inhibitor in uncomplicated influenza is not expected to be very large. The shortening of the duration of symptoms by peramivir based on median TTAS is just under one day but this degree of benefit may be considered important at least for some patients. There is a risk of serious hypersensitivity reactions. The exact frequency of such reactions is not known but they seem to be relatively rare. The limitations of the benefits of peramivir and the uncertainties surrounding the risks have been reflected adequately in the SmPC and RMP.

The benefit-risk relationship could be considered favourable for the final proposed indication.

3.7.3. Additional considerations on the benefit-risk balance

The product is presented as a multipack 3 x 200 mg vials. According to the applicant this presentation was developed to allow flexibility in dosing to patients with renal impairment and paediatric patients, who would require lower doses; and patients with normal renal function for whom the recommended dose is 600 mg. This raised concerns during the evaluation regarding the potential for contamination, confusion, prescription errors and the risk of overdose/underdose. In order to further avoid unnecessary confusion, the CHMP recommends the applicant to consider changing the package size to 1 vial of 20 mL (200 mg) or create a new strength of Alpivab 600 mg in one vial of 60 mL.

3.8. Conclusions

The overall B/R of Alpivab is positive for the treatment of uncomplicated influenza in adults and children from the age of 2 years.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Alpivab is favourable in the following indication:

“Treatment of uncomplicated influenza in adults and children from the age of 2 years (see sections 4.4 and 5.1)”

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 the first periodic 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:

1. At the request of the European Medicines Agency;
2. 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 peramivir is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0340/2016 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.