Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Peramivir

Proprietary Product Name: Rapivab

Sponsor: Seqirus Pty Ltd

November 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
α1-MG	α1-microglobulin
ACM	Advisory Committee on Medicines
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration – time curve
β2-MG	β2-microglobulin
BD	Twice daily
CK	Creatine kinase
CL	Clearance
CrCl	Creatinine clearance
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
CMI	Consumer Medicines Information
CPE	Cytopathic effect
FI	Fluorescence intensity
H1	Haemagglutinin 1 subtype
H275Y	Ssubstitution of tyrosine for histidine at NA position 275
H3	Haemagglutinin 3 subtype
H5	hemagglutinin 5 subtype
HA	Haemagglutinin
IC_{50}	50% inhibitory concentration
ITTI	Intent-to-treat infected
IV	Intravenous

Abbreviation	Meaning
ISS	Influenza Symptom Severity
IIWS	Influenza impact wellbeing scale (evaluation of activity)
MDCK	Madin-Darby canine kidney cell line
MES 2	[N-morpholino]ethanesulphonic acid
MHRD	Maximum recommended human dose
MUNANA	2-(4-methlyumbelliferyl)-α-D-N-acetylneuraminic acid
NA	Neuraminidase
NAI	Neuraminidase enzyme inhibition
NA	Polymerase chain reaction
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PI	Product Information
PK	Pharmacokinetics
PPK	population pharmacokinetic analysis
QTc	QT corrected
QTcF	QT corrected (using Fridericia method)
SD	Standard deviation
TCID50 50%	Tissue culture infective dose50
V_{ss}	Distribution volume at steady state
WHO	World Health Organization
WT	Wildtype

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	16 March 2018
Date of entry onto ARTG:	21 March 2018
ARTG number:	285559
, *Black Triangle Scheme*	Yes. This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Active ingredient:	Peramivir
Product name:	Rapivab
Sponsor's name and address:	Seqirus Pty Ltd 63 Poplar Road Parkville VIC 3052
Dose form:	Concentrate for intravenous infusion
Strength:	200 mg / 20 mL (10 mg/1 mL)
Container:	Glass vial
Pack size:	Three vials per pack
Approved therapeutic use:	*Rapivab is indicated for the treatment of acute influenza infection in adults and children 2 years and older who have been symptomatic for no more than two days. Clinical trials have not established the efficacy of repeated doses of Rapivab in patients with serious influenza requiring hospitalisation.*
Dosage (proposed):	In adult and adolescent patients 13 years of age or older – a single 600 mg dose, administered via intravenous infusion for 15 to 30 minutes. In paediatric patients 2 to 12 years of age – 12 mg/kg (up to a maximum dose of 600 mg), administered via intravenous infusion for 15 to 30 minutes. For persons hospitalised with influenza infection, one dose per day is recommended for a period of up to 5 days.
Route of administration:	Intravenous (IV)

Product background

This AusPAR describes the application by the sponsor to register peramivir, a new IV anti-viral medication. Peramivir (trade name: Rapivab) is a selective inhibitor of influenza viral neuraminidase (NA). The proposed indication is as follows:

> *Rapivab is indicated for the treatment of infections due to influenza A and B viruses in adults and children 2 years and older. Treatment should commence as soon as possible, but no later than 2 days after the onset of the initial symptoms of infection.*

Two classes of influenza antiviral agents are approved in Australia: adamantanes and neuraminidase inhibitors (NAIs). Adamantanes have no activity against influenza B virus. In recent years widespread resistance to adamantanes has been described in viruses of the H3N2 subtype, and the influenza A (H1N1pdm09) strain also demonstrated adamantine resistance. This class of drugs is currently not recommended by the United States (US) Centers for Disease Control and Prevention (CDC) for treatment of influenza.

NAIs have activity against both influenza A and B viruses. Approved NAIs include zanamivir inhalation, and oral oseltamivir phosphate (OSE). There are 2 NAIs recommended for use in Australia for influenza infection: Tamiflu (oseltamivir, capsule/suspension) and Relenza (zanamivir, oral inhalation). Tamiflu is indicated for use in adults and children, including full-term neonates, while Relenza is indicated for use in adults and children aged 5 years and older.

There is a need for an effective treatment for influenza patients who present in the urgent care and emergency room settings, and in patients for whom compliance and effective delivery of an oral or inhaled medication is of concern.

The recommended dose of Rapivab in adult and adolescent patients 13 years of age or older is a single 600 mg dose, administered via intravenous infusion for 15 to 30 minutes. The recommended dose of Rapivab in paediatric patients 2 to 12 years of age is 12 mg/kg (up to a maximum dose of 600 mg), administered via intravenous infusion for 15 to 30 minutes. For persons hospitalised with influenza infection, one dose per day is recommended for a period of up to 5 days.

Regulatory status

Table 1 shows the marketing authorisation applications for peramivir globally at the time of this submission to TGA.

Table 1: Overseas regulatory status for peramivir at the time of this submission

Country / Region	Date of submission	Status	Indications (approved or requested)	Other information
EU - centralised	December 2016	Under evaluation	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.	Trade name: Alpivab Rapporteur: UK Co-rapporteur: Norway

Country / Region	Date of submission	Status	Indications (approved or requested)	Other information
USA	December 2013	Approved	Rapivab is an influenza virus neuraminidase inhibitor indicated for the treatment of acute uncomplicated influenza in patients 18 years and older who have been symptomatic for no more than two days.	The indication for use in children aged 2 years or older was under evaluation at the time of the TGA submission and approved by FDA in September 2017
Canada	January 2016	Approved	Rapivab is indicated for the treatment of acute uncomplicated influenza in patients 18 years and older.	N/A
Japan	January 2009	Approved	Influenza A and B viral infections	Trade name: Rapiacta
South Korea	August 2009	Approved	Influenza A and B viral infections	Trade name: Peramiflu
Taiwan	February 2015	Approved	Influenza A and B viral infections	Trade name: Rapiacta

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this submission and which are detailed and discussed in this AusPAR.

Table 2: Registration timeline for this submission

Description	Date
Submission dossier accepted and first round evaluation commenced	28 February 2017
First round evaluation completed	28 August 2017
Sponsor provides responses on questions raised in first round evaluation	30 October 2017

Description	Date
Second round evaluation completed	24 November 2017
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	2 January 2018
Sponsor's pre-Advisory Committee response	15 January 2018
Advisory Committee meeting	1-2 February 2018
Registration decision (Outcome)	16 March 2018
Completion of administrative activities and registration on ARTG	21 March 2018
Number of working days from submission dossier acceptance to registration decision*	218

* Legislative timeframe is 255 working days (see *Therapeutic Goods Regulations 1990.*

III. Quality findings

Introduction

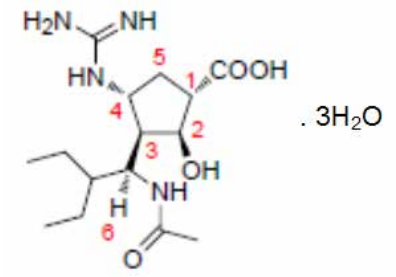
The proposed product is a clear, colourless, sterile, isotonic solution, presented in 20 mL clear flint Schott vials fitted with rubber stoppers and royal blue flip-off seals. Each 1 mL contains 10 mg peramivir (on an anhydrous basis) in 0.9% sodium chloride solution, with a final pH of 5.5 – 8.5, adjusted with sufficient quantities of sodium hydroxide and/or hydrochloric acid as required. The presentation provides 200 mg of peramivir in each 20 mL vial. The vials are presented in cartons; each carton is proposed to contain three vials.

Drug substance (active ingredient)

Peramivir, IUPAC (1*S*,2*S*,3*R*,4*R*)-3-[(1*S*)-1-(acetylamino)-2-ethylbutyl]-4-(carbamimidoylamino)-2-hydroxycyclopentane carboxylic acid, trihydrate, is a white to off-white or slightly beige powder.

The *R*-enantiomer of the drug substance is active.

Figure 1: Chemical structure



Molecular Formula: $C_{15}H_{28}N_4O_4\ 3H_2O$

Molecular Weight: 382.45 (relative molecular mass = 382.00)

pKa: 3.8 and >12.0

Partition coefficient: log D (*n*-octanol/pH 7.4) is -0.99

Peramivir is sparingly soluble in deionised water and in 0.9% sodium chloride solution. Solubility in organic solvents is generally low. The pH solubility profile in aqueous media show the drug substance is freely soluble at pH below the pKa of 3.8.

Peramivir drug substance is produced by chemical synthesis. The crystal form obtained by the manufacturing process is Form A (trihydrate). There are 5 chiral centres and control of chiral purity is achieved by chiral controls on a key starting material, and intermediates. The absolute stereochemistry was confirmed by single crystal X-Rayp diffraction study. Particle size is not considered important since the drug substance is fully dissolved during finished product formulation.

The drug substance specifications are sufficient to ensure the quality and consistency of the active pharmaceutical ingredient.

Drug product

The proposed peramivir injection is a clear, colourless, sterile, isotonic solution for intravenous administration, presented in a 20 mL clear flint Schott vial of Type I glass. Each 20 ml vial contains 200 mg of active peramivir in 0.9% (weight for weight (w/w)) sodium chloride solution. The product contains the excipient sodium chloride and Water for Injections, and may contain diluted hydrochloric acid and/or sodium hydroxide for pH adjustment to pH 5.5 to 8.5. The osmolality is in the physiological range.

The finished product specifications include tests for description, identification, assays, control of impurity levels, pH, sterility, bacterial endotoxins, particulate matter, extractable volume and osmolality. The finished product specifications are sufficient to ensure the quality of the finished product at release and throughout the shelf life. A shelf life of 60 months is supported by the stability data, when the product is stored at 25 °C.

Chemistry and quality control aspects are acceptable.

Quality summary and conclusions

Valid Good Manufacturing Practice (GMP) clearances are not in place for three of the four overseas sites of manufacture. It is anticipated that this will be resolved prior to the end of the anticipated decision phase.

Approval is recommended from a chemistry and quality perspective.

IV. Nonclinical findings

Introduction

Peramivir is a cyclopentyl transition-state sialic acid analogue influenza virus NAI which was approved by US FDA in late 2014 for the treatment of acute, uncomplicated influenza in patients 18 years and older. Pediatric use has not been approved in the USA (the indication for use in children aged 2 years or older was under FDA evaluation at the time of the submission to the TGA). Structurally and chemically related NA inhibitors include oseltamivir carboxylate (Tamiflu), zanamivir (Relenza) and laninamivir (Inavir).

The sponsor's rationale for an IV peramivir product is: (a) the need for an effective treatment for influenza patients who present in the urgent care and emergency room settings; and (b) the need for an effective treatment for influenza patients for whom

compliance and effective delivery of an oral or inhaled medication is of concern; such patients may include those who cannot comply with oral medications or those with gastrointestinal symptoms that could impair drug bioavailability. Peramivir has not been developed for influenza prophylaxis.

The US FDA Pharmacology and Microbiology/Virology Reviews form the main body of this assessment.

The nonclinical development program was in accordance with the US FDA's *Guidance for Industry Influenza: Developing Drugs for Treatment and/or Prophylaxis* (2011). The oral formulation development failed due to low bioavailability. In the USA, IV and IM peramivir products were subsequently developed based on a Health and Human Services Biomedical Advanced Research and Development Authority contract. An IV injectable product was initially approved in Japan in 2010. Two trials in normal healthy humans demonstrated bioequivalence between IV and IM peramivir; however, IM product development was abandoned due to dose related muscle irritancy (relatively mild effect in the nonclinical repeat dose studies).

Pharmacology

Primary pharmacology

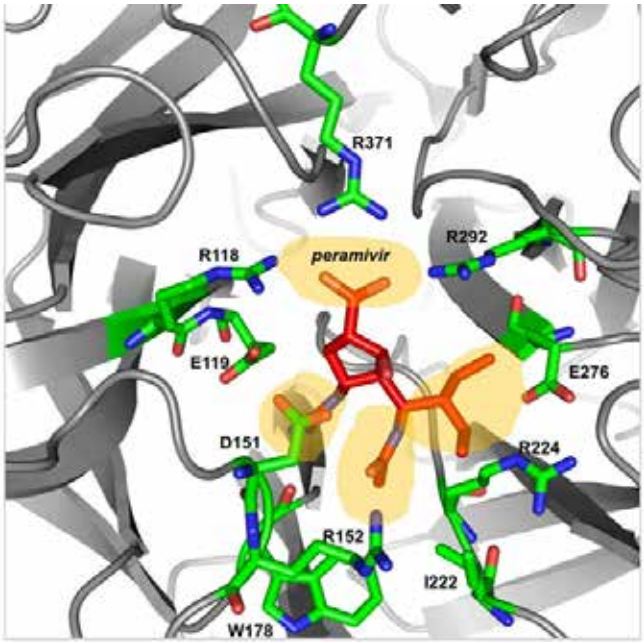
General comments

Influenza virus NAs are a family of glycoside hydrolase enzymes found on the surface of influenza viruses that facilitate the release of progeny virus from the host cell membrane. NA inhibitors interfere with the release of progeny influenza viruses from infected host cells, thus potentially limiting the spread of the infection within the respiratory tract.

Since replication of influenza virus in the respiratory tract reaches its peak at approximately 24 to 72 h after the onset of disease, NAIs should be administered as soon as possible after infection for optimal efficacy.

Peramivir blocks the four binding pockets of the influenza virus NA complex (as shown in Figure 2, below).

Figure 2: Peramivir blocking of the 4 binding pockets (yellow shaded) of the enzyme active site of the influenza A/H7N9 neuraminidase complex



There is no evidence for efficacy of Rapivab in any illness caused by agents other than influenza viruses. Rapivab is not a substitute for influenza vaccination and the use of Rapivab must not affect the evaluation of individuals for annual vaccination.

Neuraminidase binding affinity in vitro

Peramivir (concentration approximately 0.002 x maximum recommended human dose (MHRD) $C_{max\ unbound}$) had a higher in vitro binding affinity (on a mass/mass basis) for influenza A/NWS/33 (H1N1) and H1N9 (A/NWS/G70c) NAs compared with oseltamivir carboxylate and zanamivir. Oseltamivir carboxylate did not impact the binding affinity of peramivir to influenza virus NA and v/v.[1] Peramivir dissociation from N9 subclass NA ($T_{½}$ > 17h) was slower compared with oseltamivir carboxylate and zanamivir ($T_{½}$ approximately 1.25 h), implying a longer duration of action.

Neuraminidase selectivity in vitro

Peramivir was highly selective for influenza virus NAs compared with bacterial NAs. The peramivir 50% inhibitory concentration (IC_{50}) for influenza B/Hong Kong/5/72 NA was approximately ≥ 22000x lower than its IC_{50} for the bacterial NAs (*Vibrio cholerae, Arthrobacter ureafaciens*, and *Streptococcus pneumonia*). Inhibition of *Vibrio cholera* at the peramivir MHRD is theoretically possible (IC_{50}: MHRD $C_{max\ unbound}$ approximately 0.3), although unlikely in practice given the IV dosing route and the drug's pharmacokinetics.

In a second study, peramivir displayed no inhibition of *Salmonella typhimurium, Clostridium perfringens* and *Vibrio cholerae* NAs and no inhibition of rat liver sialidases.

Activity at mammalian sialidase homologues in vitro

Based on rat data, peramivir at the MHRD may have off target inhibition of liver sialidases (rat liver sialidase IC_{50}: $Cmax_{unbound}$ > approximately 3; unknown human clinical relevance; no toxicology correlates). Peramivir was inactive (IC_{50} > 5000μM) against human sialidases NEU1, NEU3 and NEU4. Peramivir at the MHRD may produce minor inhibition of human NEU2 (NEU2 IC_{50}: $Cmax_{unbound}$ approximately 2; of unknown human clinical relevance; no nonclinical toxicology correlates).

In a separate study utilising human placental lysosomal sialidase, the peramivir IC_{50} was approximately 190000x higher than the influenza B/Lee/40 NA IC_{50}.

Neuraminidase inhibitory activity of peramivir in vitro

Peramivir IC_{50} values against influenza A/H1N1, influenza A/H3N2, and influenza B virus (clinical isolates) neuraminidases were all less than approximately ≈0.1 x the MHRD $C_{min\ unbound}$. The median neuraminidase inhibitory activity (IC_{50} values) of peramivir in biochemical assays against influenza A/H1N1 virus, influenza A/H3N2 virus, and influenza B virus clinical isolates were 0.16 nM (n = 44; range 0.01 to 1.77 nM), 0.13 nM (n=32; range 0.05 to 11 nM), and 0.99 nM (n = 39; range 0.04 to 54.2 nM), respectively, in fluorescence neuraminidase inhibition assays.

Antiviral activity of peramivir in vitro

Overall, peramivir had comparable or higher antiviral potency compared with ribavirin, oseltamivir carboxylate and zanamivir. The antiviral activity (based on inhibition of cytopathic effect (CPE) and/or cytotoxicity and/or virus titre and/or inhibition of viral replication and/or viral nucleoprotein expression) of peramivir against laboratory strains and clinical isolates of influenza viruses in cell culture is summarised.

[1] Bantia S, *et al.* Antiviral Res. 2011 Sep; 91(3):288-91.

Table 3: In vitro antiviral activity of peramivir

Strain (number of samples evaluated)	EC_{50} range	$C_{min\ unbound}$: EC_{50}*	Minimum human pharyngeal mucous concentration§: EC_{50}* at t=2h	Minimum human pharyngeal mucous concentration§: EC_{50}* at t=12h
A/H1N1 (*n*=24)	0.09- >100 nM	≥≈1	≥≈53	≥≈2
A/H2N2 (*n*=2)	<1.0 - 1.4 nM	≥≈71	≥≈3770	≥≈157
A/H3N2 (*n*=30)	0.01 – >100 nM	≥≈1	≥≈53	≥≈2
A/H5N1 (*n*=3) (including avian)	0.01-0.3 nM	≥≈333	≥≈17600	≥≈700
Avian A/H5N3 (*n*=1)	24.1 nM	≈4	≥≈219	≈9
B (*n*=28)	0.06-120 nM	≥≈1	≥≈44	≥≈2

*Highest EC50 was used resulting in a conservative ratio; § 5.28 µM at 2h 0.22µM at 12h following a 600 mg IV peramivir dose, based on Kohno S, et al. Antimicrob Agents Chemother. 2011; 55(6):2803-2812 and Alame MM, et al. Front Microbiol. 2016 31(7):450.

While substantial strain differences (up to approximately 12000x depending on strain and measurement technique) in peramivir 50% effective concentrations(EC_{50}) were present, the $C_{min\ unbound}$:EC_{50} ratio remained at ≥ approximately 1 and the human pharyngeal mucous concentration: EC_{50} ratios at 2 h after a 600 mg IV peramivir dose were ≥ approximately 40, and ≥ approximately 2 at 1 2h post dose.[2] Irrespective of the large variation in viral sensitivity to peramivir, at least some degree of efficacy at a key site of action (pharyngeal mucosa) is likely.

While comparative EC_{50} data for peramivir, oseltamivir carboxylate and zanamivir are available, strict quantitative relative potency comparisons are difficult due to methodological differences. In an in vitro cytopathic effect study, peramivir was more potent than oseltamivir carboxylate and zanamivir against five highly pathogenic avian influenza viruses (H5N1 and H7N7). When tested against 2 viruses for each of the 9 avian influenza NA subtypes peramivir was comparable with, or more potent than, oseltamivir carboxylate or zanamivir.

Peramivir was inactive against adenovirus, rhinovirus, respiratory syncytial virus, parainfluenza virus type 3, and measles virus in vitro.

Viral resistance to peramivir in vitro

Overall the in vitro serial passage antiviral selection pressure resulted in two broad patterns of resistance to peramivir: mutations in HA (12 different mutations) and mutations in NA (4 different mutations). Resistant variants were from >200 x (B/Yamagata P15) to > 10^6 x (A/H2N2)) more resistant to peramivir compared with paired wild type virus (based on plaque reduction IC_{50s}).

[2] Kohno S, *et al.* Antimicrob Agents Chemother. 2011; 55(6):2803-2812; the calculated drug concentrations in human pharyngeal mucus after administration of a IV 600-mg dose of peramivir were 5,280 nM at 2h and 220 nM at 12h.

Table 4: Amino acid substitutions following in vitro serial passage plus peramivir selection pressure

Protein	Strain / Subtype		
	A/H1N1	A/H3N2	B
HA	D129S, R208K	N63K, G78D, N145D, K189E	T139N, G141E, R162M, D195N, T197N, Y319H
NA	N58D, I211T, H275Y	--	H275Y

HA mutations in both in vitro selected and in clinical samples displayed no peramivir specific patterns and had no effect on peramivir NA IC_{50s} compared with paired wild type virus. A reassortant virus in which the HA gene of an influenza A/WSN/33 virus was substituted with the HA gene of the A/Charlottesville/31/95 virus, showed decreased susceptibility to peramivir in a plaque reduction assay. This study found that sialylation of oligosaccharide chains in the vicinity of the HA receptor-binding site likely provides a compensatory mechanism for the lack of NA activity and allowed emergence of NA deficient mutants.

The H273T NA mutation in the B/Yamagata/16/88 strain increased the peramivir NA IC_{50} by approximately 16 x. Reduced susceptibility of A/Charlottesville/31/95 (H1N1) to peramivir in vitro was also caused by deletions in RNA segment 6, which encodes NA. Some peramivir NA resistance mutations were disadvantageous, for example mutations at G119 NA resulted in an unstable NA phenotype and the A292L NA mutation resulted in decreased in vitro infectivity by approximately 450x.

Cross resistance to peramivir, zanamivir and oseltamivir carboxylate in vitro

Cross resistance in NA inhibition assays: The data for the most commonly observed NA point mutations in non-recombinant viruses is summarised in Table 5, below.

Table 5: NA point mutations and NA inhibitor resistance (non-recombinant viruses) in vitro based on NA inhibition assays

Influenza virus	NA substitution	Peramivir	Oseltamivir carboxylate	Zanamivir
A	E119V	S	S	R
	H275Y	IR	R	S
	R292K	I	R	I
B	H274Y	R	R	S
	R152K	R	R	R
	D198E/N/Y	S	S	S

R = resistant (IC_{50}>50nM); S = sensitive (IC_{50}<20nM); I = intermediate sensitivity (IC_{50}>20nM<50nM); IR = intermediate susceptibility or resistance depending on virus genetic background

Based on NA inhibition assays, NA mutations result in complex patterns of partial resistance, resistance and/or cross resistance. Notably, different virus subtypes and genetic backgrounds with the same amino acid substitution demonstrated varying

susceptibility to individual NA inhibitors, that is the viral background was often as important as the mutation.

Notably, the cut off point for resistance classification used in the table above (IC_{50} >50 nM) is > approximately 6 x 10^{-4} times the peramivir MHRD $C_{max\ unbound}$. This again implies that peramivir may retain clinical efficacy in vivo despite the present of NA point mutations and/or viral backgrounds associated with drug resistance. While resistance profiles for peramivir, oseltamivir carboxylate, and zanamivir generally differed for influenza A viruses, most of these viruses were susceptible to at least one out of the three drugs based on in vitro NA inhibition assays. Influenza B viruses (except R152K mutation) were susceptible to peramivir and/or zanamivir. All influenza B viruses with NA gene mutations (clinical and cell culture selected) were resistant to oseltamivir carboxylate.

Cross resistance in culture: The available data again demonstrated complex, strain dependent, patterns of peramivir, zanamivir and oseltamivir carboxylate cross resistance. Based on plaque reduction assays, peramivir resistant A/PR/8 (H1N1) virus displayed resistance to both zanamivir (EC_{50} increase of 20000 times compared with paired wild type virus) and oseltamivir carboxylate (EC_{50} increase of 100 times compared with paired wild type virus). Peramivir resistant X121 (H3N2) virus also displayed resistance to both zanamivir (EC_{50} increase 10000 times compared with paired wild type virus) and oseltamivir carboxylate (EC_{50} increase of 1000 times compared with paired wild type virus). Peramivir resistant B/Yamagata/16/88 virus displayed somewhat lower levels of resistance to both zanamivir (EC_{50} increase < 20 times compared with paired wild type virus) and oseltamivir carboxylate (EC_{50} increase 20 times compared with paired wild type virus). The NA deficient, peramivir resistant influenza A/Charlottesville/31/95 (H1N1) strain also displayed cross resistance to peramivir, zanamivir and oseltamivir carboxylate.

Recombinant H1N1 virus carrying the H275Y NA mutation conferred decreased susceptibility to peramivir and oseltamivir carboxylate but not to zanamivir. The recombinant H1N1 virus carrying the E119Q NA mutation demonstrated decreased susceptibility only to oseltamivir carboxylate. A recombinant pandemic H1N1/09 virus containing the N146S NA mutation had an approximately 2 times decrease in susceptibility for both zanamivir and oseltamivir carboxylate , but not for peramivir, while the D198G NA mutation conferred an approximate 10 times decrease in susceptibility to zanamivir, oseltamivir carboxylate and peramivir. A recombinant H1N1/09 virus carrying the D198G and H275Y NA mutations was highly resistant to oseltamivir carboxylate and peramivir, but not to zanamivir. In A1/Hokkaido/15/02 (H1N1), the NA Y155H mutation conferred reduced susceptibility in enzyme inhibition assays to peramivir (decrease of approximately 30 times), as well as to oseltamivir carboxylate and zanamivir (decrease > approximately 100 x) compared with wild type virus. Both the NA Y155H mutation and an HA D225G mutation rescued the peramivir susceptible small plaque phenotype of the Y155H virus, and affected receptor binding and drug susceptibility in cell culture and binding assays. The NA G141E mutation also decreased the inhibition of NA by peramivir but to lesser extent compared with the Y155H and D225G mutations. A Clade 1.1 avian H5N1 virus carrying a P154S NA mutation did not exhibit a change in susceptibility to peramivir, while a 2 to 3 times decrease in susceptibility to oseltamivir carboxylate and zanamivir was noted compared with matched wild type virus. Further, Clade 2.1 avian influenza viruses carrying I222T, I222M, or I222V NA mutations exhibited 2 to 3 times decreased susceptibility to peramivir and zanamivir and 3 ≥ 10 times decreased susceptibility to oseltamivir carboxylate compared with a reference Clade 2.1 WT avian H5N1 virus.

Viruses with decreased susceptibility have also been generated by serial passage in cell culture with zanamivir and oseltamivir carboxylate, that is, NA inhibitor drug class resistance will often (but not always) result in cross resistance to peramivir.

Notably the IC_{50} range for the influenza viruses classified as peramivir resistant (EC_{50} increased ≥ 10 times compared with wild type virus) ranged from approximately $0.5x10^{-4}$ to > 0.01 times the MHRD $C_{max\ unbound}$. This again implies that at least some antiviral activity is likely at the MHRD even for highly resistant virus strains. This is supported by the finding that peramivir remained efficacious in vivo in mice infected with A/Shandon g/09/92 (H3N2) with the K189E HA mutation (conferring an approximately 3200 times increase in peramivir EC_{50}; observed effects were not due to reversion in vivo).

Effects of combination treatment on antiviral activity in vitro

In some, but not all studies, combinations of peramivir and oseltamivir carboxylate and/or rimantadine and/or ribavirin displayed additive and/or synergistic antiviral activity in vitro. In a viral neuraminidase assay with combinations of oseltamivir carboxylate and peramivir at 0.01 to 10 nM, no significant antagonistic or synergistic interactions were observed across the range of concentrations.[3] Additive drug interactions with a narrow region of synergy occurred with combinations of oseltamivir carboxylate and peramivir at 0.32 to 100 μμM used against A/NWS/33 (H1N1) virus in vitro. A combination of rimantadine with peramivir, oseltamivir carboxylate, or zanamivir markedly reduced extracellular influenza A/New Caledonia/20/99 (H1N1) and A/Panama/2007/99 (H3N2) virus titres in vitro compared with single drug treatment.[4] The combination of peramivir and ribavirin generally produced synergistic antiviral effects against A/NWS/33 (H1N1) in vitro.

Evaluation of NA inhibitor resistant isolates from wild birds in vitro

Based on NA inhibition (H2N1, H7N1 and H9N1), avian strains with NA gene mutations did not have peramivir resistance but retained resistance against oseltamivir carboxylate.

Evaluation of NA inhibitor resistant clinical isolates in vitro

H1N1, pH1N1 and influenza B peramivir resistant strains have been detected in patients. Markers of resistance were associated with a single NA mutation in each virus strain (Q136K and H275Y for viruses of the N1 NA subtypes, R292K for viruses of the N9 subtype, R152K and D198E for influenza B viruses). The Q136K mutation likely occurred due to cell culture selection and is not regarded as a reliable susceptibility marker for human clinical isolates.

In vivo efficacy of IV dosing

Peramivir was been evaluated in mice (IV, oral, IM, intranasal), ferrets (IV, oral, IM), and cynomolgus monkeys (oral and IV). While all studies were evaluated, only the IV exposure (proposed route of administration) studies are discussed.

Mice: A single IV peramivir (1 to 10 mg/kg) dose administered 1h before intranasal inoculation resulted in dose-related, significantly ($P< 0.05$) increased survival in mice inoculated with a 100% lethal dose of A/Duck/MN/152 5/81 (H5N1; avian). 100% survival occurred following a dose of 10 mg/kg (approximately 0.05 x MHRD body surface area (BSA) comparison; 70% survival occurred with oseltamivir carboxylate 10 mg/kg BDD PO 5 days starting 4 h before inoculation).

A single IV peramivir (1 to 10 mg/kg) dose administered immediately after intranasal inoculation resulted in dose-related, significantly ($P < 0.05$) increased survival in mice infected with a 100% lethal dose of A/PR/8/34 (H1N1), A/Kumamoto/Y5/67 (H2N2), A/Victoria/3/75 (H3N2), B/Lee/40, or B/Maryland/1/59 virus. 100% survival occurred following a dose of 1 to 10 mg/kg (approximately 0.005 to 0.1 times the MHRD BSA comparison; 50 to 100% survival with oseltamivir carboxylate 10 mg/kg BD PO 5 d).

[3] Smee DF, *et al.* Antiviral Res. 2010; 88(1):38-44.
[4] Govorkova EA, *et al.* Antimicrob Agents Chemother. 2004; 48(12):4855-63.

When a highly pathogenic strain (A/Hong Kong/483/97 (H5N1)) was used, a single IV dose of peramivir administered immediately after intranasal inoculation resulted in dose-related, significantly ($p < 0.05$) increased survival in mice. However lower efficacy was observed (60% survival at 10 mg/kg, 70% survival at 30 mg/kg compared with 0% survival in control). Repeated daily IV dosing for 5 days starting immediately following inoculation improved efficacy with 100% survival achieved at 30 mg/kg/day (approximately 0.2 times MHRD; BSA comparison).

A single IV peramivir (1 to 10 mg/kg) dose administered 48h post-intranasal inoculation resulted in dose-related, significantly ($p < 0.05$) increased survival in mice inoculated with a 100% lethal dose of A/WS/33 (H1N1) virus. 100% survival occurred following a dose of 4 to 10 mg/kg (approximately 0.02 to 0.05 times the MHRD BSA comparison; survival equivalent to oseltamivir carboxylate 10 mg/kg BID PO 5d). Increasing the post-inoculation to first dose (10 mg/kg; approximately 0.05 times the MHRD; BSA comparison) interval to ≥ 72 h resulted in reduced efficacy with 0 to 10% survival occurring if dosing was delayed until 84h. Increasing the number of peramivir IV doses (2 to 4 doses over 48 to 57 h post inoculation) reduced the dose required for 100% survival to 2 mg/kg (approximately 0.01 times the MHRD; BSA comparison). Repeated daily dosing for 5d commencing 48h after viral inoculation increased the efficacy of peramivir with 90-100% survival being achieved at a dose of ≥ 1 mg/kg/day (approximately 0.005 times MHRD BSA comparison; survival equivalent to oseltamivir carboxylate 10 mg/kg BD PO 5 days).

Ferrets: A single IV peramivir IV dose (30 mg/kg; approximately 1 x MHRD, area under the plasma drug-concentration time curve(AUC) comparison; approximately 4 x MHRD C_{max} comparison) at 24 h after intranasal inoculation of female ferrets with B/Kadoma/1/2005 virus (300 $TCID_{50s}$/animal; dose induced fever and viral shedding in nasal washes; in vitro peramivir NA inhibition IC_{50} approximately 2 x 10^{-5} x MHRD $C_{max\ unbound}$) had the following effects: (a) an approximate 40% decrease in nasal wash viral titre at 2 days post-inoculation ($p < 0.05$; no significant reductions on Days 3 to 4 post-inoculation); (b)an approximate 20% decrease in nasal wash viral titre AUC from dosing to infinity ($AUC_{0-\infty}$) measured over 2 to 4 days post-inoculation; (c) significantly ($p < 0.05$) decreased body temperatures and body temperature change AUC compared with controls; (d) significantly ($p < 0.05$) increased body weight compared with controls; and (e) decreased clinical signs. Doubling the dose had little additional effect except for reducing inflammatory cell counts and protein levels in nasal wash fluid (that is, further reduces the level of respiratory tract inflammation).

Monkeys: In adolescent female cynomolgus monkeys intranasally inoculated with B/SendaiH/1051/2007 virus (2 x 10^5 TCID50; in vitro NA inhibition IC_{50} approximately 5 x 10^{-5} x MHRD $C_{max\ unbound}$), a single IV dose (30 mg/kg; approximately 2 x MHRD AUC comparison; approximately 3 x MHRD C_{max} comparison) of peramivir either immediately after or 24 h after viral inoculation resulted in significant ($p < 0.05$) reductions (> approximately 40% compared with controls) in nasal swab virus titres on Days 1, 2, 5 and 7 post-infection compared with controls. Both groups displayed significantly ($p < 0.05$) lower virus titre $AUC_{0-\infty}$ compared with controls. Peramivir administered at 24 h post inoculation was slightly more efficacious compared with peramivir administered immediately after infection. Treatment with peramivir also decreased the serum IL-6 $AUC_{0-\infty}$, but not those of TNFα or MCP-1 compared with control. Peramivir treatment had no effect on serum anti-HA antibody production.

In vivo efficacy of combination therapy in mice infected with influenza A

The IV route of exposure was not evaluated. Overall, the studies demonstrated that combination treatment with peramivir + oseltamivir carboxylate or ribavirin, or rimantadine, or favipiravir resulted in synergistic or additive effects on survival and increased post-infection survival period. In addition, improvements were generally seen in

the number of days to death, decreased weight loss, and decreased lung injury and/or increased oxygen saturation levels.

A PO (dosing for 5 days starting 4 h before viral inoculation) combination study of peramivir ± ribavirin (dosing of both drugs was at sub-therapeutic levels) was conducted in the mouse influenza A/NWS/33 (H1N1) model. Peramivir treatment alone improved survival only at the high dose (1 mg/kg/day), whereas RBV treatment alone did not improve survival at any dose tested. With all combinations (peramivir and RBV at 1 and 20 mg/kg/day, 0.32 and 20 mg/kg/d, 0.1 and 20 mg/kg/day, 1 and 6.25 mg/kg/day, 0.32 and 6.25 mg/kg/day, and 0.1 and 6.25 mg/kg/day, respectively), increased survival was observed compared with monotherapy. There was also synergy in extending the mean days to death and for increased oxygen saturation.

In the same model IM peramivir dosing alone reduced mortality at doses ≥ 0.2 mg/kg/day. Combination IM dosing with peramivir + PO oseltamivir carboxylate resulted in additive effects in terms of post-infection survival with 0.4 mg/kg/day PO oseltamivir carboxylate + 0.1 mg/kg/day IM peramivir having the greatest improvement over monotherapy with either drug alone.

In the mouse A/Victoria/3/75 (H3N2) virus model, treatment with IM peramivir (0.3, 1 and 3 mg/kg/day) ± PO rimantadine (5, 10, and 30 mg/kg/day) for 5 days starting 1 hour before viral inoculation resulted in dose-related decrease in weight loss, with synergistic effects associated with peramivir doses ≥ 1 mg/kg/day.

In mice infected with an adapted influenza A/California/04/2009 (H1N1) virus, BD treatment for 5 day with IM peramivir (0.0125 to 0.5 mg/kg/d) + PO favipiravir (10, 20, and 40 mg/kg/day) starting 4 h post-inoculation resulted in additive effects on survival compared with monotherapy. By Day 6 after 5 days of treatment with a combination of 20 mg/kg/day PO favipiravir + IM peramivir (0.1, 0.25, 0.5, and 1 mg/kg/day BID) mice had increased body weight, decreased lung weight, decreased lung haemorrhage and decreased virus titres compared with controls and in general combinations of favipiravir and peramivir had better efficacy than suboptimal monotherapy alone.

In vivo efficacy of IV peramivir in immunocompromised mice infected with influenza virus

Overall, IV peramivir displayed modest efficacy against influenza infection in cyclophosphamide treated mice and a 5 or 20 day IV peramivir regimen generally had higher efficacy compared with PO oseltamivir carboxylate.

Infection of normal and cyclophosphamide treated mice with A/Osaka/129/2009 (NWS/H1N1; $1x10^3$ $TCID_{50}$; >10 MLD_{50}) followed by IV treatment with peramivir (40 mg/kg/day; approximately 0.2 x MHRD BSA comparison; claimed to be equivalent to human AUC for 600 mg peramivir IV) for 1, 5, 10, or 20 days, (starting at 1 h post-inoculation) resulted in: (a) significantly ($p < 0.05$) increased survival rate compared with control with 10 days treatment duration; (b) significantly ($p < 0.05$) increased body weight compared with control with treatment for ≥ 10 days; (c) significantly ($p < 0.05$) decreased lung viral titre compared with control on post infection on Day 2 post infection for 5 days of treatment, on Days 2 to 10 post infection for 10 days of treatment and on Days 10 to 14 post infection for 20 days of treatment; (d) a trend ($p > 0.05$) towards decreased lung IL-6 and TNFα compared with control on Day 14 post-infection; (e) significantly ($p < 0.05$) decreased lung MCP-1compared with control on Day 14 post-infection; and (f) decreased histopathological effects in lung.

In a separate experiment using the cyclophosphamide immunosuppressed A/Osaka/129/2009 (NWS/H1N1) infected mouse model: (a) survival with peramivir (40 mg/kg/day for 20 days; approximately 0.2 x MHRD BSA comparison) decreased compared with control if treatment was delayed for > 24 h post-infection; (b) commencement of

peramivir treatment at 24 to 72 h post-infection resulted in significantly ($p < 0.05$) decreased body weight loss compared with control; (c) commencement of peramivir treatment at 24 to 72 h post-infection resulted in significantly ($p < 0.05$) lung virus titre compared with control; (d) a trend ($p > 0.05$) towards decreased lung IL-6 and TNFα compared with control on Day 14 post-infection; (e) significantly ($p < 0.05$) decreased lung MCP-1 compared with control on Day 14 post-infection; and (f) decreased histopathological effects in lung. However, apart from reducing survival, delaying treatment for 48 to 72 h post infection had no consistent effects on body weight loss, lung virus titres or lung cytokine levels.

In the cyclophosphamide immunosuppressed A/WS/33 (H1N1) infected (2×10^4 $TCID_{50}$) mouse model, IV peramivir treatment (single dose 1 to 30 mg/kg; 0.05 to 0.2 x MHRD BSA comparison) starting at 48 h post-infection was ineffective (100% mortality). Dosing at 100 mg/kg (approximately 0.5 x MHRD BSA comparison) was associated with 40% survival (significantly ($p < 0.05$) increased compared with control). Repeated IV peramivir dosing (10 to 100 mg/kg, QD x 5 days; approximately 0.05 to 0.5 x MHRD BSA comparison) starting at 48 h post-infection resulted in significantly ($p < 0.05$) increased survival (≥ 80% compared with 0% in controls with 100% survival in the 100 mg/kg QD x 5 day group). The overall ED_{50} for QD x 5 day dosing was 6.8 mg/kg/day (approximately 0.03 x MHRD BSA comparison).

In vivo efficacy of IV peramivir against infection with peramivir resistant viruses

Treatment with a single IV dose (1 to 100 mg/kg; approximately 0.005 to 0.5 x MHRD BSA comparison) immediately following inoculation of mice with recombinant influenza A/PR/8/34 (H1N1) virus (6.4×10^{-5} $TCID_{50}$; containing the mutation H275Y in the NA gene) resulted in significant ($p <0.05$) dose related increased survival compared with control. Dosing at 100 mg/kg (approximately 0.5 x MHRD BSA comparison) resulted in100% survival.

Consistent with the above, PO or IM peramivir were also efficacious against infection of mice with the following peramivir resistant influenza A viruses: A/Shandong/09/92 (H3N2) containing the K189E mutation in the HA gene and recombinant influenza A/PR/8/34 (H1N1) virus containing the H275Y mutation in the NA gene.

Virulence of viruses exposed to peramivir in vitro or in vivo

In vivo virulence of viruses generated in vitro with reduced susceptibility to peramivir and other NA inhibitors: Overall, the in vivo virulence in mice of influenza A viruses with reduced susceptibility to peramivir (A/PR/8/34 P-15 R2A virus with HA mutations R208K and D129S; A/Singapore/1/57 (H2N2) virus D15*(1812)RS of 11-3-99 with mutations in both the HA (G130/135D H2/H3) and NA (R292K) genes) generated by passage in cell culture was similar to or less than that of WT viruses, based on lung titre, lung consolidation, and/or survival.

Paradoxical results were obtained with influenza B viruses. Influenza B/Yamagata/15/88 (Passage #15; R2A) variant virus with HA mutations T139N, G141E, R162M, D195N and Y319H, and NA mutation H274Y was more virulent that matched wild type virus in one experiment but of equal virulence in a repeat study.

Other studies

Peramivir (concentration ≤ approximately 11x MHRD $C_{max\ unbound}$) displayed little or no mammalian cell cytotoxicity in vitro.

Based on studies in A/WS/33 (H1N1) infected mice, the efficacy of IV peramivir is most closely correlated with plasma AUC and not dosing schedule.

Secondary pharmacodynamics, safety pharmacology and pharmacodynamic drug interactions

Overall there are no nonclinical secondary pharmacodynamics or safety pharmacology effects of concern. All studies were validated by the appropriate use of controls. No pharmacodynamic drug interaction studies were supplied (except as discussed in the primary pharmacology section).

Relatively low concentrations of peramivir (approximately 1 x 10^{-4} times $C_{max,unbound}$) had pharmacologically negligible binding to and/or inhibition of adenosine, adrenergic, cannabinoid, dopamine, GABA, glutamate, histamine, muscarinic, opiate, serotonin, σ or vasopressin receptors, no pharmacologically relevant binding to calcium and potassium channels and no pharmacologically relevant binding at serotonin, monoamine and dopamine transporters. Binding inhibition >20% only occurred at human alpha-1A-adrenergic (25.46%) and human serotonin 5HT2B (40.42%) receptors.

The CNS, cardiovascular, respiratory, gastrointestinal and renal system safety pharmacological properties of peramivir were evaluated.

PO dosing of peramivir at ≤300 mg/kg had no effect on spontaneous locomotion in mice. No peramivir-associated adverse effects were observed in a mouse Irwin screening study at PO doses up to 100 mg/kg QD for 14 days. Likewise no peramivir-associated adverse effects were detected in a functional observational battery (FOB) study in rats at IV doses up to approximately 1 x MHRD (BSA comparison). Negative FOB findings were also recorded in the 26 week repeat IM dose rat toxicity study at doses up to 75 mg/kg IM weekly.

Peramivir at up to the highest feasible concentration (≤ approximately 3 x MHRD $C_{max,unbound}$) had no detectable on hERG channel currents in vitro. Peramivir at concentrations ≤ approximately 3 x MHRD $C_{max,unbound}$ had no effect on cardiac action potentials in isolated guinea pig papillary muscle under normokalaemic conditions. IV peramivir at doses ≤ approximately 0.1 x MHRD (BSA comparisons) had no adverse haemodynamic or electrocardiographic effects in the anesthetised rat model. Similarly, IV peramivir at doses of ≤ approximately 0.2 x MHRD (BSA comparisons) had no effect on heart rate or mean arterial pressure in the anesthetized guinea pig model. In the acutely prepared, open-chest, anesthetized dog model, intraduodenal administration of 100 mg/kg of peramivir did not induce adverse haemodynamic or electrocardiographic changes. IV dosing peramivir at ≤ approximately 1 x MHRD (BSA comparison) to telemetered monkeys also did not result in adverse haemodynamic or electrocardiographic changes. No adverse effects on the ECG were noted in IV dosed monkeys with exposures up to ≤ approximately 29 x MHRD (AUC comparison).

In the rat whole body plethysmography model IV doses of peramivir at ≤ approximately 1 x MHRD (BSA comparison) had no adverse effects on respiratory parameters. Likewise no adverse effects on respiratory parameters were noted in anesthetized guinea pig model at doses ≤ approximately 0.2 x MHRD (BSA comparison).

PO peramivir at doses ≤ 300 mg/kg had no adverse effects on gastrointestinal propulsion in the mouse charcoal meal model and no adverse effect on urine volume or urine electrolyte concentrations in rats.

Potential interference with the efficacy of live attenuated influence vaccinations was not studied in the nonclinical dossier. The US label states that:

> *Live attenuated influenza vaccine (LAIV), intranasal: Avoid use of LAIV within 2 weeks before or 48 hours after administration of Rapivab, unless medically indicated.*

A live attenuated intranasal influenza vaccine is registered in Australia (FluMist quadrivalent influenza virus vaccine nasal spray applicator).

As noted in the draft PI, the sponsor does not consider peramivir as a substitute for influenza vaccination.

Pharmacokinetics

Peramivir pharmacokinetics was evaluated following IV, IM and PO dosing. While all studies were evaluated, the emphasis of this section of the assessment is on the IV studies.

The core features of the clinical pharmacokinetics of peramivir in humans, as claimed by the sponsor, are: dose proportionality over a wide range of IV doses, distribution into the extracellular fluid spaces (including tissue compartments of interest with respect to activity against influenza), multi-exponential decline in plasma concentrations over time, no significant metabolism in humans, extensive clearance of parent drug via the renal route of elimination, and low risk of drug-drug interaction. The overall nonclinical pharmacokinetic properties of IV peramivir in the evaluated animal models are broadly consistent with the human situation. However, C_{max} and $AUC_{0\text{-}24h}$ were substantially less than dose proportional in the PO 2 year rat carcinogenesis study and plasmatic accumulation occurred. While sampling was performed during the incomplete PO 104 week mouse carcinogenesis study, the toxicokinetic analysis is incomplete.

In nonclinical animal models, IV peramivir generally (but with exceptions) has linear and dose-proportional pharmacokinetics following dosing at ≤10 mg/kg in mice and ≤ 30 mg/kg in rats and monkeys. The V_d was less than or equal total body water with $T_{½}$ of ≤ approximately 4h in mice, approximately 15 h in rats, approximately 8 h in dogs and approximately 15 to 20 h in monkeys. Peramivir was primarily excreted in the urine of all species studied following IV dosing. Repeated IV administration of peramivir in adults does not result in accumulation of peramivir or material changes to its pharmacokinetics.

Peramivir pharmacokinetics was evaluated in mice, rats, ferrets, rabbits, dogs and monkeys (toxicology studies: mice, rats, rabbits, dogs and monkeys; reproductive toxicology studies: rats and rabbits). The routes of administration evaluated were IV, IM and PO. While all studies were evaluated, only the IV (intended route of exposure) studies are discussed. Given the IV route of administration, absorption is by default 100%. Two different radiolabelled peramivir species ([acetyl-2-^{14}C]-peramivir and [(2-ethyl)-butyl-1-^{14}C]-peramivir) were used to evaluate distribution, metabolism and excretion.

Following a single IV dose (10 mg/kg; approximately 0.2 x MHRD; AUC comparison) in male rats, $V_{d\ ss}$ (1.201 mL/kg) implied a wide distribution and C_L (424 mL/h/kg) and $T_{½}$ (12.4h) were modest. Repeated daily IV dosing (10 mg/kg; approximately 0.2 to 0.3x MHRD; AUC comparison) of male rats for 14 days resulted in similar pharmacokinetic values (C_L = 373-439 mL/h/kg; $V_{d\ ss}$= 457 to 533 mL/kg; terminal $T_{½z}$=7.09 to 9.08 h). The plasma elimination curves were distinctly biphasic showing classical distribution (α) and elimination (β) phases. Repeated dosing was not associated with plasmatic accumulation or changes in the plasma elimination curves (no evidence of metabolic or distributional adaptation).

In an oral bioavailability study in ♂ ferrets, a single IV dose (10 mg/kg; approximately 1 x MHRD AUC comparison) resulted in similar pharmacokinetic parameters to rats (C_L = 298 mL/h/kg; $T_{½}$=3.65 h; $V_{d\ ss}$ 355 mL/kg. The pharmacokinetic results of the IV component of the dog oral bioavailability study (single IV dose; 5 mg/kg; approximately 0.3 x MHRD AUC comparison) resemble those of the dog. Likewise, the pharmacokinetic findings in rabbits repeatedly IV dosed (10 mg/kg; approximately 3 to 4 x MHRD; AUC comparison) over 14 days resembled those in rats and ferrets. No relevant sex differences were observed in rabbits.

In female monkeys, peramivir displayed linear pharmacokinetics over the 3 to 30 mg/kg dose range (approximately 0.2 to 2x MHRD; AUC comparisons). Mean half-life, total body

clearance and volume of distribution at steady state were similar across the dose range studied, ranging from 15.2 to 19.6 hours, 132 to 140 mL/hr/kg and 233 to 239 mL/kg, respectively. Following a single IV dose (10 mg/kg) in females, the $V_{d\ ss}$ was 234 mL/kg and the $t_{½}$ was 16.0h. The IV component of the oral bioavailability study demonstrated that there were no meaningful sex differences.

The extent of binding of ^{14}C-peramivir to plasma proteins was determined in mice, rats, rabbits, dogs, monkeys and humans using equilibrium dialysis at concentrations at ≤approximately 0.02 x MHRD C_{max}. The tissue distribution of ^{14}C-peramivir has been studied in juvenile, mature, and pregnant rats. Across species, binding was not concentration dependent and ranged from approximately 5 to 14% and remained relatively constant over 1.5 to 4 h of incubation. Peramivir had a preference for plasma over erythrocytes with mean partition values ranging from 0 to 0.044. In a second human study, mean plasma protein binding displayed substantial variation and ranged from 18 to 30%. A value of 30% has been used in this evaluation. In this study, there were no conclusive trends in the extent of plasma protein binding and no apparent gender differences in the plasma protein binding.

After a single IV dose, drug associated radioactivity concentrated in the major and minor drug excretory systems (kidney, bladder, bile) in mature rats. Detectable drug associated radioactivity was only present at low levels in CNS (≥ approximately 300 x lower than kidney levels) and only a short period of time post-dose (≤ 8h). Tissue: plasma ratios >1 were detected for GI tract and kidney. Tissue $T_{½}$ for blood, plasma, brain, lung, liver and kidney were all ≤approximately 4 h. Dose level (10 to 100 mg/kg) and age did not affect the overall pattern of distribution of drug associated radioactivity. Tissue persistence was not detected. However, the persistence of drug-associated radioactivity was higher in juveniles with $t_{½}$ for blood, brain and lung being approximately 1 day and $T_{½}$ for kidney, liver and plasma being approximately 8 to 12 h. Multiple daily IV dosing (up to 14 day), was associated with increased liver and lung tissue $T_{½}$ (13.6 h and 43 h, respectively) and increased blood $T_{½}$ (187 h) *compared with* single IV dosing. Kidney tissue $T_{½}$ remained low (approximately 1 h).

Across all distribution studies, drug associated radioactivity had relatively low brain penetration and retention, although this was increased in juveniles. Broadly this supports the sponsor's claims of a low risk of CNS activity due to low CNS drug penetration. However, the sponsor's draft PI has noted that abrupt onset/rapid recovery neuropsychiatric events with an uncertain cause and effect relationship have been observed with the use of neuramidase inhibitors in influenza patients, particularly in paediatric patients. This may correlate with the findings of increased CNS drug associated radioactivity persistence in juvenile rats.

Based on rat and human biomaterial studies, peramivir undergoes limited cyclopentyl ring oxidation (< 4% in humans, ≤ 2% in rats based on metabolism by hepatic S9 preparations in vitro) to metabolite M1 (*syn:* oxo-RWJ-270201), whereas no detectable metabolism occurs in normal healthy humans following single or repeated IV exposure (excreted unchanged in urine). In vitro liver S9 metabolism was not detected in the dog*. In vivo,* rats oxidised the cyclopentyl ring in a limited manner following IV dosing; however an acyl glucuronide metabolite (≤ 4% of dose following a single IV dose) was produced by rabbits. Substantially higher levels of the acyl glucuronide metabolite (male 33%, female 14%) were detected in the urine of rabbits following PO dosing, implying a possible first pass effect. The Sponsor has postulated that the formation of the acyl glucuronide metabolite by rabbits is responsible to its apparent increased susceptibility to peramivir induced renal injury. Renal injury was only observed in rabbits and not in all other evaluated species, including humans. From the overall pharmacokinetic standpoint, metabolism is a more important route of elimination for peramivir in rabbits than in other species (including humans).

PO dosing of rats resulted in a hydroxylate metabolite (M2; *syn* OH-RWJ-270201) in urine (5% of PO dose). There were no metabolites detected in the urine of dogs or monkeys.

Following IV dosing of rats and monkeys, almost all of drug-associated radioactivity was excreted in urine as peramivir within 24 h. Over this time period small amounts of drug-associated radioactivity were excreted in faeces and bile (≤ approximately 6% in both media) as peramivir. Following a single IV dose excretion was effectively complete by approximately 48 h post dose in rats. No metabolites were detected in plasma, urine, faeces or bile; that isperamivir was excreted mostly unchanged in these media. No sex differences were detected. Like humans, the acyl glucuronide metabolite of peramivir was not detected. The same pattern of elimination was detected after single and multiple IV doses.

Based on drug radioactivity, mid-lactation galactogenic excretion occurred in IV dosed rats with a milk-plasma ratio of approximately 7 at 4 h post dose. T_{max} in milk was at 0.75 h post maternal dosing. Lactation did not change the basic IV pharmacokinetic features of peramivir in rats.

Peramivir is actively secreted in the rabbit kidney via organic anion transporters (OAT; inhibited by probenecid implying OAT1 and/or OAT3) but not in the rat. Again, this species specific effect may correlate with the susceptibility of rabbits to peramivir-induced renal injury.

Pharmacokinetic drug interactions

Based on in vitro cell based or biomaterial assays that were validated by the use of appropriate controls and used pharmacologically relevant concentrations in relation to the MHRD, peramivir was neither a substrate nor an inhibitor of p-glycoprotein, neither induced nor inhibited pharmacologically-relevant human CYPs (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, AND CYP3A4) and did not inhibit glucuronosyl transferase catalysed biotransformation of paracetamol to paracetamol glucuronide (APAP-G). As noted above, peramivir is actively secreted in the rabbit kidney via organic anion transporters (OAT; inhibited by probenecid implying OAT1 and/or OAT3) but not in the rat. Based on information in the draft PI, the sponsor has claimed that co-administration of PO probenecid peramivir did not result in any interactions. Accordingly the dependency on OAT1 and/or OAT3 in the rabbit kidney may be a species specific effect.

In Caco-2 cell monolayers, apical to basolateral transport of peramivir was inhibited by indomethacin and cimetidine implying that the drug may be a weak substrate for OCT1 and OSTα-OSTβ. However drug-drug interactions of clinical importance involving these enterothelial transporters are highly unlikely given the proposed IV route of administration.

Pharmacokinetic studies in influenza infected mice

Infection of female BALB/cAnNCrlCrlj mice with influenza virus type A/WS/33 (H1N1) did not materially alter the basic pharmacokinetic features of peramivir IV injected 2 days post-infection.

Toxicology

Overall, IV (bolus or continuous infusion) peramivir was well tolerated in single and repeat dose studies in rats and monkeys at doses ≤ approximately 5 x MHRD for IV boluses and ≤ approximately 29 x MHRD for continuous infusion (all AUC comparisons).

Testing strategy

Peramivir was evaluated in nonclinical studies following single- and/or repeat doses in the mouse, rat, guinea pig, rabbit, dog, and cynomolgus monkey, first by the oral route, and subsequently by the IV and IM routes of administration. The initial US IND was for an IV development program. This was then followed by a subsequent IM IND development program. With agreement from the US FDA, the IV toxicology program was bridged to the IM program with the conduct of one month bridging studies in two species. FDA also noted that that an additional 6-month chronic toxicity study in rodents, and a 9 month chronic toxicity study in a non-rodent model were required for parenteral administration of peramivir.

Toxicology studies with daily administration up to 28 to 31 days duration were conducted with IM and IV (both bolus and continuous infusion) routes of administration in the rat and monkey, as well as IV reproductive and developmental toxicity studies in the rat and rabbit. Chronic studies were conducted using weekly or biweekly IM dosing for 26 weeks (rats) or 52 weeks (monkeys).

In addition, studies evaluating genotoxicity and antigenicity were conducted. Studies in juvenile animals were conducted by IV (one month duration in juvenile rats) and PO (two weeks duration in juvenile rats and rabbits), and several IV nephrotoxicity studies were conducted in rabbits. A full complement of reproductive studies (IV dosing) was completed, which included teratology and perinatal and postnatal studies, as well as mouse and rat carcinogenicity studies utilising PO dosing.

While all studies were evaluated, the IV studies have been emphasised in this assessment because of the proposed clinical route of administration. Where appropriate other routes of administration are discussed.

Acute toxicity

Peramivir had low IV single dose toxicity with the maximum non-lethal IV doses (MNLDs) for rats, rabbits and monkeys were ≥300 mg/kg. The rabbit was the most susceptible species (MNLD ≥300 mg/kg) and the monkey was the least susceptible (MNLD > 720 mg/kg). There was no evidence of toxicity noted in the rat at doses up to 400 mg/kg IV or in monkeys dosed at 60 mg/kg BD every 4 hours times or after 720 mg/kg IV, infused over 24 h (infusion study included haematology and clinical chemistry evaluations).

In a peramivir IV acute nephrotoxicity study in rabbits, non-lethal nephrotoxicity (expressed as increased BUN, increased blood creatinine, increased urine volume, disturbances in Na and Cl excretion and renal tubular epithelial necrosis) were noted at doses ≥ approximately male 6, female 7 x MHRD (AUC comparisons). While dose adjustment is recommended for human patients with creatinine clearance below 50 mL/min, the sponsor's draft PI does not indicate that nephrotoxicity was an adverse finding in any of the human clinical trials. Peramivir acute nephrotoxicity is likely species specific (acyl glucuronide metabolite and/or dependence on renal OAT-mediated excretion).

Local IV tolerance was generally acceptable in these studies.

Repeat-dose toxicity

Relative exposure following IV dosing

Exposure ratios have been calculated based on animal: human plasma AUC_{0-24h} ratios. Justification for the human reference values is shown below. The AUC data used for animals is the mean of male and female values on the last sampling occasion (except as noted). AUC data is available for IV, IM and PO dosing; while all data were evaluated,

relative exposures have only been calculated for the IV route of administration (except for the chronic duration studies as noted below). Notably, for similar oral doses (100 to 150 mg/kg/day), the rabbit had much higher exposure levels (AUC) compared with mice, rats, or monkeys (exposure in rabbits PO dosing was approximately 10 x increased compared with mice and rats, and 2 to 3 x increased compared with monkeys). Bioavailability across the three species is similar. The reason for these differences is unknown and these differences were not as evident following IV administration.

Table 6: Relative exposure in repeat-dose toxicity and carcinogenicity studies

Species	Study duration [Study no.]	Dose (mg/kg/day)	AUC_{0-24h}^ (µg·h/mL) Except as noted	Exposure ratio#
Mouse (CD)	2 years DS00310]	Study was not completed		
Rat (SD)	7 d [DS99318] IV bolus	20	34.2	≈0.3
		50	157.7	≈2
		200	308.6	≈3
	14 or 15 d [DS99031] Continuous IV infusion	96	C_{ss} =7.0 µg/mL	≈1 (BSA)
		384	C_{ss} =23.2 µg/mL	≈4 (BSA)
		768	C_{ss} =55.5 µg/mL	≈8 (BSA)
		1152	C_{ss} =69.3 µg/mL	≈12 (BSA)
	28 or 29 d [0527-07232] IV bolus	15	42.9	≈0.4
		40	117.6	≈1
		120	383.2	≈4
	30 d [S-021812-TF-112-L] Continuous IV infusion Sampling on day 21	160	201.0	≈2
		480	637.5	≈6
		1440	1975.0	≈19
	26 weeks [WIL-196046] IM Dosed biweekly	12	38.6	0.4
		36	91.1	0.9
		75	215.5	2.1
	104 weeks (Carcinogenicity) [6336-143]	150	2.9	<0.1
		1000	14.9	0.1
		3000	35.5	0.3

Species	Study duration [Study no.]	Dose (mg/kg/ day)	AUC_{0-24h}^ (µg·h/mL) Except as noted	Exposure ratio#
	PO Sampling during week 78			
Rabbit (NZW)	7 d [DS99022] IV bolus	10	32.7	≈0.3
		25	88.8	≈1
		50	173.2	≈2
		100	337.7	≈3
Monkey (Cynomolgus)	14 d [806-023] Slow IV bolus	5	27.8	≈0.3
		15	118.0	≈1
		45	249.0	≈2
	28 d [0527-07233] Slow IV bolus	10	44.5	≈0.4
		30	149.6	≈2
		90	541.6	≈5
	30 d [S-021812-TF-091-L] Continuous IV infusion Sampling on day 14	120	506.5	≈5
		360	1480.0	≈14
		720	2945.0	≈29
	52 weeks [WIL-196047] IM, Dosed weekly	6	25.0	≈0.2
		18	81.5	≈0.8
		54	239.2	≈2
Human (Adult)	BCX1812-113	600 mg	102.5	–

= animal:human plasma AUC_{0-24h} or BSA ratio where indicated; ^ = data are for the sexes combined at the last sampling occasion; †toxicokinetic analysis was incomplete and only C_{ss} values were provided. Exposure ratios have been estimated from the $AUC_{0-\infty}$ data in the 13 week dose ranging study;

Justification for human pharmacokinetic parameters: To allow for consistency with the US FDA evaluation, the mean AUC_{0-24h} value used (102.5 µg.h/mL approximately 268 µM.h was derived from the human IV/IM bioequivalence study (Study BCX1812-113). The mean C_{max} was 46.8 µg/mL (approximately 122 µM). Human plasma protein binding ranged from 18to 30%. For evaluation purposes, the upper level (30%) was used. Accordingly, the $C_{max\ unbound}$ was approximately 34µg/mL (approximately 89 µM). C_{min} values were not derived in the population pharmacokinetic analyses; it was estimated to be approximately

0.050 µg/mL (approximately 0.13 µM). Thus the $C_{min\ unbound}$ was estimated to be approximately 0.1 µM.

Human data indicates that only about 3 to 9% of the drug distributes into the nasal cavity and pharyngeal mucus (a key site of action) of healthy subjects.[5] For comparison purposes, the pharyngeal concentration of peramivir used was 0.22µM which is the expected level in human patients at 12 h post-dose.

The population pharmacokinetic modelling (Study BCX1812-PPK1) demonstrated that the AUC will decrease with decreasing creatinine clearance while the C_{max} remains relatively constant. On this basis the Sponsor has concluded that since peramivir would be administered as a single dose treatment and no significant accumulation would be expected, no dosage adjustment is needed for patients with renal impairment who receive peramivir IV single dose treatment for acute uncomplicated influenza. Accordingly, adjustment of exposure comparisons for advanced renal failure has not been performed. Notably, the sponsor's argument regarding the single dose situation may not apply in the case of multiple dosing in the presence of advanced renal failure where drug accumulation may occur. Based on Study BCX1812-105, peramivir AUC increased by 28%, 302%, and 412% in subjects with mild, moderate, and severe renal impairment compared with normal healthy humans while C_{max} remained unchanged.

Two out of 4 studies (Studies. CB-137-C and CB-139-C) determined that AUC and C_{max} were minimally dependent on age. Exposure (AUC0-12 SS) to peramivir was approximately 34% higher in elderly subjects compared with young adults. Accordingly, the exposure ratios shown above may be approximately 34% lower than shown in the table above. However the sponsor has determined that dose adjustment in the elderly is not required.

The sponsor has claimed that:

> *Response to peramivir exposure in paediatric subjects administered either a 12 mg/kg or 600 mg dose was not markedly different from exposure in adults. The observed plasma concentrations in subjects aged 2 to < 13 years were in the range of those of the subjects aged ≥ 13 years to < 18 years who received a fixed 600 mg dose rather than the weight-adjusted dose. Peramivir PK parameters were comparable with those in adults from Study BCX1812-113; truncated AUC_{0-3h} in paediatric subjects was similar to that of adults.*

Based on this claim, specific exposure ratios for the 2 to <13 year old and ≥ 13 years to < 18 years old age ranges have not been calculated.

AUC and C_{max} were not altered by co-treatment with oseltamivir carboxylate. Plasma concentration profiles of peramivir in infected patients were approximately similar to those in healthy subjects.

Major toxicities following IV exposure

Renal toxicity: Unexpected, dose related increased mortality compared with controls was observed in the rabbit IV developmental toxicity dose ranging study following repeated daily dosing at ≥300 mg/kg/day (≥ approximately 8 x MHRD; BSA comparison) from gestational Days 7 to 19 (sacrifice on gestational Day 29). This correlated with dose-related increases (compared with controls on gestational Day 29) in anatomic pathology findings of pale, mottled kidneys, cortical tubular epithelial necrosis of varying severity (affected all ribociclib treated animals) and secondary glomerulopathy (affected all surviving ribociclib treated animals) in animals doses at ≥ 200 mg/kg/day (≥ approximately 5 x MHRD BSA comparison). All ribociclib treated animals (dosed at ≥

[5] Based on data from Kohno S, *et al.* Antimicrob Agents Chemother. 2011; 55(6):2803-2812 and Alame MM, *et al.* Front Microbiol. 2016 31(7):450.

approximately 5 x MHRD BSA comparison) had clinical chemistry signs of renal compromise (2 to 3 x increases in serum BUN, creatinine and GGT compared with controls). Because of these findings, a series of specific studies on nephrotoxicity were performed in rabbits.

The clinical chemistry (increased serum BUN and creatinine; serum sodium, potassium and chloride disturbances; glucosuria, proteinuria, positive urine occult blood, increased urine GGT, ALP and NAG; increased urine volume, reduced urine concentrating ability) and anatomic pathology findings (pale mottled kidneys, light brownish discoloration of the cortex or medulla, increased absolute and relative kidney weights, renal tubular nephrosis/necrosis with dilation and hyaline cast formation and renal tubular regeneration) associated with peramivir renal tubular injury were similar across all the rabbit studies. Limited serum chemistry evidence of liver injury were noted in the 4 day IV study (small to moderate, 2 to 3 x increases in serum ALT, AST, GGT and bilirubin; and 2-7x increases in serum cholesterol, and triglycerides), but were not correlated with gross anatomic pathology evidence of hepatic injury (no histopathology). There were no clear sex differences in susceptibility. The single IV dose NOAEL for peramivir nephrotoxicity in rabbits was established as 100 mg/kg (approximately 3x MHRD AUC comparison). With continuous IV infusion or repeated daily IV bolus dosing for 7 days, the NOAEL was 100 mg/kg (approximately 2 to 3 x MHRD AUC comparison).

In the 14 day repeat IV dosing nephrotoxicity study (single dose: 200 mg/kg), overt nephrotoxicity (based on histopathology findings) was apparent after ≥1 day of treatment. Due to excessive male after 6 to 8 days of treatment, the treatment duration was reduced to 9 days. Based on electron microscopy studies, the initial target was the renal proximal convoluted tubule and no initial glomerular injuries were detected. Overall, nephrotoxicity was more severe in males than in females. Hepatocellular injury (fatty change) and associated clinical chemistry changes (1.5 to 7 x upper limit of controls for serum AST, ALT, GGT and/or bilirubin dosing days 2-8 with peak levels on day 4; 2-7x increase in serum cholesterol and triglycerides with increasing incidence and severity from dosing Days 2 to 8). Smaller clinical chemistry changes indicative of hepatocellular injury (not correlated with histopathology findings) occurred in females. Notably, by Day 7 the pre-dosing peramivir plasma concentration in surviving males was approximately 150 x higher compared with females (male644065 ng/mL; female 4315 ng/mL), implying plasmatic accumulation in males due to reduced renal excretion (a similar phenomenon was observed in the 7 day study where the Day 7 AUC in males was approximately 1.8 x higher compared with the Day 1 value). In five moribund males (subsequently died on dosing Days 7 to 8), higher levels of plasmatic accumulation were observed (males approximately 1354 to 1466 µg/mL; surviving females approximately 0.8 to 11 µg/mL). Given these pharmacokinetic circumstances, the relatively mild liver injuries observed in the males were likely due to a combination of extreme drug concentrations, possibly combined with effects secondary to acute renal failure. IV peramivir associated mortality in male rabbits was almost certainly due to acute renal failure and associated secondary failure of drug excretion. Across studies, the NOAEL for IV peramivir induced nephrotoxicity was 100 mg/kg/day (approximately 2 to 3 x MHRD AUC comparison; confirmed by histopathology). IV dosing at ≥ 200 mg/kg was definitively nephrotoxic. The PO peramivir NOAEL in rabbits was substantially higher (300 to 1200 mg/kg/day depending on duration), likely due to lower bioavailability; however nephrotoxicity consistent with the findings in the IV dosing studies occurred after PO dosing.

Overt, clearly demonstrable nephrotoxicity only occurred in rabbits and not in any other tested species (mice, rats, dogs, monkeys). Mild, reversible effects on urine chemistry parameters (males: higher sodium/creatinine, potassium/creatinine, chloride/creatinine, and protein/creatinine ratios; females: lower urine sodium and potassium) which lacked histopathology correlates were noted in the 4 week repeat PO dosing study in rats; however these changes were thought to reflect mild (non-adverse) changes in renal

function rather than overt nephrotoxicity and did not occur in any of the other PO dosing studies in rats.

However, an increased incidence of renal pelvic mineralisation (approximately 3 x increase) and transitional cell hyperplasia (6 x increase) in male unscheduled deaths following PO dosing at ≥ 1000 mg/kg/day (≥ approximately 0.1 x MHRD AUC comparison) occurred in the rat carcinogenesis study. In female terminal sacrifice and unscheduled deaths, similar changes in the renal pelvis were accompanied by an increased incidence of renal tubule mineralisation occasionally accompanied by renal pelvic inflammation, minimal to slight renal tubular dilatation, renal tubular epithelial vacuolation and urothelial hyperplasia (particularly at PO doses ≥ 1000 mg/kg/day). These findings were attributed to mechanical irritation by mineral deposits and were not the same as the nephrotoxicity observed in rabbits. A conclusive relationship between these findings and peramivir was not established; however it is notable that small pulmonary alveolar granulomas (minimal severity) occurred in a dose-related manner in the seven day IV repeat dose study in rats. These granulomas were associated with the deposition of unidentified variably shaped, refractile particles. The granules were not hair fragments from the IV injection site and were not detected in other IV studies. Precipitate formation in renal tubules and the renal pelvis (and likely lung) is likely consistent with the low water solubility of peramivir.

Overall peramivir induced nephrotoxicity after short term IV exposure is likely a species specific effect in rabbits and may be correlated with the species specific formation of the acyl glucuronide metabolite of peramivir (although a definitive cause and effects relationship was not established). Crystaline irritancy effects in the urinary tract were only observed in the near life-time study in rats. These are unlikely to be relevant to short-term treatment with peramivir particularly the since the lower baseline urine osmolality in humans compared with rats is likely less conducive to drug precipitation in urine.

Other observations

Except as described above, peramivir was not associated with any adverse effects on mortality, body weight, food consumption, ophthalmology, coagulation parameters, clinical chemistry, urinalysis, haematology, serum T4, ECG, intravascular injection sites, and anatomic pathology. Peramivir (IV and SC dosing) was not antigenic in a guinea pig passive cutaneous anaphylaxis assay that was appropriately validated by the use of a positive control.

Mild, sporadic clinical signs that were associated with PO peramivir dosing included changes in stool (discolouration) decreased faecal volume, anogenital staining, abdominal distension, and/or excessive salivation. IM injection was associated with reversible, dose related, increased incidence and severity of injection site injury (with increased serum AST of muscle origin levels in some studies).

Across all species IV peramivir exposure was generally dose proportional and its kinetics was consistent with the findings of the pharmacokinetics studies.

Based on information contained in the sponsor's draft PI there have been reports of neuropsychiatric events in patients with influenza being treated with peramivir. A cause and effect relationship between peramivir and these events has not been established. Abnormal neurobehaviour was not detected in nonclinical animal screening studies. However these screening studies are not necessarily completely predictive of the human clinical situation.

Genotoxicity

Peramivir displayed a low genotoxic potential (bacterial reverse mutation assay, in vitro chromosomal aberration assay, in vivo mouse bone marrow micronucleus assay with IV or PO dosing) in an appropriately validated ICH S2(R1) screening panel. Peramivir (±S9) at

concentrations up to 3280 µg/mL were not substantially cytotoxic (that is, cell growth inhibition of <50%) in mammalian cells in vitro (Chinese hamster ovary (CHO) cells). No mortality or adverse clinical signs were noted in the IV mouse bone marrow micronucleus assay following IV dosing at ≤360 mg/kg (practical limit of formulation and dose volume; approximately 2 x MHRD BSA comparison). PO dosing did not affect the outcome of the mouse bone marrow micronucleus test.

Carcinogenicity

Based on ICH S1A, carcinogenicity studies are not required for peramivir since it is not intended for continuous use for ≥6 months, unlikely to be used repeatedly in an intermittent manner, does not have a prolonged delivery system and it is not a substance of concern in terms of its carcinogenic potential.

In the completed 2 year rat carcinogenesis study, PO peramivir at doses equivalent to approximately 0.3 x MHRD (AUC comparison) were not associated with adverse effects on mortality, body weights, clinical signs, ophthalmic findings, haematology, clinical chemistry or gross anatomic pathology. Histopathology findings of uncertain relevance: slightly greater incidences of benign pheochromocytoma of the adrenal medulla (female benign: ≤ approximately 12% compared with 10.9% mean historical control incidence) in males dosed at ≥ approximately 0.1 x MHRD (AUC comparison) and malignant phaeochromocytoma of the adrenal medulla (approximately 3% compared with 1.4% mean historical control incidence) in males dosed at approximately 0.1 x MHRD (AUC comparison). This was accompanied by a small increased incidence of adrenal medullary hyperplasia in males dosed at ≥approximately 0.1 x MHRD. Overall, the adrenal neoplasia findings are most likely to be due to chance given the small differences in incidence compared with mean historical control values. Statistically significant ($p < 0.05$) decreases in the incidence of tumours compared with control occurred for : thyroid carcinoma (males at 3,000 mg/kg/day), benign interstitial cell carcinoma in the testis (males given 1,000 mg/kg/day), malignant astrocytoma in multiple organs (males given 1,000 mg/kg/day), combined adenoma and carcinoma of thyroid (females at 1,000 mg/kg/day), and benign islet cell adenoma of the pancreas (females at 150 and 1,000 mg/kg/day). The human relevance of these findings is uncertain. Overall, there is no conclusive evidence of peramivir induced/influenced neoplasia in rats. The findings in the rat study were not replicated in the incomplete mouse study (histopathology not performed). The urinary system findings of this study are discussed in the repeat-dose toxicity section.

No definitively adverse effects associated with peramivir were detected in the incomplete mouse carcinogenesis study (no histopathology was performed).

Overall, peramivir likely has a low risk of inducing or influencing carcinogenesis.

Reproductive toxicity

Fertility/early embryonic development and general reproductive toxicity studies were conducted in male (fertility only; 10 to 13 weeks of dosing) and female rats (fertility and early embryonic development; 3 to 6 weeks of dosing). Embryofetal development studies were conducted in rats and rabbits and a pre-post-natal study was conducted in rats. All studies utilised IV dosing. No adverse effects on the reproductive systems were noted in the repeat dose toxicology studies. No changes that could impair mating were observed in the IV repeat dose toxicology studies (IM injection site lesions were possibly sufficient to impair mating due to pain; however this was not evaluated by the sponsor).

Relative exposure

Relative exposure, except where noted, was calculated based on BSA comparisons due to deficiencies in the toxicokinetic aspects of the studies and/or absence of toxicokinetic data. Based on these comparisons supratherapeutic exposures were achieved in all studies.

Table 7: Relative exposure in reproductive toxicity studies

Species	Study [Study no.]	Dose (mg/kg/day)	AUC_{0-24h} (µg·h/mL) or plasma concentration (µg/mL)	Exposure ratio#
Rat (SD)	Male fertility [DS99307] IV bolus	50	ND*	≈0.5 (BSA)
		200	ND	≈2 (BSA)
		400	ND	≈4 (BSA)
		600 (Male NOAEL; maximum practical dosing level)	ND	≈6 (BSA)
	Female fertility [DS99309] IV bolus	50	ND	≈0.5 (BSA)
		200	ND	≈2 (BSA)
		400	ND	≈4 (BSA)
		600 (Female NOAEL; maximum practical dosing level)	ND	≈6 (BSA)
	Embryofetal development Dose ranging [DS99402] IV bolus	200	ND	≈2 (BSA)
		300	ND	≈3 (BSA)
		400	ND	≈4 (BSA)
		500	ND	≈5 (BSA)
		600 (Maternal NOEL; maximum practical dosing level)	ND	≈6 (BSA)

Species	Study [Study no.]	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (µg·h/mL) or plasma concentration (µg/mL)	Exposure ratio#
	Embryofetal development [DS99316] IV bolus	200	248.3 µg/mL (plasma concentration GD17)	≈2 (BSA)
		400	491.1 µg/mL (plasma concentration GD17)	≈4 (BSA)
		600 (Maternal and fetal NOEL; maximum practical dosing level)	755.8 µg/mL (plasma concentration GD17)	≈6 (BSA)
	Embryofetal development [DS00312] IV infusion	50 (Maternal and fetal NOEL; maximum practical dosing level)	3.490 µg/mL (plasma concentration GD17)	≈0.5 (BSA)
		400	29.824 µg/mL (plasma concentration GD17)	≈4 (BSA)
		1000	61.471 µg/mL (plasma concentration GD17)	≈10 (BSA)
	Pre- postnatal development [DS99310] IV	50	ND	≈0.5 (BSA)
		200	ND	≈2 (BSA)
		400	ND	≈4 (BSA)
		600 (Maternal and fetal NOAEL; maximum practical dosing level)	ND	≈6 (BSA)
Rabbit (NZW)	Embryofetal development dose ranging	200	ND	≈5 (BSA)
		300	ND	≈8

Species	Study [Study no.]	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (µg·h/mL) or plasma concentration (µg/mL)	Exposure ratio#
	[DS99403]			(BSA)
		400	ND	≈10 (BSA)
		500	ND	≈13 (BSA)
		600	ND	≈15 (BSA)
	Embryofetal development [DS99317]	25	27.1 µg/mL (plasma concentration GD19)	≈0.6 (BSA)
		50	64.8 µg/mL (plasma concentration GD19)	≈1 (BSA)
		100 (Maternal NOAEL)	138.0 µg/mL (plasma concentration GD19)	≈3 (BSA)
		200 (Fetal NOAEL)	476.2 µg/mL (plasma concentration GD19)	≈5 (BSA)
Human (Adult)	BCX1812-113	600 mg	102.5	–

= animal: human plasma $AUC_{0-24\,h}$; * ND = no data

Galactogenic transfer: Radiation from IV dosed ^{14}C-peramivir was excreted in non-colostral milk of lactating rats (11 to 13 days post-partum; milk: plasma 0.08 at 0.5 h post dose and approximately 7.4 at 4 h post-dose; milk C_{max} 0.919 µg eq/mL, $AUC_{0-\infty}$ 8.99 µg eq x hr/mL, terminal half-life ≈6.55 h, T_{max}0.75h). In bile duct cannulated lactating rats, drug associated radioactivity levels in milk were below the limit of quantitation by 24 h post PO dose. In this system fasting had a substantial effect on the pharmacokinetics of PO drug associated radioactivity in milk: in fasted rats, milk concentrations over the 1 to 8 h post dose period were higher than those of non-fasted rats (fasted: T_{max} 2 h C_{max} approximately 0.04 µg eq/g; non fasted: highest concentration recorded was at 8h, C 0.01 µg eq/g).

Placental transfer: Following a single PO dosing of pregnant rats with ^{14}C-peramivir fetal tissue (including placenta and amnion) were lower than plasma levels. Based on this limited data, a sub-plasma concentration level of fetal exposure is likely following IV dosing. However in this study, approximately 89% of the orally delivered drug associated radioactivity was excreted in the faeces (almost all of which was likely not systemically absorbed). Accordingly these data may not accurately reflect the proposed IV route of exposure.

Male fertility and reproductive system: The submitted study conformed with ICH S5 (R2) stage A (adult male reproductive functions, mating behaviour and fertilisation) and stage B (paternally mediated effects) requirements and was designed to detect functional effects (for example, effects on libido or epididymal sperm maturation) that may not histologically detectable. No adverse effects on male fertility and the male reproductive system were detected following IV dosing at up to 600 mg/kg/day (approximately 6 x MHRD BSA comparison) for up to13 weeks.

Female fertility and reproductive system: The submitted study conformed with ICH S5 (R2) stage A (female reproductive functions, mating behaviour and fertilisation) and stage B (female reproductive effects, pre-implantation development and implantation) requirements and was designed to detect effects on effects on the oestrous cycle, tubal transport, implantation and development of pre-implantation stages of the embryos of female rats. No adverse effects were noted following IV dosing at up to 600 mg/kg/day (approximately 6 x MHRD BSA comparison) for up to 42 days.

Embryofetal development in rats: three studies were provided (IV bolus dose ranging study, main IV bolus study, and continuous IV infusion study). No adverse maternal or fetal effects were noted in the IV bolus dose ranging or in the main IV bolus study following dosing at up to 600 mg/kg/d (maternal and fetal NOEL; (approximately 6 x MHRD BSA comparison).

In the continuous infusion study significant ($p < 0.05$) dose related increased number of fetuses (and litters containing affected fetuses) with reduction of the renal papillae and ureteral dilation at doses ≥400 mg/kg/day (LOAEL; approximately 4 x MHRD BSA comparison) and a significant ($p < 0.05$) increase in the number of fetuses with megaureters following dosing at 1000 mg/kg/day (approximately 10 x MHRD BSA comparison). These findings may indicate delayed urinary tract development. The NOEL for these effects was 50 mg/kg/day (approximately 0.5 x MHRD BSA comparison).

Megaureters are a finding in human congenital obstructive uropathy and the effect is associated with urine flow impairment with secondary impairment of renal precursor cell turnover and survival (with an important source of fetal renal stem cells being located in the renal papillae).[6, 7] A human-relevant obstructive nephropathy/uropathy mode of action is consistent with the findings of renal tubular and renal pelvic mineralisation in the rat carcinogenesis study and with the low water solubility of perimivir; however, crystalline deposits were not observed in the fetuses.

Adverse effects on the urinary tract were not observed in the F_1 generation of the pre-postnatal rat study following maternal F_0 IV bolus dosing at up to 600 mg/kg/d and were not observed in the rat IV bolus embryofetal development studies. Thus while the findings of renal papillary reduction and ureteral dilation/megaureters in fetal rats following maternal IV continuous infusion dosing are likely human relevant, they did not occur following IV bolus dosing (the proposed clinical dosing method).

Embryofetal development in rabbits: Dose related increased mortality occurred in the dose ranging study at doses ≥ 300 mg/kg/day (approximately 8 x MHRD BSA comparisons; clinical signs: decreased food consumption, decreased faeces, hypernoea, laboured breathing, weight loss with rebound weight gain at dosing cessation). The deaths were associated with evidence of acute renal failure (white/mottled kidneys, dose-related renal glomerular nephrosis and cortical tubular nephrosis). Lung discolouration was noted in some animals. Azotemia and elevated GGT were detected in survivors. Dose related fetal weights occurred at ≥200 mg/kg/day (approximately 5 x MHRD BSA comparisons). However dosing at ≤ approximately 600 mg/kg/day (approximately 15 x MHRD BSA

[6] Woolf AS, Thiruchelvam N. Adv Ren Replace Ther. 2001. 8(3):157-163.
[7] Al-Awqati Q, Oliver JA. Stem Cell Rev. 2006;2(3):181-4.

comparisons) had no effects on pregnancy rates, reproductive parameters (no effects on number of corpora lutea, implantation sites, live fetuses, pre and post-implantation loss, and early and late resorptions) or embryofetal development.

In the main study, dosing at 200 mg/kg/day (approximately 5 x MHRD BSA comparison) was associated with maternotoxicity (emaciation, weight loss, reduced food consumption, pale renal cortices) and an increased incidence of abortion. However no reproductive or embryofetal effects occurred following dosing at ≤ 200 mg/kg/day.

Pre-postnatal development in rats: No adverse effects (no effects on mortality, clinical observations, body weight, body weight gain, parturition, litter parameters) on the F_0 generation were detected following dosing at up to 600 mg/kg/day (approximately 6 x MHRD BSA comparisons; the maximum practical dosing level). Likewise, dosing of the F_0 generation at up to 600 mg/kg/day had no adverse effects on the F_1 generation (no effects on mortality, clinical observations, body weight, body weight gain, behaviour, mating, fertility, reproductive parameters and embryofetal development).

Pregnancy classification

The sponsor has proposed Pregnancy Category B2. Category B2 states:

> *Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.*

However, adequate studies in two species have been supplied by the sponsor and there is evidence of human relevant effects on urinary tract development in one species. The congenital obstructive uropathy effects observed were consistent with the maternal nephrotoxicity observed in the rabbit embryofetal studies, the nephrotoxicity/mineralisation observed in the rat carcinogenesis study and the known low water solubility of peramivir.

Two areas of uncertainty remain: (a) the effects were on urinary tract development in rats were only present following 11 days of continuous IV infusion whereas the proposed clinical dosing method is IV bolus; and (b) the relative lower sensitivity of humans *compared with* rats due to the lower baseline urine osmolality of humans (that is, lower propensity for drug precipitation).

Accordingly, Pregnancy Category B3 is a more appropriate classification for peramivir.[8] Category B3 is also consistent with the current FDA Pregnancy category of C for peramivir.

Local tolerance

IV local tolerance

IV tolerance was acceptable in rats (IV bolus doses up to 200 mg/kg/day), rabbits (IV bolus dosing up to 300 mg/kg/day) and monkeys (IV bolus dosing up to 90 mg/kg/day). In these studies, injection/infusion site injuries were largely associated with the dosing procedure rather than the administration of peramivir.

IM local tolerance studies

IM injection tolerance studies were conducted in rats and rabbits. In the rat single dose (14 day observation) local tolerance study, peramivir concentrations up to 150 mg/mL (in citrate buffered normal saline; pH of approximately 3) produce similar muscle, interstitium and fascial injury/inflammation compared with control at 24 h post injection. For the most part, healing was mostly complete by observation Day 14; however there were small increases (in incidence and/or severity) in injection site damage at peramivir injected sites.

[8] Pregnancy category B3 states: 'Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.'

The effect of peramivir formulation (pH 3.0) tissue irritation on toxicokinetics was evaluated in a rat single dose (15 day observation) IM study. In this study there were no clear or definitive treatment-related effects on injection site injury compared with control. No important toxicokinetic differences were detected.

An acidic formulation (30 w/v% Peramivir acidic formulation with 0.8 M HCl; controls 0.435 w/v% and 1.70 w/v% acetic acid aqueous solutions) was used in the rabbit single dose (14d observation period) IM injection tolerance study. Based on anatomic pathology evaluation, the local irritability of 30 w/v% peramivir acidic formulation was judged as comparable to that of 1.70 w/v% acetic acid and was Graded 4 or 5 in terms of severity. Although not systematically evaluated, the irritancy was considered likely to be due to the 0.8 M HCl present in the formulation. The formulations used in this study are not relevant to the currently proposed IV formulation.

Immunotoxicity

Systemic anaphylaxis and passive cutaneous anaphylaxis studies were conducted in guinea pigs (assays validated by the use of a positive control). In this system, peramivir did not induce systemic or passive cutaneous anaphylaxis. However, animal assays of anaphylactic potential are not necessarily predictive of the human clinical risk.

Based on information contained in the sponsor's draft PI rare cases of serious reactions including erythema multiforme, anaphylaxis and Stevens Johnson syndrome have been reported in humans. These effects were not observed in the nonclinical studies and the animal models used in the nonclinical studies are not reliable models of these reactions.

Phototoxicity

No data was submitted. Peramivir (0.1 mg/mL) displayed no UV absorption in acid (pH ≤2) or neutral (pH = 7) environments. Absorption in the UVC range (215 nm) was present when peramivir was in a strongly alkaline environment (pH ≥ 10). Given UVC is not a component of terrestrial level sun-light, this finding is irrelevant in terms of phototoxicity risk assessment. Overall, the risk of clinically relevant drug-associated phototoxicity is negligible and no data is required (as per ICH S10).

Impurities

All drug substance and drug product impurities are qualified as per ICH Q3 standards.

Paediatric use

IV studies were conducted in rats and oral studies were conducted in rats and rabbits.

Relative exposure

Table 8: Relative exposure in IV juvenile studies

Study	Study [Study no.]	Dose (mg/kg/day)	Age (d)	$AUC_{0-24\ h}$ (µg·h/mL)*	Exposure ratio#
Rat (SD)	S-021812-TF-109-L Single dose IV Age: 9 or 21 d	10	9	59.1	≈1
			21	21.0	≈0.2
		120	9	662.5	≈7
			21	291.5	≈3
		240	9	1360	≈13

Study	Study [Study no.]	Dose (mg/kg/ day)	Age (d)	$AUC_{0-24\ h}$ (µg·h /mL)*	Exposure ratio#
			21	469	≈5
	S-021812-TF-110-L 1 month IV Starting age: 9 d	60	9	315.5	≈3
			15	111.5	≈1
			29	84.5	≈1
		120	9	658	≈6
			15	205	2
			29	167.5	≈2
		240	9	1410	≈14
			15	452	≈4
			29	321.5	≈3
	DS00301 2 week PO Starting age: 13 d	50	13	33.2	≈0.3
			26	1.2	<0.1
		500	13	125.6	≈1
			26	8.8	<0.1
		1500	13	415.6	≈4
			26	22.2	≈0.2
Rabbit (NZW)	DS00304 2 week PO Starting age:	50	21	13.1	≈0.1
			34	9.3	≈0.1
		300	21	74.4	≈1
			34	51.4	≈0.5
		1200	21	288.3	≈3
			34	125.1	≈1
Human (Adult)	BCX1812-113	600 mg	Adult†	102.5	–

= animal: human plasma AUC0–24 h; * mean of male and female values; Juvenile rabbit study DS99312 and juvenile rat study DS99311 were considered invalid based the toxicokinetic evaluation. Both studies were repeated; † 2 year old humans (the lowest indicated age for clinical peramivir use) have more functionally mature (that is, ≈100% of adult GFR) renal system compared with the juvenile rats and rabbits used in these studies. Given that renal function is the single largest determinant on peramivir AUC the use of the human adult AUC value for a 600 mg IV peramivir dose is considered appropriate.

In the rat single dose IV study, C_0 and $AUC0_{-24h}$ values increased in a dose-dependent manner. The $T_{½}$ values tended to increase in a dose-dependent manner, but the values were similar between 120 and 240 mg/kg at 9 days of age and were comparable between 10 and 120 mg/kg at 21 days of age. When parameters were compared between animals at 9 and 21 days of age, the C_0 values were comparable but the $t_{½}$ and AUC_{0-24h} values at 9 days of age were substantially higher than those at 21 days of age. This is consistent with the normal development of renal function in rats.[9] No sex differences were noted in any TK parameter. The results of the rat 1 month repeat IV dose study were broadly consistent with the single IV dose study. C_0 and AUC_{0-24h} values were generally dose proportional. C_0 values were broadly consistent across the different age groups. Consistent with renal function development in rats the AUC_{0-24h} values on study Days 14 and 28 were substantially lower than those on study Day 1.

In the rat 2 week PO study, significantly ($p < 0.05$) lower C_{max} and AUC_{0-24h} occurred on study Day 14 compared with study Day 1. These findings are consistent with the maturation of the gastrointestinal and urinary tracts of rats. The AUC_{0-24h} changes in the rabbit 2 week PO study were also consistent with this general pattern; however the changes with age were of a smaller magnitude.

Overall, there were no notable sex differences in exposure in rats and mice.

Juvenile rats

In the single dose IV study, no deaths or abnormal clinical signs occurred in the 9 day old animals at doses up to 240 mg/kg (≤ approximately 13 x MHRD AUC comparison). Transient irregular respiration and ptosis occurred at 5 minutes post injection in 1/8 21 day old males dosed at 240 mg/kg/d (approximately 5 x MHRD AUC comparison). No adverse effects on clinical signs, physical development, behaviour, genital development, haematology, clinical chemistry, urinalysis and anatomic pathology (histopathology in high dose animals only) were detected in the rat 1 month repeat IV study following dosing at up to 240 mg/kg/day (≤ approximately 3 to 14 x MHRD AUC comparisons). A non-adverse (6 to 7%) reduced bodyweight gain from 24-34 days of age occurred in females dosed at 240 mg/kg/day.

Consistent with the poor oral bioavailability of peramivir, relatively low levels of systemic exposure were achieved in the PO studies. In the 2 week study liquid faeces were noted in 14 to 20 day old animals dosed at ≥500 mg/kg/day and reduced body weights (likely due to water loss in faeces) were noted in >19 day old animals dosed at 1500 mg/kg/day. Haemoconcentration effects in animals dosed at ≥ 500 mg/kg/day and reduced urine pH in animals dosed at 1500 mg/kg/day were noted due to increased water loss in faeces.

Overall only minor and transient effects were observed following supratherapeutic IV dosing of rats aged 9 days and older despite higher systemic exposures in younger animals due to the incomplete maturation of the major pathway of excretion of peramivir (renal system).

Juvenile rabbits

In the 2 week PO study unexpected mortality occurred in 3 kits from a single litter that were dosed at 1200 mg/kg/day and soft faeces were noted in all peramivir treated kits between 23 to 30 days of age. The unexpected mortalities may have been related to drug-associated gastrointestinal disturbances given that rabbits (particularly juveniles) are prone to such effects. However, no definitive cause of death was established.

Mild renal proximal tubule changes (minimal cytoplasmic accumulation of eosinophilic material in renal tubular epithelial cells) occurred in females dosed at 1200 mg/kg/day

[9] Provoost AP, *et al.* Ren Physiol. 1983;6(1):1-9.

(approximately 1 x MHRD AUC comparison). However there was no evidence of overt acute renal failure.

Conclusions

Based on studies in juveniles and adults, the juvenile and adult rabbit is the most susceptible species for nephrotoxicity. Mild renal proximal tubular injury in the absence of acute renal failure occurred in juvenile female rabbits with systemic exposures of approximately 1 x MHRD (AUC comparisons). However, as noted in the repeat dose toxicology section the increased susceptibility of rabbits may be species specific and may be correlated with the species specific formation of the acyl glucuronide metabolite of peramivir (although a definitive cause and effects relationship was not established).

Critically, the higher levels of systemic exposure, particularly in rats, that was associated with the immaturity of the major pathway of peramivir excretion (urinary system) had minimal to no effects on toxicity. Notably, incomplete renal functional maturation was present in rat and rabbit age ranges evaluated in the juvenile studies.[10]

In humans renal function, as determined by GFR, steadily increases over the first 9 weeks of life (approximately 20 to 30% of adult GFR at birth, 75% of adult GFR at 26 weeks of age and approximately 100% of adult GFR by 78 weeks of age).[11] By the lowest intended age for peramivir use in humans (2 years), juvenile human patients will have achieved a fully mature renal function (that is, approximately100% of adult GFR). Accordingly the juvenile rabbit and rat studies may substantially overestimate the risk of peramivir induced toxicity in juvenile human patients. The findings in the juvenile rat and rabbit studies thus have uncertain human health relevance.

Nonclinical summary and conclusions

Summary

- A high quality ICH compliant dossier was submitted. Pivotal safety-related studies were GLP compliant. Where appropriate the submitted studies were validated by the use of positive and negative controls.
- Peramivir is a cyclopentyl transition-state sialic acid analogue neuraminidase (NA) inhibitor (related to oseltamivir, zanamivir and laminamivir). Peramivir has a higher in vitro binding affinity for influenza A/NWS/33 (H1N1) and H1N9 (A/NWS/G70c) NAs implying comparable or higher antiviral potency and a possibly longer duration of action compared with oseltamivir and zanamivir. Oseltamivir had no effects on peramivir binding affinity and v/v. Peramivir is highly selective for influenza virus NAs compared with bacterial and mammalian NAs/sialidases (human NEU2 inhibition may occur; no nonclinical toxicology correlates). Irrespective of the presence of resistance in vitro, peramivir likely retains substantial anti-influenza A and B activity in vivo (at both the MHRD plasma $C_{min\ unbound}$ and human pharyngeal mucous peramivir concentrations at 2h and 12h post dose). Peramivir is only active against influenza viruses. Peramivir selection generates HA, NA mutations and NA deficient strains in vitro. Specific patterns of viral mutations conferring resistance to peramivir were not identified. Peramivier resistance is not correlated with influenza A virulence (paradoxical results with influenza B). Peramivir displayed complex patterns of cross-resistance with other NA inhibitors and M2 ion channel inhibitors. Peramivir was not cytotoxic.

[10] Peters CA. Prenat Diagn. 2001; 21(11):917-923.
[11] Rhodin MM, *et al.* Pediatr Nephrol. 2009; 24(1):67-76.

- In vivo efficacy was evaluated in mice, ferrets, and monkeys. IV peramivir was efficacious in vivo (including in immunocompromised mice, against peramivir resistant strains and against avian strains) when dosed before, immediately after or within 72 hours of inoculation. Repeated dosing and/or combination therapy with NA inhibitors and/or M2 ion channel inhibitors increased efficacy. Evidence that peramivir prevents viral entry into uninfected cells and/or limits viral spread in vivo was not provided. The relationship between in vitro antiviral activity and/or in vitro NA inhibition and inhibition of influenza virus replication in humans was not evaluated. In mice efficacy correlated with plasma AUC rather than dosing interval.
- There are no nonclinical secondary pharmacodynamics or safety pharmacology effects of-concern. The effect of peramivir on live attenuated influenza virus vaccination (for example, FluMist) is unknown.
- The animal models used were adequate models of human pharmacokinetics that is, displayed low oral bioavailability (rationale for IV product), IV dose proportionality, wide distribution (≤ total body water), short to moderate $T_{½}$ (mice ≤ approximately 4 h, rats approximately 15h, dogs approximately 8 h, monkeys approximately 15 to 20 h), multi-exponential plasma elimination, negligible to low levels of metabolism (<5% of IV dose), dominance of renal elimination, and no evidence of metabolic and/or distributional adaptation. There were no human specific metabolites. Peramivir undergoes limited liver S9 mediated cyclopentyl ring oxidation (humans: <4%, rats: ≤2%, dogs: 0%) to metabolite M1. M1 was not detected in humans in vivo (peramivir excreted unchanged in urine). Rabbits have an acyl glucuronide metabolite (≤4% of IV dose). Peramivir is also actively secreted (via probenecid susceptible OAT1 and/or OAT3) in the rabbit kidney (but not in rats or humans). These rabbit specific characteristics correlated with peramivir induced nephrotoxicity (likely species specific; uncertain human relevance). Reduced renal function (renal immaturity) in animals resulted in substantial increases in AUC (see juvenile studies below). Influenza virus infection did not affect IV pharmacokinetic parameters.
- Drug interactions are unlikely (interactions at rabbit renal OAT1 and/or OAT3 are likely species specific). Based on in vitro data peramivir is a weak enterothelial OCT1 and OCT1 and OSTα-OSTβ substrate; however clinically relevant drug interactions are unlikely (due to IV dosing route + dominance of renal excretion).
- Supratherapeutic IV peramivir had negligible acute toxicity in rodents and monkeys (maximum non-lethal IV dose ≥ 400 mg/kg). High relative exposures were achieved in the repeat IV dose studies. In the repeat IV dose rodent and monkey studies, peramivir had no consistent adverse effects on mortality, body weight, food consumption, ophthalmology, coagulation parameters, clinical chemistry, urinalysis, haematology, serum T4, ECG, intravascular injection sites, and anatomic pathology. Renal proximal tubular and renal pelvic mineralisation occurred in the near life-time PO carcinogenicity study in rats (unlikely human relevance: effect was not apparent after shorter periods of dosing and likely associated with peramivir's low water solubility + higher baseline urine osmolality in rats compared with humans). The nephrotoxicity observed in the repeat dose rabbit studies is of unlikely relevance to humans.
- Peramivir has a low genotoxic potential based on appropriately validated screening studies (bacterial reverse mutation assay, in vitro chromosomal aberration assay, in vivo mouse bone marrow micronucleus assay). Because of the proposed duration of use carcinogenicity studies are not required for peramivir. PO dosing with peramivir likely has a low carcinogenic potential based on the completed 2 year rat carcinogenesis study.
- Peramivir placental transfer occurred in rats (fetal concentrations < maternal plasma concentrations). IV bolus dosing of peramivir at ≤ 6 x MHRD (BSA comparisons) had

no adverse effect on male or female fertility or embryofetal development in rats. Maternal dosing of rats using continuous IV infusion resulted in fetal ureteral dilation/megaureters and reduction of the renal papillae (loss of renal stem cells; LOAEL approximately 4 x MHRD BSA comparison; resembled human congenital obstructive uropathy). Critically, these effects only occurred with continuous (that is, 24 h/day) IV infusion maternal dosing and not with bolus dosing. Furthermore maternal F_0 IV bolus dosing did not induce adverse effects on urinary tract development in F_1 rats in a pre-postnatal development study. Short-term IV bolus dosing of humans is unlikely to affect urinary tract development. However, based on the animal data, peramivir should only be used during pregnancy if the benefits of treatment outweigh the risks. Continuous (that is, 24 h/day) infusion should be avoided during pregnancy. Despite the presence of severe maternal nephrotoxicity IV bolus dosing of rabbits at ≤ approximately 15 x MHRD (BSA comparison) did not adversely affect reproduction or embryofetal development. Non-colostral galactogenic transfer occurred in rats (milk terminal half-life approximately 6.55 h, T_{max} 0.75 h) following PO dosing. The evaluator has proposed Pregnancy Category B3.

- Renal immaturity (that is, reduced GFR) was associated with very high plasma AUC in juvenile rats following IV bolus dosing. Due to differences in renal maturity in juvenile rats and rabbits compared with children, elevated peramivir plasma AUCs are unlikely in children aged 2 years and older (2 year old children have ≥≈95% of adult GFR). Despite the increased systemic exposures in juvenile rats no adverse effects on clinical signs, physical development, neuro-behaviour, genital development, haematology, clinical chemistry, urinalysis and anatomic pathology were detected. Transient (non-adverse) irregular respiration and ptosis was observed at 5 minutes post dosing in one study. Peramivir nephrotoxicity occurred following sub-therapeutic PO dosing of juvenile rabbits (likely not human relevant).
- Peramivir had acceptable IV local tolerance in animals. Peramivir is unlikely to be phototoxic. Peramivir did not induce passive cutaneous or systemic anaphylaxis in guinea pigs. However results in animals are poorly predictive of human risk and serious reactions (erythema multiforme, anaphylaxis and Stevens Johnson Syndrome) are reputed to have occurred in humans.

Conclusions and recommendation

- Approval is supported by the nonclinical evaluation
- Pregnancy Category B3 is recommended rather than Category B2
- The draft PI should be amended as indicated in the assessment
- The risk management plan (RMP) should be amended as indicated in the assessment. In particular, the RMP uses the product name Alpivab. This should be replaced with the proposed product name Rapivab.

V. Clinical findings

Introduction

Clinical rationale

The Antibiotic Therapeutic Guidelines 2014) state that regardless of the duration of symptoms, treatment should be offered to all individuals with established complications or to patients requiring admission to hospital for management of influenza. Treatment

should be considered for individuals at high risk of poor outcomes from influenza (for example, complications, severe influenza, hospitalisation, or death).

Guidance

There was no specific TGA guidance in the application. The submission does include post-marketing data from paediatric studies requested by the FDA.

Contents of the clinical dossier

This submission includes 17 Phase I studies in healthy volunteers (single and multiple-dose studies), 4 Phase II studies and 6 Phase III studies to evaluate the efficacy and safety of peramivir in the treatment of influenza. Seven influenza studies exclusively or predominantly enrolled patients with acute uncomplicated influenza (non-hospitalised). The remaining three influenza studies were conducted in subjects who were hospitalised with influenza.

Post-marketing: One ongoing clinical study (Study BCX1812-305) is being performed in children with uncomplicated influenza as a post marketing requirement from the FDA for the approval of the adult indication. Safety data from post-marketing studies in routine clinical use, paediatric patients and patients with high risk factors and the elderly conducted in Japan is also included in the summary of clinical safety. There is also an ongoing clinical study being conducted in elderly and high risk subjects (Study BCX1812-306) as a post marketing requirement from the FDA. A planned study to demonstrate superiority of peramivir compared to oseltamivir in paediatric patients hospitalised with serious influenza infection (Study BCX1812-307) was committed to be conducted in the EU Paediatric Investigation Plan (EMEA-001856-PIP02-16).

Paediatric data

Interim data from Study BCX1812-305 is included in this submission.

Good clinical practice

These studies have been conducted in compliance with Good Clinical Practice (GCP.

Pharmacokinetics

Studies providing pharmacokinetic data

Peramivir has been evaluated in an extensive clinical development program consisting of studies across all developmental phases, three routes of administration (SC, IM, and IV), and multiple subject and patient populations. This submission includes 17 Phase I clinical studies involving a total of 596 subjects receiving a single dose and 95 subjects receiving multiple doses of peramivir, as well as 4 Phase II studies and 6 Phase III studies involving a total of 2155 patients (1453 adults and 117 paediatric patients with uncomplicated influenza and 585 with complicated influenza requiring hospitalisation) dosed with peramivir.

Phase I studies included:

- Single- and multiple-escalating dose tolerance studies (StudiesBCX1812-101, BCX1812-102, BCX1812-103, 0712T0611, and 0714T0612). These studies were conducted in healthy volunteers with IV doses ranging from 0.5 mg/kg to 8 mg/kg on a weight based dose, and 100 to 800 mg daily on a fixed dose basis.

- A special population study in renally impaired patients (Study BCX1812-105).
- A special population study in elderly subjects (Study BCX1812-104).
- Drug interaction studies with rimantadine (Study BCX1812-108), oseltamivir (Study BCX1812-109), and the oral contraceptive ethinyl estradiol/levonorgestrel (Study BCX1812-110).
- Thorough QT (TQT) study conducted to examine peramivir effect on cardiac repolarisation (Study BCX1812-106) in healthy subjects administered single IV doses of 600 mg (clinical dose) and 1200 mg (supra-therapeutic dose).
- Single-escalating IM dose tolerance studies (Studies BCX1812-111, BCX1812-112, and BCX1812-116). These studies were conducted in healthy volunteers with IM doses ranging from 75 to 900 mg QD on a fixed-dose basis.
- Bioequivalence Study BCX1812-113 utilised both IV and IM doses to demonstrate bioequivalence of these two routes of administration.
- Study BCX1812-117 designed to assess the effect of needle length and BMI on peramivir exposure.
- Single SC dose tolerance study (Study BCX1812-118) conducted in healthy volunteers with a fixed SC dose of 300 mg.

Of the 10 Phase II and Phase III studies, 7 were performed using the IV formulation (Studies BCX1812-201, 0722T0621, BCX1812-301, BCX1812-303, 0815T0631, 0816T0632, and 0918T0633) and 3 were performed using the IM formulation (Studies BCX1812-211, BCX1812-212, and BCX1812-311). The Phase III Study 0918T0633 was performed with the IV formulation in a paediatric population.

Table 9: Submitted pharmacokinetic studies

PK topic	Subtopic		Study ID
PK in healthy adults	General PK	- Single dose	BCX1812-105 BCX1812-106 BCX1812-108 BCX1812-109 BCX1812-110 0712T0611 0712T0612
		- Multi-dose	BCX1812-101 BCX1812-102 0712T0611 O712T0612 BCX1812-103 BCX1812-104
	Bioequivalence †	- Single dose	BCX1812-113 BCX1812-111 BCX1812-112
		- Multi-dose	BCX1812-116
PK in special populations	Target population §	- Single dose	0722T0621
		- Multi-dose	BCX1812-201

PK topic	Subtopic	Study ID
	Hepatic impairment	N/A
	Renal impairment	BCX1812-105
	Neonates/infants/children/adolescents	0918T0633 BCX1812-303
	Elderly	BCX1812-104
	Other special population	BCX1812-117 BCX1812-118
PK interactions	Moxifloxacin	BCX1812-106
	Rimantadine	BCX1812-108
	Oseltamivir	BCX1812-109
	Ethinyl Estradiol/Levonorgestrel	BCX1812-110

† Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

Evaluator's conclusions on pharmacokinetics

The clinical pharmacology of peramivir has been investigated in healthy volunteers following single and multiple dose IV administration, single dose IM and SC administration, and at IV doses that encompass the proposed therapeutic dose of 600 mg. Peramivir was also investigated in subjects with renal impairment and in a variety of patients, both in the US and in Asia (Japan, Taiwan, and Korea), in whom the drug was administered as a single dose for acute uncomplicated influenza or as a multiple-dose treatment for influenza requiring hospitalisation.

The conclusions from the clinical pharmacology studies in both patients and healthy volunteers are summarised below:

- The pharmacokinetics of peramivir are characterized by rapid and nearly complete absorption following IV (by default), IM, and SC administration, dose linearity over a wide range of IV doses (that is, 50 to 1200 mg), and a multi-exponential PK behaviour with a terminal-phase elimination half-life of approximately 20 hours.
- The bioavailability (AUC) of IM and SC peramivir was comparable to that following IV administration, with the peak and time-of-peak exposure of drug after IV administration being dependent on the duration of infusion.
- Mean values of peramivir clearance following IV administration ranged between 6.03 L/hr and 6.78 L/hr across a broad range of IV doses (300-1200 mg), which included the proposed therapeutic dose of 600 mg. Therefore, the average exposure level (AUC) derived from CL is expected to the same in both the US and Asian population.
- Peramivir undergoes extensive renal elimination, with the clearance of parent drug paralleling that of renal glomerular filtration. While there was no significant change in C_{max}, the AUC of peramivir increased incrementally with declining renal function. However, since peramivir would be administered as a single dose treatment, no significant accumulation (ordinarily associated with multiple dosing) would be expected.

- A simulation comparing normal and really-impaired patients showed that C_{max} is essentially unchanged between the two populations. AUC_{∞}, while higher in the renal failure population than would occur with the same dosing in normal renal function, is substantially lower than what would be expected with qd dosing for 5 days in subjects with normal renal function. Based on these findings, no dose adjustment is required for administration of single doses to subjects with decreased renal function in view of no observed increase in C_{max}.
- The results of three drug interaction studies indicated that at therapeutic doses peramivir had no effect on the PK of rimantadine, oseltamivir, and oral contraceptives.
- The results of multiple population pharmacokinetic analyses performed at various stages of clinical development to investigate the effects of multiple demographic factors (for example, age, weight, gender, creatinine clearance, and ethnicity) on the PK of peramivir has revealed that there were no clinically relevant covariate findings that would influence the proposed dose. Otherwise, the population PK results were consistent with the PK results of the individual Phase I studies.
- The results of the definitive population pharmacokinetic analysis suggest that 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% versus 12.7%) and for all viral IC_{50} values, collectively (52.1% versus 43.6); intravenous doses in the range of 300 to 600 mg are on the ascending part of the peramivir exposure-response curve with respect to target time above viral IC_{50}, and 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}.

Therefore, the clinical pharmacology results, reviewed collectively with the efficacy and safety data, support the use of peramivir 600 mg administered IV over at least 15 minutes as a single dose for the treatment of acute uncomplicated influenza.

Pharmacodynamics

Studies providing pharmacodynamic data

See Table 10, below.

Table 10: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Effect on clinical symptoms §	BCX1812-211	*
		BCX1812-212	*
		BCX1812-311	*
		0815T0631	*
		0815T0632	*
		0918T0633	*
Gender other genetic and Age Related Differences in PD Response	Effect of gender	N/A	
	Effect of genetic characteristic	N/A	
	Effect of genetic characteristic	N/A	

PD Topic	Subtopic	Study ID	*
	Effect of age ‡	BCX1812-301 BCX1812-303 0918T0633	
Population PD and PK-PD analyses	Healthy subjects	N/A	
	Target population§	BCX1812-301 BCX1812-303	* *

* Indicates the primary PD aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication. ‡ And adolescents if applicable.

Evaluator's conclusions on pharmacodynamics

The only treatment-emergent mutation of significance associated with peramivir exposure was the H275Y mutation in influenza A/H1N1 that has been previously associated with resistance to OSE. Presence of this mutation results in a partial loss of susceptibility to peramivir. The incidence of development of treatment-emergent H275Y substitutions in response to treatment with peramivir appears to be low.

Dosage selection for the pivotal studies

Pharmacokinetics and pharmacodynamics: dose finding studies

Studies 0712T0612, 0712T0611, BCX1812-201, BCX1812-103, BCX1812-111, BCX1812-112, BCX1812-116, BCX1812-117 were all Phase I dose finding studies, carried out in either Japan or the USA. Following these, it was decided that 600 mg would be taken forward as the dose for the Phase II and the pivotal studies.

Phase II dose finding studies

These studies include Studies BCX1812-211 and 0722T0621. Study 0722T0621 is the pivotal study in this submission.

Results of the placebo-controlled Study 0722T0621 support the efficacy of both 300 mg and 600-mg single IV infusions of peramivir and provide evidence that the 600-mg dose results in superior virologic effects.

- For the primary endpoint of time to alleviation of symptoms, statistically significant improvement was seen for both randomised doses (300 mg and 600 mg) of peramivir compared with placebo. The magnitude of clinical benefit in time to alleviation of symptoms was similar for both randomised doses of peramivir.

Phase III pivotal studies investigating more than one dose regimen

Study 0815T0631 was a Phase III trial (conducted in Japan, Taiwan and South Korea) in patients with influenza, assessing the 300 mg and the 600 mg dose in comparison to Oseltamivir. Study 0816T0632 was also conducted in Japan in people with uncomplicated influenza, which compared the 300 mg and the 600 mg dose in relation to time to symptom resolution.

Evaluator's conclusions on dose finding for the pivotal studies

Results of the integrated analyses of efficacy support efficacy of both 300 mg and 600 mg single IV infusions of peramivir for treatment of acute uncomplicated influenza, and provide some supporting evidence that the 600 mg dose results in superior clinical and virologic effects. For the primary endpoint of time to alleviation of symptoms, a dose-ordered response was seen in the integrated ITTI population, with a larger difference from placebo seen for subjects who received a 600 mg dose of peramivir (-28.3 hours), compared with subjects who received a 300 mg dose (-24.8 hours). A dose-ordered response was seen for viral shedding at Day 3. At this time point, 51.5% of placebo subjects (50/97 subjects) had a positive viral titre, compared with 36.8% of subjects in the 300-mg dose group (35/95 subjects) and 25.8% of subjects in the 600-mg dose group (24/93 subjects).

Results of the ongoing Study BCX1812-305 demonstrates that a single dose of IV peramivir (600 mg for children 13 to 18 years or 12 mg/kg for children 2 to 12 years) produced PK parameters (plasma concentration and truncated $AUC_{0\text{-}3h}$) that were comparable with those in adults. Effectiveness of peramivir in this study was similar to oseltamivir and resolution of influenza signs and symptoms and viral shedding for paediatric patients administered peramivir in this study was consistent with that observed in placebo-controlled studies in peramivir treated adults with influenza. The study also demonstrated the safety and tolerability of peramivir in this population at these doses. These results are supported by Study 0918T0633 in Japanese children. Analyses of adverse events and laboratory safety indicators support the safety and tolerability of both 300 mg and 600 mg or 12 mg/kg for patients ≤ 12 years of age, single IV infusions of peramivir for the treatment of influenza and provide no evidence of inferior safety at the higher dose.

Given the clinical evidence of efficacy of the 600 mg dose of peramivir, the range of susceptibility of viral subtypes, and the PK-PD modelling results, a dose of 600 mg peramivir in adults is likely to benefit more patients than would a lower dose of peramivir for the treatment of influenza. A 5-day treatment regimen of a single IV infusion of 600 mg (for patients > 12 years of age) or 12 mg/kg for patients ≤ 12 years of age (up to a maximum of 600 mg) of peramivir is recommended for the treatment of patients hospitalised with influenza.

Efficacy

Studies providing efficacy data

The companies involved in the development of peramivir completed a total of ten Phase II and Phase III clinical studies (nine in adults and one in children) to evaluate the efficacy and safety of peramivir in the treatment of influenza. Seven studies exclusively or predominantly enrolled patients with acute uncomplicated influenza. The remaining 3 studies were conducted in subjects who were hospitalised with influenza. In addition, there is one ongoing clinical study being performed in children with uncomplicated influenza and one post marketing study in children conducted in Japan.

The pivotal study for the use of IV peramivir to treat subjects with acute uncomplicated influenza is Study 0722T0621, a Phase II double blind, placebo controlled, single dose study that enrolled 300 Japanese subjects with confirmed influenza. Both dosages of peramivir (single IV doses of 300 or 600 mg) significantly shortened the time to alleviation of influenza symptoms (duration of influenza, the primary endpoint) compared with placebo.

Studies BCX1812-211, BCX1812-311, and BCX1812-212 provide supportive data for the use of single parenteral doses of peramivir to treat influenza in the outpatient setting; in these studies, peramivir was administered as a single dose via bilateral IM injections to subjects with influenza.

Study BCX1812-211 was a Phase II, randomised study that enrolled 344 subjects with acute, uncomplicated influenza who received placebo, 150 mg peramivir or 300 mg peramivir as a single, divided IM dose. Study BCX1812-311 was similar in design and was planned as a Phase III study, but was terminated early after 82 subjects had enrolled and were randomised 2:1 to receive placebo or 300 mg peramivir in a single, divided IM dose. The study was terminated in order to study higher doses in subsequent studies. These 2 studies had almost identical eligibility criteria, had identical primary and secondary efficacy endpoints, and were conducted in successive influenza seasons. When the results from studies BCX1812-211 and BCX1812-311 were retrospectively combined in a post-hoc analysis (following an agreement with the FDA), both primary and secondary endpoints for peramivir-treated subjects were improved compared to placebo. Study BCX1812-212 was a placebo-controlled study of 405 subjects who were randomised 1:1 to receive either placebo or 600 mg of peramivir as a single divided IM dose. This study was conducted during a season in which the dominant circulating strain of influenza A showed reduced susceptibility to peramivir, and the results showed a non-significant trend favouring peramivir in the primary endpoint of time to alleviation of symptoms.

Two additional studies are included as supportive efficacy studies. Study 0815T0631 was a double blind, double-dummy study of 1099 subjects from Japan, Taiwan and South Korea who were randomised to receive a single dose of IV peramivir (300 mg or 600 mg) or 5 days of oral OSE twice per day (BD). For the primary endpoint of time to alleviation of symptoms, both peramivir treatment regimens were non-inferior to OSE. Study 0816T0632 was a double blind, non-controlled study in high-risk patients with influenza; in this study, the duration of influenza illness was shorter among subjects who received 600 mg doses of peramivir compared with those in the 300-mg treatment group, although the 90% confidence intervals (CI) overlapped.

Three studies in hospitalised subjects with acute serious or potentially life-threatening influenza are included as supportive efficacy studies. Study, BCX1812-201 was a Phase II, double masked, double dummy pilot study in 137 subjects from the USA, South Africa, Canada, Australia, Hong Kong, New Zealand and Singapore who were randomised to receive IV peramivir (200 mg or 400 mg) once daily for 5 days or 5 days of oral OSE BD. For the primary endpoint of time to clinical stability, similar results were observed in both peramivir treatment regimens and OSE. Study BCX1812-301 was a Phase III, randomised, double blind, controlled study in 405 subjects from Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Czech Republic, Germany, Hungary, India, Israel, Latvia, Lebanon, Peru, Poland, Russia, Slovakia, South Africa, Ukraine and the USA who were randomised to receive IV peramivir (600 mg for >18 years; 10 mg/kg for 12 to 17 years; 12 mg/kg for 6 to 12 years) once daily for 5 days or placebo in addition to institution's standard of care (SOC). Subjects could receive an additional 5 days of dosing if clinical resolution was not achieved by Day 5. For the primary endpoint of time to clinical resolution, similar results were observed in peramivir treatment and standard of care alone. Study BCX1812-303 was a Phase III, open-label, study in 234 subjects from the USA, Canada, Australia, New Zealand and Mexico who were randomised to receive IV peramivir (600 mg for adults (10 mg/kg for children <18 years) once per day (QD) or 300 mg BD for adults (5 mg/kg for children <18 years) for 5 days. Subjects could receive an additional 5 days of dosing if clinical resolution was not achieved by Day 5. For the primary endpoint of assessment of antiviral activity, similar results were observed in both peramivir treatment regimens.

Two studies in children with acute influenza are included as supportive efficacy studies. Study 0918T0633 was a non-controlled, open-label study conducted in paediatric subjects

with influenza (either inpatient or outpatient). For the primary endpoint of duration of influenza illness, no differences were noted between the age groups of 28 days to <2 years, 2 to < 6 years, 6 to < 12 years, and 12 to < 16 years of age. Study BCX1812-305 (ongoing) is a Phase III, open-label, active-controlled, study in 108 subjects (interim) from the USA were randomised to receive a single dose of IV peramivir (600 mg for >12 years; 12 mg/kg for 2-12 years; once daily or 5 days of oral OSE BD. The primary endpoint of the study was safety, however similar effectiveness outcomes were observed in peramivir and OSE.

Evaluator's conclusions on efficacy

Treatment with peramivir was associated with a significant reduction in the primary efficacy endpoint, time to alleviation of symptoms, with a median improvement of approximately 1 day for peramivir treatment compared with placebo. The size of this treatment effect is consistent with that observed for the approved neuraminidase inhibitors. The response for this endpoint was dose ordered, with the greatest improvement (-28.3 hours) seen among adult subjects who received a dose of 600 mg peramivir. Peramivir treatment was also associated with a significant improvement in the time to resolution of fever compared with placebo, which again was dose ordered, with the largest decrease in time to resolution of fever (-10.7 hours) seen among adult subjects who received 600 mg peramivir. Similarly, the time to resumption of usual activities also demonstrated a benefit for peramivir treatment. Adult subjects who received a 600-mg dose of peramivir resumed usual activities 4 days earlier compared with placebo, a significant difference. The effectiveness findings from active-controlled paediatric Study BCX1812-305 are in line with the efficacy results from the adult studies. There were no notable differences in the effectiveness of peramivir stratified by influenza virus subtypes, and no evidence of changes in susceptibility in virus isolates. There were no notable differences in the effectiveness of peramivir by age cohort, and no apparent age-related trends.

The virologic efficacy of peramivir was assessed by the time-weighted change from Baseline in log10 $TCID_{50}$/mL, the absolute change from Baseline in log10 $TCID_{50}$/mL, and by the proportion of subjects shedding virus. Although the outcome varied by study and did not demonstrate a consistent dose ordered effect, the results for time weighted and absolute change from baseline in $TCID_{50}$/mL favoured peramivir treatment compared with placebo. In relation to the proportion of subjects shedding virus, peramivir treatment groups, clearly demonstrate the benefit of peramivir over placebo at Day 2 and Day 3. The lowest proportion of subjects shedding virus was seen in the 600 mg treatment group. Analysis of hospital use of peramivir also indicates that peramivir and oseltamivir have similar clinical efficacy in the treatment of severe seasonal influenza.

Given the available clinical evidence of the effectiveness of the indicated dose of peramivir in adult and paediatric patients and the PK analysis results, a single IV infusion of peramivir at the dose levels of 600 mg or 12 mg/kg for patients ≤ 12 years of age (up to a maximum of 600 mg) seems appropriate for treatment of influenza in paediatric patients aged 2 years and older.

Safety

Studies providing safety data

The safety of peramivir administered IV or IM has been evaluated in Phase I, II, and III clinical studies involving 3,676 subjects (3,540 adults and 136 children under the age of 18), including 2,155 peramivir subjects in influenza studies, 1,128 of whom received ≥ 1 dose of ≥ 600 mg of peramivir. Twenty-seven clinical trials were undertaken to evaluate the clinical pharmacology, safety, and efficacy of peramivir: 17 studies in healthy

volunteers (single and multiple-dose studies), 7 clinical trials in acute uncomplicated influenza, and 3 clinical trials in subjects hospitalised with influenza. These studies have included 1,570 adult and paediatric peramivir subjects with acute uncomplicated influenza and 585 peramivir subjects (100% peramivir IV) with influenza admitted to hospital, of which approximately 120 were managed in an intensive care setting. The patient exposure for all these patient groups and all different doses (and cumulative dose) is summarised in Tables 11 to 19, below. An additional study of peramivir in 78 paediatric patients (Study BCX1812 305) is ongoing; the results from subjects aged 2 to 18 years are included in this document however this data has not been integrated with data from the completed studies.

Pivotal studies that assessed safety as the sole primary outcome

Not applicable.

Pivotal and/or main efficacy studies

The following Pivotal Phase II study provided safety data: Study 0722T0621

Other studies

The common TEAEs in both the single and multiple dose studies reflected anticipated risks with an injection as well as the low pH of peramivir for intramuscular injection. Otherwise, there were no safety risks to emerge from the Phase I studies. The following Phase II and III studies provided safety data.

- In uncomplicated influenza:
  - Phase II
    - BCX1812-211
    - BCX1812-212
  - Phase III
    - BCX1812-311
    - 0815T0631
    - 0816T0632
    - 0918T0633 (paediatric)
- In hospitalised patients:
  - Phase II
    - BCX1812-201
  - Phase III
    - BCX1812-301
    - BCX1812-303
    - BCX1812-305 (paediatric ongoing)

Patient exposure

The table below outlines the distribution of all the patients in the Phase II/III studies included in the safety cohort.

Table 11: Distribution of all subjects across ISS pools in Phase II/III studies of peramivir in influenza (Safety Population)

ISS Pool	Placebo	Active Control	Peramivir	Row Total	Row Total as % of Grand Total
Adult Acute Uncomplicated Influenza	441	365	1453	2259	71.9%
Pediatric Acute Uncomplicated Influenza	0	0	117	117	3.7%
Hospitalized Influenza Studies BCX1812-201/301)	49	131	355	535	17.0%
Hospitalized Influenza Study BCX1812-303	0	0	230	230	7.3%
Column Total	490	496	2155	3141	
Column Total as % of Grand Total	15.6%	15.8%	68.6%		

Total exposure of adult subjects across all Phase II and Phase III studies in acute, uncomplicated influenza are displayed. In adult subjects with acute uncomplicated influenza, the number of days of peramivir treatment ranged 1 day to 5 days, with a mean of 1 day of exposure. In Study 0816T0632, enrolling high risk subjects, multiple days of therapy were allowed. The most common dosing period was 2 days, but 3 subjects were treated with peramivir for 3 days, 1 subject for 4 days, and 1 subject for 5 days. In Studies 0722T621 and 0815T0631, as well as BCX1812-211, BCX1812- 212, and BCX1812-311, subjects were administered a single dose of peramivir given either intravenously or intramuscularly. Cumulative peramivir exposure in adult subjects receiving study drug ranged from 75 mg to 2400 mg, with a mean of 442 mg of peramivir.

Table 12: Distribution of subjects receiving at least 1 dose of peramivir across ISS pools in Phase II/III studies of peramivir in influenza (Safety Population)

ISS Pool	< 300 mg	300 - < 600 mg	≥ 600 mg	Row Total	Row Total as % of Grand Total	Total N in ISS Pool	Row Total as % of ISS Pool
Adult Acute Uncomplicated Influenza	113	655	685	1453	67.4%	2259	64%
Pediatric Acute Uncomplicated Influenza	55	56	6	117	5.4%	117	100%
Hospitalized Influenza Studies BCX1812-201/301)	76	49	230	355	16.5%	535	66%
Hospitalized Influenza Study BCX1812-303	21	2	207	230	10.7%	230	100%
Column Total	265	762	1128	2155		3141	69%
Column Total as % of Grand Total	12.3%	35.4%	52.3%				

Table 13: Exposure to peramivir in studies of acute, uncomplicated influenza in adults (Safety Population)

	Peramivir			
Variable	< 300 mg N = 113	≥ 300-< 600 mg N = 665	≥ 600 mg N = 685	Overall Peramivir N = 1453
Days on Study Drug				
Mean (SD)	1 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Min, Max	1, 1	1, 5	1, 4	1, 5
Total Cumulative Dose of Peramivir (mg)				
Mean (SD)	149 (7.1)	308 (68.0)	619 (122.2)	442 (196.3)
Min, Max	75, 150	300, 1500	600, 2400	75, 2400

Table 14: Total cumulative exposure to peramivir in studies of acute, uncomplicated influenza in adults (Safety Population)

	Number of Subjects Exposed to Peramivir per dose			Total number of subjects/cumulative exposed dose
Cumulative exposed dose	<300 mg N = 113 n (%) [a]	300-<600 mg N = 655 n (%) [a]	≥600 mg N = 685 n (%) [a]	n (%) [b] 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

Exposure of hospitalised patients is detailed, which reveal numbers for each dose and cumulative exposure. Total exposure in all subjects hospitalised with influenza (excluding Study BCX1812-303) is displayed. In subjects hospitalised with influenza, the duration of peramivir exposure ranged from 1 day to 11 days, with an average duration of exposure of 5 days (excluding Study BCX1812-303). Cumulative exposure to peramivir in hospitalised subjects (excluding Study BCX1812-303) ranged from 100 mg to 6000 mg, with an average cumulative peramivir exposure of 2608 mg as shown in Tables 15 and 16, below.

Table 15: Exposure to peramivir in hospitalised influenza (Safety Population, excluding Study BCX1812-303)

	Peramivir Monotherapy			Peramivir plus Other Active Study Drug				
Variable	<300 mg N = 51	300-600 mg N = 46	≥600 mg N = 101	<300 mg + Non-NAI N = 25	300-600 mg + Non-NAI N = 3	≥600 mg + Non-NAI N = 6	≥600 mg + NAI N = 123	Overall Peramivir N = 355
Days on Study Drug								
Mean (SD)	6 (1.1)	5 (1.0)	5 (1.7)	6 (2.6)	5 (0.0)	5 (0.0)	5 (1.9)	5 (1.7)
Min, Max	2, 10	2, 6	1, 10	1, 10	5, 5	5, 5	1, 11	1, 11
Total Cumulative Dose of Peramivir (mg)								
Mean (SD)	1063 (704.8)	1913 (336.4)	3212 (1033.0)	1389 (1148.1)	2733 (293.0)	3000 (0.0)	3237 (1118.1)	2608 (1289.5)
Min, Max	200, 5550	400, 2000	600, 6000	100, 4650	2400, 2950	3000, 3000	600, 6000	100, 6000

Table 16: Total cumulative exposure to peramivir in hospitalised influenza (Safety Population, excluding Study BCX1812-303)

	Peramivir Monotherapy			Peramivir plus Other Active Study Drug				
Number of Subjects Exposed to Peramivir Dose, n (%)	<300 mg N = 51	300-600 mg N = 46	≥600 mg N = 101	<300 mg + Non-NAI N = 25	300-600 mg + Non-NAI N = 3	≥600 mg + Non-NAI N = 6	≥600 mg + NAI N = 123	Overall Peramivir N = 355
<300 mg	1 (2.0 %)	0	0	4 (16.0 %)	0	0	0	5 (1.4 %)
≥300-<600 mg	3 (5.9 %)	1 (2.2 %)	0	3 (12.0 %)	0	0	0	7 (2.0 %)
≥600-<1200 mg	44 (86.3 %)	2 (4.3 %)	2 (2.0 %)	6 (24.0 %)	0	0	3 (2.4 %)	57 (16.1 %)
≥1200-<2400 mg	2 (3.9 %)	43 (93.5 %)	3 (3.0 %)	5 (20.0 %)	0	0	5 (4.1 %)	58 (16.3 %)
≥2400-<3600 mg	0	0	85 (84.2 %)	6 (24.0 %)	3 (100.0%)	6 (100.0%)	99 (80.5 %)	199 (56.1 %)
≥3600 mg	1 (2.0 %)	0	11 (10.9 %)	1 (4.0 %)	0	0	16 (13.0 %)	29 (8.2 %)

Table 17: Total cumulative exposure to peramivir in hospitalised influenza in Study BCX1812-303 (Safety Population)

	Peramivir		
Cumulative dose of peramivir	<300 mg N = 21	300-600 mg N = 2	≥600 mg N = 207
<300 mg	4 (19.0 %)	0	0
≥300-<600 mg	3 (14.3 %)	1 (50.0 %)	3 (1.4 %)
≥600-<1200 mg	7 (33.3 %)	0	8 (3.9 %)
≥1200-<2400 mg	3 (14.3 %)	1 (50.0 %)	9 (4.3 %)
≥2400-<3600 mg	0	0	140 (67.6 %)
≥3600 mg	4 (19.0 %)	0	47 (22.7 %)

Table 18: Exposure to peramivir in a paediatric study in acute, uncomplicated influenza by age (Safety Population; Study 0918T0633)

	Overall Peramivir				
Variable	Age ≥ 28 days to < 1 year	Age ≥ 1 year to < 6 years	Age ≥ 6 years to < 12 years	Age ≥12 years to < 18 years	All pediatric subjects exposed to peramivir
	N = 4	N = 29	N = 47	N = 37	N = 117
Days on Study Drug					
Mean (SD)	2 (0.6)	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.3)
Min, Max	1, 2	1, 2	1, 2	1, 2	1, 2
Total Cumulative Dose of Peramivir (mg)					
Mean (SD)	109 (43.9)	161 (68.4)	350 (128.3)	513 (171.8)	346 (190.6)
Min, Max	67, 156	83, 400	190, 760	250, 1200	67, 1200

Table 19: Total cumulative peramivir exposure in a paediatric study in acute, uncomplicated influenza (Safety Population 0918T0633)

Number of Subjects Exposed to Peramivir Dose, n (%)	Overall Peramivir N = 117
<300 mg	51 (43.6 %)
≥300-<600 mg	57 (48.7 %)
≥600-<1200 mg	8 (6.8 %)
≥1200-<2400 mg	1 (0.9 %)

Safety issues with the potential for major regulatory impact

Liver function and liver toxicity

Integrated safety analyses

In uncomplicated influenza, no notable changes or differences were noted. In hospitalised patients with influenza, changes in graded laboratory values in subjects hospitalised with influenza, excluding those in Study BCX1812-303, were generally similar across treatment groups. Changes in AST values were more frequent in subjects treated with peramivir (3.4%) than in subjects treated with placebo (0%), active non-NAI (0%), and oseltamivir (0.8%). These shifts were mostly shifts of 1 grade from baseline, with the exception of 1 subject (0.3%) treated with peramivir who had a 2 grade shift in AST values from Baseline. Changes in ALT were balanced across all treatment groups (overall peramivir 5.7%, placebo 6.3% and oseltamivir 6.5%) and were mostly shifts of 1 grade from baseline values, with the exception of 5 subjects (1.5%) treated with peramivir who had a 2 grade shift in ALT values, 1 subject (0.3%) treated with peramivir who had a 3 grade shift in ALT values, 1 subject (2.1%) treated with placebo who had a 2-grade shift in ALT values, and 1 subject (0.8%) treated with oseltamivir who had a 3-grade shift in ALT values.

Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

Pivotal and/or main efficacy studies

There were no major changes observed in the AST, ALT, LDH or ALP.

Other studies

This is discussed above.

Renal function and renal toxicity

Integrated safety analyses

No abnormalities reported.

Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

Pivotal and/or main efficacy studies

There were almost no changes in the mean values for the serum creatinine in either the 300 mg group or the 600 mg group before and after dosing, and the results were the same as those observed in the placebo group.

Other studies

See discussion above.

Other clinical chemistry

Integrated safety analyses

In hospitalised patients, changes in glucose levels were balanced across treatment arms (13.0% peramivir-treated subjects, 12.5% placebo treated subjects, and 13.8% oseltamivir treated subjects). These shifts tended to be shifts of 1 grade from baseline, except for 8 subjects (2.4%) treated with peramivir, 1 subject (2.1%) treated with placebo, and 3 subjects (2.4%) treated with oseltamivir who experienced 2 grade shifts in glucose levels. Due to the increased severity of baseline disease in subjects hospitalised with influenza, there was an increase in the incidence of laboratory shifts in these subjects compared to studies of healthy subjects or studies of acute uncomplicated influenza. Increased blood glucose was reported in 5.3% of peramivir 600 mg treated subjects compared to 4.8% placebo and 3.3% OSE. 'White blood cells in the urine' was reported in 2.8% of peramivir 600 mg treated subjects compared to 1.8% placebo and 4.4% OSE.

Changes in graded laboratory values for Study BCX1812-303 indicated that the < 300 mg peramivir group tended to have more changes in calcium (15.0%), magnesium (15.0%), and protein in the urine (16.7%) when compared to the 600 mg peramivir group (4.0%, 7.1%, and 7.9%, respectively). These shifts were primarily shifts of 1 grade from baseline values. Subjects treated with < 300 mg peramivir or ≥ 600 mg peramivir experienced a similar incidence of increased glucose levels (21.1% and 15.5%, respectively).

Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

Pivotal and/or main efficacy studies

No significant changes were observed in the mean values for the chemistry, total protein, albumin, uric acid, CK or blood glucose during the study.

Other studies

See discussion above.

Haematology and haematological toxicity

Integrated safety analyses

In the ISS, Decreased neutrophil count was reported in 5.7% of peramivir 600 mg treated subjects compared to 0% placebo and 8.8% OSE. Despite what appears to be an imbalance in neutrophil count decreased, all but 1 report of decreased neutrophil count came from a single non-placebo controlled Study 0815T0631. In the 3 arms, decreased neutrophil count was reported in 39 (10.7%) subjects receiving 300 mg peramivir, 38 (10.4%) subjects receiving 600 mg peramivir and 34 (9.3%) subjects receiving OSE. In placebo controlled trials with a 600 mg dose of peramivir, the AEs of decreased neutrophil count and neutropenia were reported in 0.3% of subjects treated with peramivir and 0.3% of subjects treated with placebo.

Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

Pivotal and/or main efficacy studies

The most frequently observed adverse event (clinical laboratory test value) in Study 0722T0621 was ''monocyte fraction increased',' but the incidence of this event was higher in the placebo group. Adverse events of ''lymphocyte fraction increased',' ''lymphocyte morphological abnormality'' and ''white blood cell count decreased'' were frequently observed in each peramivir treatment group, but because these events were also observed in the placebo group, and because the variations were approximately the same, it was believed that these changes were due to the underlying influenza or the recovery process.

Other studies

See discussion above.

Other laboratory tests

Integrated safety analyses

Not applicable.

Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

Pivotal and/or main efficacy studies

Not applicable.

Other studies

Not applicable.

Electrocardiograph findings and cardiovascular safety

Integrated safety analyses

A small number of subjects had prolonged QT, without any clinical symptoms.

Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

Pivotal and/or main efficacy studies

Adverse events of ''ECG QT prolonged'' were defined by a 60 ms or more increase in the QTc from the baseline. This was observed in 2 subjects in the 300 mg group, 1 subject in the 600 mg group and 3 subjects in the placebo group. Of these events, there was 1 case in the 300 mg group for which this adverse event was judged to be severe, but the QTcF at the time of onset was within the normal range, the ECG findings were normal, and there were no subjective symptoms observed.

Other studies

Not applicable.

Vital signs and clinical examination findings

Integrated safety analyses

Vital signs were similar across all subjects with uncomplicated influenza. While some potentially clinically significant values and changes were reported, these were similar across all treatment groups. No signals in vital signs were noted and no differences between peramivir, placebo or NAI were observed.

Pivotal studies that assessed safety as the sole primary outcome

Not applicable.

Pivotal and/or main efficacy studies

No significant differences between groups were reported.

Other studies

See discussion above.

Immunogenicity and immunological events

Integrated safety analyses

Angioedema occurred in one patient who receive OSE.

Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

Pivotal and/or main efficacy studies

None reported.

Other studies

Not applicable.

Serious skin reactions

Integrated safety analyses

These occurred rarely and are discussed more fully in the post-marketing data.

Pivotal studies that assessed safety as the sole primary outcome

Not applicable.

Pivotal and/or main efficacy studies

Not applicable.

Other studies

Not applicable.

Other safety parameters

Integrated safety analyses

A number of events were chosen as events of special interest because they had been observed with other NAIs. In particular, neuropsychiatric events, rash, hypersensitivity, liver enzyme abnormalities, and haemorrhagic colitis are events noted in the safety information of other NAIs. Renal toxicity was specified as an event of special interest due to the preclinical toxicity findings noted in rabbits. Other events of special interest were based on particular TEAE patterns noted in clinical trials for peramivir and other NAIs, including leukopenia, neutropenia, infusion-site reaction, and muscle injury, or in the post marketing safety experience such as orthostatic hypotension/shock.

None of these events of interest had relevant findings other than ''infusion site reaction''.' Intravenously administrated peramivir may be associated with a very low rate of infusion site reactions, including pain, similar to rates observed in control cohorts in influenza studies. Infusion site reactions are associated with intravenous medications in general. In addition, mild muscle injury and injection site pain were noted in association with IM peramivir use. There is little clinical evidence that IV peramivir use leads to any muscle injury. Muscle enzyme elevations are noted in influenza, particularly in more severe cases which is consistent with the clinically reported data. In the ongoing Study BCX1812-305 there were similar observations to adults and no new safety signals identified.

Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

Pivotal and/or main efficacy studies

Not applicable.

Other studies

Not applicable.

Post-marketing data

Three post marketing studies have been undertaken in Japan, one study in routine clinical use (Study 1303-H148-04 in 1309 patients), one study in paediatric patients (Study 1303-H148-04 in 1254 patients), and one study in patients with high risk factors (Study 1303-H148-04 in 772 patients). In each study, efficacy was assessed in a subset of patients (1158 patients in routine clinical use; 1186 paediatric patients; and 688 patients with high risk factors). Efficacy evaluations included the percentage of patients in whom influenza viral infection was determined by the attending physician to have been cured, time to alleviation of influenza symptoms, and time to resolution of fever.

Study 1303-H148-04

This post approval observational safety study was carried out between October 2010 and February 2012. A total of 1,309 patients were enrolled at 193 institutions in Japan. The safety evaluable population was 1,174 because 133 patients who were never observed after the start of treatment and 2 patients who were treated outside the investigation period were excluded. No AEs occurred in the 2 patients who were treated outside the investigation period. There were 560 (47.7%) male and 613 (52.2%) female patients in the safety evaluable group, with 1 patient whose gender was unknown. The majority of patients were between 15 and 65 years of age. There were 130 (11.1%) patients who were aged ≥ 65 years. Although this was not a paediatric study, 69 (5.9%) patients less than 15 years of age were also evaluated in the post marketing report.

Almost all patients (1,145, 97.5%) received peramivir within 2 days of the start of influenza symptoms. Most patients were treated in an outpatient setting, but 38 (3.2%) were hospitalised for influenza, and 5 patients had serious influenza defined as either influenza encephalopathy or the need for mechanical ventilation. Almost all patients (98.3%) received only 1 day of treatment with peramivir.

A total of 51 patients experienced AEs deemed related to peramivir by the prescribing physicians. There were a total of 78 AEs, and all were non-serious. No fatal AEs were reported. Most of the AEs (71, 91.0%) occurred within 3 days after the start of treatment with peramivir. The outcome for 1 AE of diarrhoea was unknown, but the remaining 77 AEs (98.7%) were resolved or improved, and 62 (79.5%) of these AEs resolved or improved within 3 days after onset. The most common AEs were diarrhoea (22 AEs, 1.87%), vomiting (10 AEs, 0.85%), and nausea (8 AEs, 0.68%). There were no significant differences between the AE incidences in patients less than 15 years of age and the AE incidence in those between the ages of 15 and 65 years of age, and no new safety events were noted. Likewise, in the 130 elderly patients (≥ 65 years of age), there was no significant difference in the incidence of AEs between this population and those from adult patients 15 to 65 years of age, and no new safety events were noted. No new safety signals were found as a result of this post approval safety surveillance study.

Study 1303-H148-04, safety surveillance in a paediatric routine setting

This post approval observational safety and efficacy surveillance study was carried out between October 2010 and February 2012 in a routine paediatric setting and evaluated patients < 15 years of age, as described in the Paediatric Post approval Safety Surveillance Study Report. A total of 1,254 patients were evaluated at 173 institutions in Japan. The safety evaluable population was 1,199 following the exclusion of 50 patients who were never observed after the start of treatment, 1 patient who was treated outside the investigation period, and 4 patients who were duplicate cases. No AEs occurred in the patients excluded from safety analysis. There were 654 (54.5%) male and 545 (45.5%) female patients in the safety evaluable group. Fifty-four patients were < 1 year of age, including 1 patient who was < 4 weeks of age. Approximately half of the patients (527, 44.0%) were ≥ 1 to < 7 years of age, and slightly more than half (616 patients, 51.4%) were ≥ 7 to < 15 years of age. No age was reported for 2 patients. In addition, a special

analysis was performed on patients < 2 years of age and those ≥ 2 years of age. There was no significant difference in the incidence of AEs or the types of AEs in infants and toddlers versus older children.

Almost all patients (1008, 84.1%) received peramivir within 1 day of the start of influenza symptoms. Most patients were treated in an outpatient setting, but 138 (11.5%) were hospitalised for influenza, and 11 patients had serious influenza, defined as either influenza encephalopathy or the need for mechanical ventilation. Almost all patients (96.7%) received only 1 day of treatment with peramivir.

A total of 92 patients experienced 115 AEs deemed related to peramivir by the prescribing physicians. Fourteen of the AEs were serious. There were 5 SAEs of abnormal behaviour and 5 SAEs of neutropenia (2 severe). There were no fatal AEs reported. Most of the AEs (100, 87.0%) occurred within 3 days after the start of treatment with peramivir. Almost all AEs recovered or improved (108, 93.9%). However, 7 AEs had an unknown outcome, including 2 leukopeanias, 1 AST elevation, 1 eosinophil count increased, 1 severe neutropenia, and 2 neutropeanias. The AE durations were brief, with 80.9% resolving or improving within 3 days of onset. The most common AEs were diarrhoea (30 AEs, 2.50%), abnormal behaviour (27 AEs, 2.25%), vomiting (8 AEs, 0.67%), and nausea (8 AEs, 0.67%). There were no noticeable differences in AE incidence between the various paediatric age ranges. The sole enrolled newborn (< 4 weeks of age) did not experience any AEs. Patients aged ≥ 4 weeks to < 1 year had a 9.43% incidence of AEs; those ≥ 1 to < 7 years of age had a 7.21% incidence of AEs; and children ≥ 7 to < 15 years of age had a 7.95% incidence of AEs. Special attention was paid to AEs of interest, and further details on abnormal behaviour and neutrophil count decreased are presented below. No new safety signals were found as a result of this post approval safety surveillance study.

Study 1303-H148-04, safety surveillance in patients with high-risk factors

This post approval observational safety surveillance study was initiated in January 2010 and was completed in March 2013. The enrolment goal was 600 patients, including 100 children, who have high-risk factors for complicated influenza, which included pregnant women, patients with an underlying disease, and elderly patients 65 years of age or older. The total study enrolment was 772. One case was excluded due to lack of observation after the start of treatment, and one duplicate case was excluded. All 770 patients were included in the safety population. Of the 770 cases in the safety analysis set, 54 were excluded for not having any high risk factors, 25 were excluded because no influenza virus was detected or identified, 5 were excluded for being outpatients, and 2 were excluded because no clinical findings after treatment were available. The safety evaluable group was comprised of 404 (52.5%) male and 366 (47.5%) female patients. The majority of patients were ≥ 65 years of age. There were 181 (23.5%) patients < 15 years of age, 125 (16.2%) patients ≥ 15 to < 65 of age, and 463 (60.1%) patients ≥ 65 years of age. One patient's age was unreported. There was a single pregnant woman in this study. Most patients (87%) received peramivir within 2 days of the start of influenza symptoms. Almost all patients were hospitalised with influenza, and only 5 (0.6%) was treated in an outpatient setting. 49 (6.4%) patients had serious influenza, defined as either influenza encephalopathy or the need for mechanical ventilation. Most patients (752, 97.7%) received 1 day of peramivir. A total of 98 patients experienced 155 ADRs deemed related to peramivir by the prescribing physicians. There were no fatal events reported for peramivir in this study. A total of 14 serious ADRs (9.0%) occurred, the most common of which were 5 events of white blood cell count decreased and 4 events of neutrophil count decreased. The most common ADRs were aspartate aminotransferase increased (39 events) and alanine aminotransferase increased (29 events). Eighty five of the 155 ADRs (54.8%) occurred within 3 days after the start of peramivir treatment. In most cases, events such as alanine aminotransferase increased, eosinophil count increased, neutrophil count decreased, and white blood cell count decreased occurred after 4 or more days. The

ADR outcome was unresolved in 4 non-serious laboratory test-related events (2.6%), but the outcome in 131 ADRs (84.5%) was ''resolved'' or ''improved''. The 770 patients of the safety analysis set included one pregnant patient (no breast-feeding patients). No ADRs occurred in this patient.

The incidence of ADRs was 12.3% (86/699 patients) in patients treated for < 3 days and was 16.9% (12/71 patients) in patients treated for ≥ 3 days, revealing no significant differences (p = 0.2680). A total of 28 ADRs occurred in patients treated for 3 or more days: 8 events of aspartate aminotransferase increased, 5 events of alanine aminotransferase increased, 3 events each of eosinophil count increased and urine ketone body present, 2 events each of neutrophil count decreased and white blood cell count decreased, and 1 event each of viral myositis, pyrexia, blood creatine phosphokinase increased, blood creatinine increased, and diarrhoea.

Abnormal behaviour was an AE of interest because it had been noted with other NAIs. During this study, 27 patients reported 31 AEs of abnormal behaviour (as outlined in the Paediatric Post approval Safety Surveillance Study Report). Descriptions of abnormal behaviour varied greatly. In some instances, the duration of the abnormal behaviour was only a few minutes. The range was 5 minutes to 4 days. Nineteen AEs resolved within a few minutes to 1 hour of onset. Seven AEs lasted 2-4 hours, and 2 AEs lasted 10 hours. One AE lasted 4 days in a child subject, but they had influenza encephalopathy, were in an induced coma, and underwent hypothermia therapy; the description of the event indicated that they did not wake from the thiopental-induced coma easily, required mechanical ventilation after spontaneous respirations began, and continued to have eye rolling and involuntary mouth and tongue movement (dyskinesia). Five of the patients had AEs that were considered serious. In 3 of the 5 patients with an SAE of abnormal behaviour, there was a complication of influenza encephalopathy or febrile convulsion preceding the SAE. Neutropenia was an event of interest because it had been noted during clinical development. During this study, there were 6 AEs of neutrophil count decreased, 5 of which were reported as SAEs. No new safety signals have been found to date as a result of this post approval safety surveillance study involving high risk patients.

General post marketing data

It is estimated that roughly 1,618,740 Japanese patients have been exposed to commercial peramivir since marketing approval from January 2010 to 30 September 2015. In South Korea, up to the cut-off date of 30 September 2015, were 69,732 patients. In the US, up to the cut-off date of 30 September 2015, is 832 patients based on the total units sold from distributors to hospitals and the average dose administered to a single patient (600 mg). The total worldwide post marketing exposure for peramivir through 30 September 2015, based on the above data, is 1,689,304 patients. Non-serious AEs were reported for 395 patients receiving peramivir, of which 96 were paediatric patients (1 to < 18 years of age), 239 were adult patients (≥ 18 to 100 years), and 60 were of unreported age. Non-serious event sources included spontaneous reports, literature articles, and regulatory reports. There were no new safety signals identified as a result of this review.

The most common AEs reported were gastrointestinal, including diarrhoea, vomiting, and nausea. This was consistent with the TEAEs reported in clinical development and the post approval surveillance studies. In addition, rash, urticaria, dizziness, hallucinations and ALT/AST elevations were also commonly reported.

In relation to non-serious spontaneous adverse events reported in children < 18 years of age in Japan, a total of 394 non-serious AEs have been reported for 287 paediatric patients who received peramivir. The most common non-serious AEs were abnormal behaviour (52 patients), diarrhoea (50 patients), vomiting (14 patients), cough (13 patients), urticaria (11 patients), and neutrophil count decreased and nausea (10 patients each).

Serious adverse events were reported for 206 patients receiving peramivir, of which 26 were paediatric patients (1 to < 18 years of age), 165 were adult patients (≥ 18 – 94 of age), 15 were of unreported age. The most common spontaneously reported SAEs in adults were shock (15 reports), anaphylactic shock (10 reports), hepatic function abnormal (10 reports), and liver disorder (8 reports). These SAEs as well as the reports of enterocolitis haemorrhagic resulted in hepatic toxicity, shock, anaphylaxis, and haemorrhagic colitis becoming events of special interest, resulting in a thorough clinical data review as well as post marketing data review. Many of the SAEs reported are known potential complications of influenza particularly in the elderly, such as diarrhoea, white blood cell count decrease, hypotension and pneumonia.

Japanese post marketing experience

In the spontaneous post marketing AE reports in Japan paediatric patients, a total of 54 SAEs were reported in 40 paediatric patients who received peramivir. The most common SAEs were abnormal behaviour, anaphylactic shock and 'hepatic function abnormal' (4 patients each). Two patients ≤ 2 years old experienced SAEs: a 1 year old male patient experienced an SAE of abnormal behaviour that started 2 days after the first dose and resolved 2 days later, and a patient experienced an SAE of hepatic function abnormal that started 4 days after the first dose and resolved after an unreported duration. Eight of the SAEs were considered life threatening, including events of anaphylactic shock, cardiac arrest, disseminated intravascular coagulation, granulocyte count decreased, metabolic acidosis, pneumococcal sepsis, pre-renal failure, and rhabdomyolysis. All of these events resolved or improved, with the exception of the metabolic acidosis. A single death was reported: a patient in Taiwan died 3 days after the first dose of peramivir. No AEs were otherwise reported for this patient. A review of all spontaneous SAE reports received indicates that none of these events represent new safety signals for peramivir.

Adverse events of special interest in the post marketing data

Certain events were first noted after marketing approval of peramivir was obtained in Japan. These were orthostatic hypotension/shock. In addition, there were events observed in other NAIs in the post marketing setting that were also considered to be events of special interest, such as neuropsychiatric events, rash, hypersensitivity, liver enzyme abnormalities, and haemorrhagic colitis. Renal toxicity has been specified as an event of special interest due to the preclinical toxicity findings observed in rabbits. Other events of special interest are based on particular AE patterns noted in clinical trials for peramivir and other NAIs, including leukopenia, neutropenia, infusion site reaction, and muscle injury.

- *Neuropsychiatric events*: During the post marketing experience, neuropsychiatric events similar to those that have been reported with other NAIs have been reported with peramivir, although whether these are related to influenza or peramivir cannot be determined. The reported events have primarily occurred in Japanese paediatric patients. The large majority of events were non-serious and were reported in children who were febrile and unwell. Most of the adult cases involved elderly patients. The most frequently reported non-serious AE was abnormal behaviour (52 patients). Additional non-serious AEs included convulsion, psychiatric symptom, speech disorder, and delirium febrile (2 patients each), and loss of consciousness, hallucination, somnolence, illusion, disorientation, restlessness, and delirium (1 patient each). Spontaneously reported SAEs included abnormal behaviour (4 patients), convulsion and tonic convulsion (2 patients each), and psychiatric symptom, febrile convulsion, grand mal convulsion, delirium, and altered state of consciousness (1 patient each).
- *Rash:* Severe rashes, such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported during post marketing experience for

other NAIs. During peramivir development, an event of erythema multiforme was reported, although the case was highly confounded. Three cases have been reported in post marketing experience: Dermatitis exfoliative, Steven-Johnson syndrome, and Toxic skin eruption. In these cases, although the patients had confounding factors, it is possible that peramivir played a role in these more significant rashes.

- *Hypersensitivity and Allergic reaction*: Hypersensitivity and allergic reaction have been reported in the post marketing setting for other NAIs, and anaphylaxis is cited in the warnings and precautions for other NAIs. In addition, post marketing reports for peramivir from Japan have reported the event terms anaphylaxis and shock. During clinical development, no patients experienced any events of anaphylaxis or severe hypersensitivity. Fourteen events of Anaphylactic shock, 2 cases of Anaphylactic reaction, and 16 events of Shock were reported. However, a thorough analysis of these events revealed that none of the cases met the established criteria for anaphylaxis. In the database of spontaneously reported post marketing AEs in children, SAEs of anaphylactic shock were reported for 4 patients and SAEs of anaphylactic reaction were reported for 3 patients. One of these patients experienced SAEs of both anaphylactic shock and anaphylactic reaction; the event of anaphylactic reaction was life threatening but occurred 33 days after the first dose of peramivir and subsequently resolved.
- *Renal Toxicity*: Although extensive data collection, including 24-hour urine collection for protein, has demonstrated no nephrotoxicity in humans, this event has remained an event of interest because of toxicity noted in rabbits during preclinical evaluations. There were 7 cases of acute renal failure, 2 cases of renal failure, 2 cases of renal impairment, 1 case of acute kidney injury, 1 case of anuria, 1 case of prerenal failure, and 1 case of nephritis. Most of the cases occurred in elderly patients with comorbidities and multiple concomitant drugs. The underlying influenza and/or bacterial infection was severe in several cases, with multiple organs affected. None of these cases provide compelling evidence of a role for peramivir in renal failure.
- *Leukopenia and Neutropenia*: During clinical development of peramivir, neutropenia and leukopenia were frequently reported AEs. A total of 24 events were found. Among them were 7 cases of neutrophil count decreased and 4 cases of neutropenia. In addition, 8 reports of white blood cell count decreased and a single case of agranluocytosis was also reported. All of these cases were consistent with post-infection leukopenia and neutropenia, which are clinically well known phenomena. In the database of spontaneously reported post marketing AEs in children, the most frequent non-serious AE of interest was neutrophil count decreased (14 patients), followed by WBC count decreased (10 patients). Non-serious events of leukopenia were reported for 3 patients. Spontaneously reported SAEs included neutropenia (2 patients) and granulocyte count decreased and neutrophil count decreased (1 patient each).
- *Infusion Site Reaction*: In clinical trials, almost all the TEAEs consistent with injection site reactions occurred with IM peramivir. The formulation of peramivir under review is for IV infusion. Nine non-serious cases and a single serious event of vascular pain were found. Five of the cases were reported in children.
- *Orthostatic Hypotension/Shock*: Events of shock, anaphylaxis, and orthostatic hypotension were reported from Japan during post marketing experience, and these events were described with similar clinical details. The FDA requested a review and analysis of orthostatic hypotension and similar events, which was submitted on 27 May 2011. A total of 52 events were found, which included shock (16 events), anaphylactic shock (14 events), loss of consciousness (11 events) and blood pressure decreased (8 events) were the bulk of cases. A review of these cases is consistent with

vasovagal reactions related to dehydration, IV needle placement, and infusion rather than reactions to peramivir. There is no evidence that peramivir alters blood pressure.

- *Drug-Induced Hepatotoxicity*: During development and in the post marketing experience, there have been reports of liver enzyme increase. The FDA requested a review and analysis of hepatic function disorder events that was submitted on 27 May 2011. This analysis focused on a range of potential drug-induced liver injuries, and all potential sources of information were reviewed. A thorough review of hepatic function disorders apparently failed to yield convincing evidence of an association between these events and peramivir administration. A search through the post marketing data found 76 cases, of which 43 were non-serious and 33 were serious. These included reports of abnormal hepatic function and Aspartate aminotransferase increased both with 19 reports. This was followed by Alanine aminotransferase increased (16 reports) and liver disorder (13 reports). A thorough analysis of these events revealed that all were heavily confounded and had numerous potential causes for hepatotoxicity. In the database of spontaneously reported post marketing AEs in children, most of the hepatotoxicity abnormalities were non-serious. Of the prespecified list of preferred terms, the most frequently reported non-serious AE was AST increased (10 patients). Other non-serious AEs of interest included reports of ALT increased (4 patients), hepatic function abnormal (2 patients), and liver disorder and hepatic enzyme increased (1 patient each). Spontaneously reported SAEs included hepatic function abnormal (3 patients) and hepatic enzyme abnormal and hepatitis acute (1 patient each).
- *Haemorrhagic Colitis*: A search for haemorrhagic colitis revealed 17 cases with haemorrhagic enterocolitis (5 cases), Melena (4 cases) and Haematochezia (3 cases) were the only events reported in more than 1 patients. All the cases were heavily confounded, primarily with anticoagulant use, nonsteroidal anti-inflammatory use, or with a history of ischemia. In each case, a more likely cause could be found for the gastrointestinal bleeding, so the relationship to peramivir is still unclear.
- *Muscle Injury:* Increases in serum CK or CPK were among the most commonly reported events in protocols with IM injection of peramivir. There were 9 events of Blood creatinine phosphokinase increased and 2 cases of Rhabdomyolysis. All the other cases referenced renal failure or impairment and were not indicative of muscular injury after review. Rhabdomyolysis is a well-known complication of influenza. In the 2 cases of rhabdomyolysis, both patients had seizure disorders and severe influenza, both known causes of rhabdomyolysis.

Korean post marketing surveillance experience

Post marketing exposure of peramivir in South Korea up to a cut-off date of 30 September 2015 is 69,732 patients. There were 5 serious events and 19 non-serious events and none of the AEs reported were concerning. There are no safety signals arising from a review of the Korean post marketing surveillance data.

US post marketing surveillance experience

Peramivir was approved for marketing in the USA on 19 December 2014. It is estimated that 832 patients have been treated in the U.S. based on the total units sold from distributors to hospitals and the average dose administered to a single patient (600 mg). A single event of Lack of drug effect has been reported.

Assessments and conclusions of the post marketing data

Given the large number of patients exposed to peramivir in the post marketing setting, the reporting rate for all events is low and continues to demonstrate the overall favourable safety profile of peramivir. There have been safety signals to arise from the Japanese post marketing data, such as shock, anaphylaxis, and haemorrhagic colitis, analysis has

indicated that these AEs are unlikely to be risks from peramivir treatment, but are consistent with the underling influenza, concomitant medications, or comorbidities.

Two events remain safety signals with insufficient data to confirm attribution but these AEs were considered significant enough to warrant informing prescribers and patients through appropriate labelling. Neuropsychiatric events have been shown to occur mainly in Japanese children or very elderly Japanese patients. While it is most likely that these events are due to the underlying influenza and fever, a role for peramivir cannot be excluded. In addition, severe rashes such as Stevens Johnsons syndrome and erythema multiforme often have multiple possible etiologies in these patients (that is, underlying infection and concomitant medications).

- *Emergency Use Authorisation:* On 23 October 2009, the FDA issued an EUA for the use of peramivir IV in certain patients hospitalised with 2009 H1N1 infection as part of the federal government's response to the 2009 H1N1 influenza public health emergency. Peramivir IV was distributed to requesting physicians by the US CDC. From 23 October 2009 to 23 June 2010, the CDC received 1,371 clinician requests for peramivir and delivered 2,129 five-day adult treatment course equivalents of peramivir to 563 hospitals. Based on data requests made to treating physicians, approximately 1,274 hospitalised patients received peramivir through the EUA program during the H1N1 influenza. Physicians who received EUA peramivir IV from the US CDC were instructed to report medication errors, selected AEs, SAEs, and deaths to the FDA. No information on safety or outcomes of treatment in patients administered peramivir IV under this program was submitted; therefore, the safety information sources reviewed for this population consists of relevant publications and FOI data.
- The FDA received reports on 344 patients, including 28 children and 3 pregnant women. Many of these patients were critically ill, and 41% were on mechanical ventilation, while 19% were on renal replacement therapy. The most frequently reported SAEs were death (15%), H1N1 influenza (8%), respiratory failure (8%), acute renal failure (7%), and acute respiratory distress syndrome (7%). Rash was the only AE attributed to peramivir treatment. A total of 206 deaths were reported to the FDA, including 53 patients (15% of the total study population) with an outcome of death coded as an AE. None of the deaths were attributed to peramivir by the reporting physician. In addition, there were 4 known pregnancies in women receiving peramivir under the EUA. One asthmatic woman experienced a miscarriage 6 days after discontinuation of peramivir. Two women delivered healthy babies and for one, there was no information on birth outcome available.
- *California Department of Public Health EUA Experience*: In a study of 57 critically ill patients treated with peramivir during the 2009 influenza A H1N1 pandemic under the EUA, the fatality rate of patients treated with peramivir was 51%. Patients treated with peramivir were more likely to die than patients treated with another NAI and were also more likely to have adverse predictors of outcome, including a higher incidence of acute renal failure. Although fatality rates of peramivir-treated patients were higher, this study lacked a matched comparator group, and peramivir-treated patients had greater disease severity and more independent predictors of death compared to patients receiving another NAI. Similar to unpublished studies, the most common reasons for treatment with peramivir were lack of response to oral or inhaled antivirals and suspected malabsorption, creating a selection bias for peramivir treatment that favoured administration of peramivir in more seriously ill patients.

Evaluator's conclusions on safety

The safety of peramivir has been evaluated in clinical studies involving 2,155 subjects with influenza, with daily doses ranging from 75 mg to 600 mg administered over 1 to 10 days

of treatment. In these randomised, controlled studies, peramivir has been generally safe and well-tolerated. In clinical studies, a single 600 mg infusion of peramivir in adults had similar safety and tolerability to a single 300 mg dose, the approved dosage in Japan. Additionally, the safety and tolerability profiles of a single 600 mg infusion of peramivir were similar in Japanese/Southeast Asian subjects and North American subjects.

The most common TEAEs observed in clinical trials included diarrhoea, decreased neutrophil count, and increased blood glucose. These were similar to events observed in subjects administered oseltamivir or placebo and were generally consistent with the acute illness and underlying concomitant medical conditions of study subjects. Elevated blood glucose is more common in the elderly.

Safety signals were not detected in special analyses designed to evaluate the safety of peramivir in neuropsychiatric events, rash, hypersensitivity, renal function, haematological abnormalities, infusion site reactions, orthostatic hypotension, hepatic function, haemorrhagic colitis, and muscle effects. Although nephrotoxicity was noted in male rabbits in non-clinical safety studies, detailed investigations of renal function and urinary protein excretion in clinical trials have shown no evidence of nephrotoxicity in human subjects.

There was no evidence of an effect of peramivir on cardiac conduction. An adequate, thorough QT study was negative. IV peramivir administrations at doses of 600 mg and 1200 mg (supra-therapeutic) were not associated with QTc prolongation or other repolarisation abnormalities.

Laboratory findings were generally consistent with influenza illness. Enzyme elevations (for example, CK) in the studies using peramivir IM were associated with the formulation and route of administration.

In evaluations of subpopulations, no relevant safety findings were observed. Although conclusions may be limited as some of these populations were relatively small, there were no apparent differences in reported events based on gender, age, race, ethnicity, renal dysfunction, pre-existing hepatotoxicity, or pre-existing respiratory disease.

As of 30 September 2015, peramivir has also been administered to approximately 1,600,000 influenza patients following the 13 January 2010 approval in Japan. Three post marketing safety surveillance studies have been conducted with 2 reporting final conclusions. No safety signals arose from these observational studies. The spontaneous AE reports have also failed to demonstrate any new risks not previously seen with other NAIs.

First round benefit-risk assessment

First round assessment of benefits

See Table 20, below.

Table 20: Assessment of benefits

Indication	
Benefits	Strengths and Uncertainties
The present application for peramivir shows efficacy for the indication of treatment of influenza in persons 2 years and older. The primary efficacy endpoint was time to alleviation of symptoms (TTAS). In the pivotal Study 0722T0621, the treatment	The pivotal study did show a statistical benefit for peramivir over placebo for primary and secondary endpoints. Although well, it was quite small. The strongest evidence for the current

Indication	
effect for peramivir IV 600 mg in adults was -21.9 hours. For secondary clinical endpoints, in adults was associated with improvements compared to placebo of -12.2 hours in time to resolution of fever and -41.7 hours in time to resumption of usual activities. Supportive studies (when the data was pooled), supported these findings and also showed a dose related clinical improvement and decrease in viral shedding, which has resulted in the marketing of the 600 mg dose. In hospitalised subjects with acute serious or potentially life-threatening influenza, once daily dosing for 5 days demonstrated similar effectiveness to OSE or SOC, and in emergency use in seriously ill patients peramivir contributed to recovery. The clinical evidence of efficacy of the 600-mg dose of peramivir in adults showed dose-ordered efficacy findings in several analyses, the range of susceptibility of viral subtypes in different seasons, and the PK-PD modelling results, support the conclusion that 600 mg peramivir in adults is likely to benefit more patients than would a lower dose of peramivir. One open-label single-arm efficacy study of single administration of peramivir IV 10 mg/kg (maximum 600 mg) was completed in children in Japan (Study 0918T0633). The ongoing open-label active-controlled study of a single administration of peramivir IV 12 mg/kg for 2-12 years of age or 600 mg for 13 to 18 years has completed in 85 children (Study BCX1812-305). Additional experience in 1,199 children in required post-marketing studies in Japan supports the safety of peramivir injection for paediatric use. Peramivir has a very low potential for drug-drug interactions, is generally safe and well-tolerated, In subjects hospitalised with influenza multiple days of intravenous peramivir dosing was generally safe and well tolerated for a period of up to 11 days.	recommended dose (and the dose related effects on viral shedding, are seen from the pooled efficacy data (much of which is not controlled). The best evidence for 600 mg once again is from the supportive studies only, in which peramivir is compared to OSE or SOC (which can include OSE). Peramivir appears to have similar efficacy to currently available NAIs and may be very useful with oral agents cannot be tolerated. For patients with renal dysfunction however, peramivir dose should be reduced for patients with baseline creatinine clearance below 50 mL/min. In patients with chronic renal impairment maintained on haemodialysis, peramivir should be administered after dialysis at a dose adjusted based on renal function Peramivir appears to have similar efficacy in children as in adults in post the studies and post marketing data. It is a good alternative for treatment in patients who cannot take drugs orally. Peramivir does not appear to have clinically important drug interactions and be fairly safe. Many of the common TEAS had similar occurrence in both placebo and other treatment groups, suggesting that they may relate to the underlying influenza and co-morbidities. Specific issues are discussed below in Risks.

First round assessment of risks

See Table 21, below.

Table 21: Assessment of risks

Risks	Strengths and Uncertainties
There are no significant safety findings that warrant special vigilance, although the pre-marketing studies are small, there has now been significant post marketing experience with peramivir. Side effects of diarrhoea and nausea are common in this patient group. Allergic reactions have been reported with other NAIs, and vasovagal reactions have been associated with insertion or manipulation of IV cannulas in the context of peramivir administration. Side effects include: abnormal behaviour; LFT abnormalities; Neutropenia; glucose elevation; Shock has also been reported in post marketing data, although relationship to peramivir as opposed to clinical illness is unsure. Development of resistance is always a concern with antiviral agents.	Elderly subjects and Hispanic ethnicity subjects each represented only 2% of the total enrolled in acute uncomplicated influenza studies. However, there is no evidence to suggest that efficacy or safety of peramivir will be compromised in the elderly or Hispanic or other ethnic subgroups. Elevated blood glucose was more common in the elderly and this may need to be watched for, particularly in diabetics (no specific information pertaining to this group is available). Anaphylaxis and severe cutaneous reactions have been reported although rarely (in post marketing). Abnormal behaviour is more commonly reported in children than adults. Development of resistance to peramivir, as with other NAIs is definitely possible.

First round assessment of benefit-risk balance

Because of its IV route of administration, peramivir injection would be a suitable clinical choice in patients with influenza in whom oral or inhaled therapy would not be appropriate. Relevant clinical circumstances would include inability to comply with oral or inhaled medications. This includes patients with a history of poor compliance, and presence of vomiting, diarrhoea or comorbid gastrointestinal diseases that could impair drug absorption, inability to use or contraindication for inhaled medications, such as presence of bronchospasm, and other clinical circumstances where the physician feels that IV therapy is warranted. Peramivir injection would be a suitable clinical choice in patients hospitalised with acute serious or potentially life-threatening influenza.

First round recommendation regarding authorisation

Approval of peramivir is recommended for the treatment of infections due to influenza A and B viruses in adults and children 2 years and older.

Second round evaluation

There was no second round evaluation.

VI. Pharmacovigilance findings

Risk management plan

Summary of RMP evaluation[12]

- The sponsor has submitted EU-RMP version 0.2 dated 11 August 2017 (data lock point (DLP) 31 March 2017) and ASA version 2.0 dated October 2017 in support of this application.
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below.

Table 22: Summary of safety concerns

Summary of safety concerns (ASA v2.0)		Pharmacovigilance		Risk Minimisation	
		Routine (R)	Additional (A)	R	A
Important identified risks	Development of virus resistance to peramivir	ü	–	ü	–
Important potential risks	Serious skin / hypersensitivity reactions	ü	–	ü	–
	Neuropsychiatric events	ü	–	ü	–
Missing information	Use in Paediatric patients less than 2 years old	ü	ü	ü	–
	Use in immuno-compromised patients	ü	ü	ü	–

Pharmacovigilance

- In addition to routine pharmacovigilance, the sponsor has listed the following additional pharmacovigilance activities in the EU-RMP:
  - in paediatric patients:

[12] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

- § Study BCX1812-305: a Phase III, randomised, open label study in paediatric patients <2 years old, against an active comparator (ongoing, FDA post-marketing commitment, also part of an approved EU-Paediatric investigation Plan)
- § Study BCX1812-307: a Phase III, randomised, open label study in paediatric patients hospitalised with serious influenza infection (planned, part of an approved EU-Paediatric investigation Plan)

Neither of the above are considered to be 'required post authorisation efficacy studies' in the EU-RMP.

– in elderly patients and high-risk or immuno-compromised patients:

- § Study BCX1812-306: a Phase III, multicentre, single arm open label study in elderly subjects and subjects at higher risk of influenza complications (ongoing, FDA post-marketing commitment, considered a post-authorisation safety study in the EU-RMP).

Risk minimisation

· The sponsor has proposed routine risk minimisation to mitigate all the safety concerns.

New and outstanding recommendations from second round evaluation

The RMP is generally acceptable; however a minor outstanding recommendation for the nonclinical part of the safety specification should be addressed:

· Outstanding Recommendation 1 (Minor): Include a brief explanation of the renal/urothelial changes of uncertain clinical relevance in the 'key safety findings (from nonclinical studies)' in the non-clinical part of the safety specification of the EU-RMP.

Proposed wording for conditions of registration

The suggested wording is:

· Implement the peramivir (Alpivab/Rapivab) EU-RMP version 0.2 dated 11 August 2017 (DLP 31 March 2017) and ASA version 2.0 dated October 2017 and any future updates as a condition of registration.

Other advice to the Delegate

The Delegate's attention is drawn to the dosage advice, which the sponsor has amended in the sponsor's post-first round response as follows:

· A subheading for 'Hospitalised patients' has been added to separate the dosage information in this population from the paediatric advice. This change is in response to an RMP recommendation and improves the clarity of the advice.

· The sponsor has added a statement regarding pandemic dosing experience and recommended one dose a day for duration of up to 5 days. This change is outside the scope of the RMP evaluation

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

The application and the supporting data relating to the composition, development, manufacture, quality control and stability of the product have been assessed and checked for compliance, as applicable, with Australian legislation and requirements for new medicines and in accordance with Pharmacopoeia standards and the technical guidelines adopted by the TGA. The evaluator has informed the Delegate the sponsor does not have evidence of current GMP clearance for a number of sites and the PARs require amendment following the GMP clearance. The approval is otherwise recommended from a pharmaceutical perspective.

Nonclinical

Approval is supported by the nonclinical evaluation. Pregnancy Category B3 is recommended rather than Category B2.

The draft PI should be amended as indicated.

The RMP should be amended as indicated. In particular, the RMP uses the product name Alpivab. This should be replaced with the proposed product name Rapivab.

Clinical

The report includes the following data:

- 17 Phase I studies in healthy volunteers (single and multiple-dose studies);
- 4 Phase II studies; and
- 6 Phase III studies.

There are also post-marketing safety data and Japanese post marketing safety surveillance studies, which are included in the summary of clinical safety.

Pharmacology

Peramivir has been evaluated in an extensive program consisting of studies across all phases, three routes of administration (SC, IM, and IV), and multiple subject and patient populations. This submission includes 17 Phase 1 studies involving a total of 596 subjects receiving a single dose and 95 subjects receiving multiple doses of peramivir. The Phase I studies included:

- Single and multiple escalating dose tolerance studies (Studies BCX1812-101, BCX1812-102, BCX1812-103, 0712T0611, and 0714T0612).
- A special population study in really impaired patients (Study BCX1812-105).
- A special population study in elderly subjects (Study BCX1812-104).
- Three drug interaction studies: rimantadine (Study BCX1812-108), oseltamivir (Study BCX1812-109), and the oral contraceptive ethinyl estradiol/levonorgestrel (Study BCX1812-110).

- Thorough QT study (BCX1812-106) in healthy subjects (single 600 mg and 1200 mg by IV route)
- Single escalating IM dose tolerance studies (Studies BCX1812-111, BCX1812-112, and BCX1812-116).
- Bioequivalence Study BCX1812-113 (bioequivalence between IV and IM doses).
- Study BCX1812-117 (the effect of needle length and BMI on peramivir exposure).
- Single SC dose tolerance study (Study BCX1812-118) in healthy volunteers with 300 mg SC dose.

The clinical pharmacology of peramivir has been investigated in healthy volunteers following single and multiple IV dose, single-dose IM and SC administration. Peramivir was also investigated in a variety of patient populations, both in the US and in Asia, in whom the drug was administered as a single dose for acute uncomplicated influenza or as a multiple-dose for influenza requiring hospitalisation. The conclusions from the clinical pharmacology studies are summarized below:

- The PKs of peramivir are characterized by rapid and nearly complete absorption following IV, IM, and SC use, dose linearity over a wide range of IV doses (that is, 50 to 1200 mg), and a multi-exponential PK behaviour with a terminal-phase elimination half-life of approximately 20 hours.
- The bioavailability (AUC) of IM and SC peramivir was comparable to that following IV use, with the peak and time-of-peak drug exposure after IV use being dependent on infusion duration.
- Mean values of peramivir clearance following IV use ranged between 6.03 L/hr and 6.78 L/h across a broad range of IV doses (300 to 1200 mg), which included the proposed dose of 600 mg.
- Peramivir undergoes extensive renal elimination, with the clearance of parent drug paralleling that of renal glomerular filtration. While there was no significant change in C_{max}, the AUC increased incrementally with declining renal function. However, since peramivir would be administered as a single dose, no significant accumulation would be expected.
- A trial was conducted in subjects with various degrees of renal impairment. When compared to subjects with normal renal function, no change in mean C_{max} was observed. However, mean $AUC_{0-\infty}$ increased after a single IV dose in subjects with impaired renal function. A simulation comparing normal and really-impaired patients showed that C_{max} is essentially unchanged. AUC∞, while higher in the renal failure population than that in subjects with normal renal function, is substantially lower than what would be expected with qd dosing for 5 days in subjects with normal renal function. Based on these findings, no dose adjustment is required for use of single dose to subjects with decreased renal function in view of no observed increase in C_{max}. Haemodialysis was effective in reducing systemic exposure of peramivir by 73% to 81%. A reduced dose is recommended for patients with creatinine clearance below 50 mL/min
- The results of three drug interaction studies indicated that at therapeutic doses peramivir had no effect on the PK of rimantadine, oseltamivir, and oral contraceptives.
- The results of multiple population PK analyses to assess the effects of multiple demographic factors on the PK of peramivir revealed that there were no clinically relevant covariate findings that would influence the proposed dose.
- The results of the definitive population PK analysis suggest that 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% versus 12.7%) and for all viral IC_{50} values, collectively. The PK simulation suggested that IV doses in the range of 300 to 600 mg are on the ascending part of the peramivir exposure-response curve with respect to target time above viral IC_{50}, and because of the timing of 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}.

Overall, the clinical pharmacology results, reviewed collectively with the efficacy and safety data, support the use of single IV peramivir 600 mg over at least 15 minutes for the treatment of adults with acute uncomplicated influenza.

Efficacy

Phase I studies (Studies 0722T0612, 0712T0611, BCX1812-201, BCX1812-103, BCX1812-111, BCX1812-112, BCX1812-116, and BCX1812-117) were also dose finding studies. With the outcomes from these studies, peramivir 600 mg dose was taken forward as the dose for the Phase II and the pivotal studies. The Phase II dose finding studies include Studies BCX1812-211 and 0722T0621. Study 0722T0621 is also considered as the pivotal efficacy study in this submission.

The submission included the following 10 completed Phase II/III clinical studies:

- 1 pivotal placebo-controlled study in adults with acute uncomplicated influenza
- 3 supportive placebo-controlled studies in acute uncomplicated influenza (IM formulation)
- 2 non-placebo controlled studies in adult patients with acute uncomplicated influenza
- 3 studies in hospitalised subjects with acute serious influenza
- 1 uncontrolled study in Japanese paediatric subjects

Of these 10 studies, 7 studies used the IV formulation and 3 studies used the IM formulation. Seven (7) studies predominantly enrolled patients with acute uncomplicated influenza and there (3) studies were conducted in subjects hospitalised with serious influenza. There is one uncontrolled open label study completed in children with uncomplicated influenza (Japan). In addition, the ongoing active controlled US-study in paediatric subjects (Study BCX1812-305) is also discussed.

Pivotal study in acute uncomplicated influenza: Study 0722T0621

For the treatment of adults with acute uncomplicated influenza, Study 0722T0621 is considered as the pivotal study. The three placebo-controlled IM peramivir studies provided supportive data.

Study 0722T0621 is a Phase II, double blind, randomised, placebo-controlled, multi-centre study of single-dose IV peramivir in subjects with acute uncomplicated influenza. The primary objective was to evaluate the efficacy of peramivir compared to placebo. The secondary objectives and the detailed inclusion and exclusion criteria are described in the CER. The planned sample size was 240 patients (80 patients/group × 3 groups), up to 300 patients in total.

The primary endpoint was TTAS (time to alleviation of symptoms). Secondary endpoints include:

- Change in composite symptoms at 24, 36, 48 and 96 hours after treatment
- Time to resolution of fever (<37.0°C, axillary)
- Change in influenza virus titre by $TCID_{50}$

- Incidence of adverse events and adverse reactions
- Plasma concentration of unchanged drug

Number of enrolled patients: 300 subjects

- 300 mg group: 99 subjects
- 600 mg group: 100 subjects
- placebo group: 101 subjects

Effectiveness analysis sets*:*

- ITTI (Intent to treat infected) set:
  - 296 subjects (99 in 300 mg group; 97 in 600 mg group; 100 in placebo group)
- PPS (Per protocol set):
  - 276 subjects (92 in 300 mg group: 89 in 600 mg group; 95 in placebo group)

The overall efficacy population (n=297), consisted of subjects with confirmed influenza and administered study drug. Among the subjects enrolled in the 600 mg dose group, the mean age was 34 years; 55% were male; 34% were smokers; 99% were infected with influenza A virus and 1% were infected with influenza B virus. The majority of subjects (53%) had influenza illness lasting less than 24 hours at the time of presentation.

The Intent to treat infected (ITTI) analysis set consisted of all patients treated with the investigational product, and who were confirmed to have an influenza virus infection. The PPS consisted of the patients remaining when excluding ineligible subjects, subjects showing violation of the study method and subjects with insufficient number of observations from the ITTI. The primary analysis set used for effectiveness was the ITTI.

In order to evaluate the effectiveness of peramivir in comparison to the placebo, a consolidated group (combined group of 300 mg and 600 mg) and the placebo group were compared, and a Cox proportional hazards model was used, with the existence of current tobacco use and the composite influenza symptoms (7 symptoms) score prior to dosing as the covariates. The recommended dose level was investigated only if a statistically significant difference was observed in this analysis.

Results for the primary efficacy outcome

The study met its primary endpoint of time to alleviation of symptoms. The combined peramivir group (300 mg and 600 mg) showed a significant shortening of the time to alleviation of symptoms (one-sided P value: 0.0010) in comparison to the placebo group. The median (95% CI) duration of influenza was 59.1 (50.9, 72.4) hours in the 300 mg group, 59.9 (54.4, 68.1) hours in the 600 mg group, and 81.8 (68.0, 101.5) hours in the placebo group. The hazard ratio in relation to the placebo group was 0.681 in the 300 mg group and 0.666 in the 600 mg group, with both groups showing significant shortening of the duration of influenza versus placebo (adjusted one-sided P values: 0.0046 and 0.0046, respectively).

Results for other efficacy outcomes

Key secondary endpoints included change in composite influenza symptoms score, time to resolution of fever, time to resumption of daily activities, change in virus titre ($TCID_{50}$) from baseline, and proportion of subjects shedding virus. Statistically significant differences were observed in the change in the composite influenza symptoms score comparing both the 300 mg and the 600 mg group with the placebo group at 24, 36, 48, 72, 96, and 120 hours after dosing. The median value for the time to resolution of fever (< 37.0°C) was 29.3 hours in the 300 mg group, 30.2 hours in the 600 mg group, and 42.4 hours in the placebo group, with subjects in both the 300 mg and 600 mg groups showing

significant reductions in comparison with the placebo group (P = 0.0010 and 0.0005, respectively).

The median value for the time to resumption of daily activities was 5.2 days (125.6 hours) in the 300 mg group, 5.3 days (127.4) hours in the 600 mg group, and 7.0 days (169.1) hours in the placebo group, with both the 300 mg and 600 mg groups showing significantly shorter times to resumption of daily activities in comparison to the placebo group (P = 0.0367 and 0.0152, respectively).

The median change in virus titre ($log_{10}TCID_{50}$) from the time of Screening up to Day 3 of dosing was significantly larger in the 600 mg group (-1.50, P = 0.0027) but not in the 300 mg group (-1.48, P = 0.0968) in comparison to the placebo group (-1.22). The proportion of subjects shedding virus at Visit 3 (Day 3) was significantly lower in both the 300 mg (35/95, 36.8%) and 600 mg (24/93, 25.8%) groups than in the placebo group (50/97, 51.5%), P =0.0485 and P = 0.0003 respectively. Few subjects in any of the treatment groups had detectable virus on Visit 5 (Day 9).

Three supportive placebo-controlled studies in acute uncomplicated influenza

The three placebo controlled IM peramivir studies (StudiesBCX1812-211, BCX1812-212, and BCX1812-311) provided supportive data for treatment of acute uncomplicated influenza. Bioequivalence of the IM and IV peramivir was demonstrated in Phase I study (Study BCX1812-113), thus permitting use of the IM studies in support of IV peramivir. These 3 studies have similar inclusion criteria (Male and female adult subjects, with symptoms consistent with a diagnosis of acute uncomplicated influenza infection could be screened for enrolment. Other inclusion criteria included the presence of fever of ≥ 38.0 ºC, at least 1 respiratory symptom of any severity, and at least 1 constitutional symptom of any severity. Subjects must have had a positive RAT for influenza A or B and symptom duration of ≤ 48 hours at enrolment).

Study BCX1812-211 (IM)

Study BCX1812-211 was a Phase II randomised, double blind study comparing the efficacy and safety of IM peramivir versus placebo in adults with acute uncomplicated influenza. Randomisation to peramivir 150 mg, 300 mg, or placebo was stratified according to smoking behaviour. Study drug was administered as IM injections. Efficacy evaluations included subject self-assessments of temperature; severity of symptoms; ability to perform usual activities; doses of antipyretic, expectorant, and/or throat lozenges. Virologic assessments included anterior nasal and posterior pharyngeal swab specimens for influenza viral culture and PCR assay. This study enrolled 344 subjects. Outcomes are detailed; in brief, this study found that compared with placebo, peramivir was associated with statistically significant decreases in influenza viral titres in nasopharyngeal secretions at 24 and 48 hours after treatment. Clinical efficacy of peramivir was suggested by reductions in the TTAS (time to alleviation of symptoms) when compared to placebo, but the magnitude of improvement was not statistically significant.

Study BCX1812-311(IM)

Study BCX1812-311 was a Phase III, multicentre, randomised, double blind study comparing the efficacy and safety of 300 mg IM peramivir versus placebo in adults with acute uncomplicated influenza. Randomisation to peramivir 300 mg or placebo in a ratio of 2:1 was stratified according to smoking status and RAT result for influenza A or B. Efficacy evaluations included subject self-assessments of oral temperature every 12 hours; presence and severity of influenza symptoms; time lost from work or usual activities and rating of productivity; and doses of antipyretic, expectorant, and/or throat lozenges. Virologic assessments included anterior nasal and posterior pharyngeal swab specimens for influenza viral culture and PCR assay. This US-only study was terminated early in order to utilise a higher concentration product in subsequent studies. At the time of termination,

103 sites had been initiated and 82 of the planned 600 subjects were enrolled at 37 study sites.

Study BCX1812-212 (IM)

Study BCX1812-212 was a Phase II, multicentre, randomised, double blind, and placebo controlled, single dose adult study to evaluate the efficacy and safety of a single IM peramivir 600 mg versus placebo in adults with acute uncomplicated influenza. Randomisation to peramivir 600 mg or placebo was stratified according to smoking status. Efficacy outcomes included presence and severity of influenza symptoms; and doses of antipyretic, expectorant, and/or throat lozenges. Virologic assessments included anterior nasal and posterior pharyngeal swab specimens for influenza viral culture and/or PCR assay. This study enrolled 405 subjects in the US, South Africa, Australia, and New Zealand. Improvement in TTAS was observed for subjects treated with 600 mg peramivir (91.1 hours) compared to placebo (106.9 hours), although this difference was not statistically significant. No statistically significant differences were observed between treatment groups for the secondary endpoints measured. This study was conducted during a season in which the dominant circulating strain if influenza A/H1N1 virus had the NA H275Y substitution, which resulted in reduced susceptibility to neuraminidase inhibitors.

Two non-placebo controlled studies in acute uncomplicated influenza

Study 0815T0631 (oseltamivir-controlled)

This was a Phase III, multicentre, OSE controlled, double blind study in adult subjects with acute uncomplicated influenza. Randomisation (1:1:1) to a single dose of peramivir 300 mg, 600 mg, or OSE 75 mg BD for 5 days was stratified according to smoking status, composite symptom score at screening, region, and influenza virus type. Subjects must have had a temperature of 38.0°C or above. Subjects must have had at least 2 influenza symptoms of moderate or greater severity. Subjects must have had a positive RAT for influenza A and/or B and symptom duration of ≤ 48 hours at enrolment. Efficacy evaluations included self-assessments of temperature and influenza symptoms. Virologic assessments included anterior nasal and posterior pharyngeal swab specimens for PCR assay. This study enrolled 1099 subjects in Japan, South Korea, and Taiwan. Clinical response was equivalent in all groups. This study met its primary endpoint. The median TTAS was 78.0 hours (95% CI: 68.4, 88.6) in 300 mg group, 81.0 hours (95% CI: 72.7, 91.5) in the 600 mg group, and 81.8 hours (95% CI: 73.2, 91.1) in the OSE group. In both the 300 mg and 600 mg groups, the upper limits of the 97.5% CI for the hazard ratio to the oseltamivir group were lower than the predefined non-inferiority margin of 1.170. The study demonstrated that a single IV dose of 300 and 600 mg of peramivir were non-inferior to 75 mg of OSE twice daily for 5 days.

Study 0816T0632 (uncontrolled study in subjects with high-risk factors)

This was a Phase III, double blind, non-controlled Japanese study of IV peramivir in influenza subjects with high-risk factors. Hospitalisation was permitted, and most subjects were not inpatients. In addition, dosing was continued on Days 2 -5. For those reasons, this study is considered supportive. Subjects > 20 years of age were eligible. Enrolled subjects were randomised to receive IV peramivir 300 mg or 600 mg daily for 1 to 5 days. Subjects must have had at least 2 influenza symptoms of moderate severity or greater and an axillary temperature of ≥ 37.5°C within 12 hours prior to screening. Subjects must have had a positive RAT for influenza A and/or B and symptom duration of ≤ 48 hours at enrolment. Subjects must also have had at least one of the high-risk factors. Efficacy evaluations included self-assessments of temperature, severity of influenza symptoms, and ability to perform daily activities. The following evaluations were also performed: virological tests, measurement of oxygen saturation, CRP levels, and influenza-associated symptoms, chest X-ray or CT scans where feasible. This study enrolled 42 subjects in Japan. The median time to alleviation of symptoms (TTAS) for the pooled peramivir group

was 68.6 hours (90% CI: 41.5, 113.4). The median TTAS was shorter for the 600 mg group than the 300 mg group (42.3 versus 114.4 hours). Symptom resolution and eradication of influenza virus on PCR was more rapid in the 600 mg group but did not reach statistical significance.

Three studies in hospitalised subjects with acute serious influenza

Study BCX1812-301 (peramivir 600 mg + SOC / placebo + SOC)

This was a multinational, randomised, double blind, controlled study comparing the efficacy and safety of IV peramivir versus IV placebo daily for 5 days in addition to the institution's SOC in adults, adolescents, and children ≥ 6 years old who were hospitalised due to acute influenza. The primary objective was to evaluate the effect of peramivir plus SOC compared to placebo plus SOC on time to clinical resolution in subjects who are hospitalised with influenza. Male and female subjects, ≥ 6 years (US only) or age ≥ 12 years (rest of world), were eligible for enrolment. Efficacy evaluations included time to clinical resolution (temperature, oxygen saturation, respiration rate, heart rate and systolic blood pressure). Other efficacy assessments included reduction in virus titre, time to alleviation of influenza symptoms, time to resolution of fever, time to resumption of daily activities and incidence and duration of ICU admission after initiation of treatment. This study enrolled 405 subjects from many countries. Eligible subjects were randomised 2:1 (Group 1: Group 2) to peramivir or placebo. SOC could include a neuraminidase inhibitor (NAI) such as OSE; thus the primary analysis population consisted of subjects with confirmed influenza who had not received a NAI as part of their SOC regimen (ITTI-Non-NAI). The ITTI-Non-NAI population comprised of only 121 subjects.

For this population (n = 121), the median time to clinical resolution was similar between treatment groups (49.5 hours for placebo, 42.5 hours for peramivir; P = 0.973; hazard ratio = 1.03). As a secondary analysis, time to clinical resolution was calculated for the ITTI population. As in the ITTI-Non-NAI population, time to clinical resolution was not significantly different between treatment groups (P = 0.794; hazard ratio = 0.93). The median values for time to clinical resolution (48.0 hours for placebo subjects and 41.8 hours for peramivir subjects) were very similar to those seen in the ITTI-Non-NAI population. Again, the range of times to clinical resolution was very broad, ranging from 0.3 to 686.8 for placebo subjects, and 0.3 to 830.0 hours for peramivir subjects.

In summary, this study did not demonstrate a significant difference between placebo + SOC, and peramivir + SOC for the primary endpoint of time to clinical resolution.

Study BCX1812-201 (Peramivir 200 mg, 400 mg, and OSE)

This was a Phase II multinational, randomised, double-masked, double dummy study. The study compared the efficacy and safety of IV peramivir once daily for 5 days versus oral OSE BD for 5 days in adults hospitalised with acute serious or potentially life-threatening influenza. Subjects over 18 years or older were eligible to enrol. Subjects with signs and symptoms compatible with acute influenza infection (present for no more than 72 hours) and positive RAT or other similar test results were eligible for enrolment. Efficacy evaluations included time to clinical stability (temperature, respiration rate, blood pressure, heart rate and oxygen saturation). Other efficacy assessments included viral shedding, relapse of influenza, incidence of influenza-related complications, presence and severity of symptoms of influenza, and time to return to usual activity. The study enrolled 137 subjects in USA, South Africa, Canada, Australia, Hong Kong, New Zealand and Singapore. Similar results were observed in each group with median time to clinical stability of 23.7 hours for peramivir 200 mg, 37.0 hours for peramivir 400 mg, and 28.1 hours for oseltamivir. Analyses of secondary efficacy endpoints did not demonstrate statistically significant differences among the 3 groups. Changes in quantitative viral titres during treatment for all virus types combined were similar among the 3 groups, however

for subjects with influenza B infection, a greater antiviral effect was observed for peramivir compared with oseltamivir.

Study BCX1812-303 (5 days of peramivir 300 mg BD or 600 mg QD)

Study BCX1812-303 was a randomised, open-label study. The study assessed the antiviral activity, safety, and tolerability of IV peramivir 300 mg BD or 600 mg QD for 5 days in adults and adolescent hospitalised with confirmed or suspected influenza infection. Male and female subjects, 6 years of age or older, were eligible for enrolment. Efficacy evaluations included assessment of reduction in influenza virus titres. Other efficacy assessments included analysis of temperature, oxygen saturation, vital signs, clinical symptoms of influenza, usual daily activities, number of subjects requiring more than 5 days of study drug, time to hospital discharge, incidence of influenza-related complications, incidence and duration of ICU admission after initiation of treatment, 28-day mortality following treatment, and changes in viral sensitivity to other antiviral drugs. This study enrolled 234 subjects at 59 study sites. No differences were found between the two treatment regimens (IV peramivir 300 mg BD or 600 mg QD for 5 days).

Two open label paediatric studies

Study BCX1812-305 (peramivir versus OSE)

This study is being performed in children with uncomplicated influenza as a post marketing requirement by FDA. It is a Phase III, multicentre, open label, randomised active controlled study to evaluate the safety, PK, and effectiveness of IV peramivir in paediatric patients with acute uncomplicated influenza. Subjects between the ages of 28 days to 17 years of age were eligible to enrol. Patients must have had clinical signs and symptoms consistent with acute influenza or a positive influenza rapid antigen test (RAT). Up to 130 patients were planned for enrolment in the following age cohorts:

- ≥ 28 days to < 2 years: up to 20 patients
- ≥ 2 to < 7 years: up to 40 patients
- ≥ 7 to < 13 years: up to 40 patients
- ≥ 13 to < 18 years: up to 30 patients

Patients were randomised 4:1 to IV peramivir or oral oseltamivir. Patients received either a single dose of IV peramivir (600 mg for ≥ 13 years or 12 mg/kg IV for ≤ 12 years) or oral OSE BID for 5 days. The primary endpoint was the safety of peramivir compared to OSE. Secondary endpoints included effectiveness (time to resolution of fever, time to resolution of influenza symptoms, viral shedding, and virus susceptibility). Effectiveness was evaluated through assessments of body temperature, symptoms, virus titres, and changes in viral sensitivity to peramivir and other antiviral drugs, incidence of influenza-related complications, use of antipyretic medications, assessments of the patient's ability to perform daily activities.

Overall, 108 subjects enrolled. A total of 85 subjects were randomised to peramivir; of these, 78 received peramivir. A total of 23 subjects were randomised to OSE; all 23 received OSE. To date, 75 patients were included in the ITTI Population. The analysis showed that fever resolved more rapidly for patients in the OSE group than in the peramivir group (median hours = 34.7 hours in the OSE group and 40.5 hours in the peramivir group). Influenza symptoms were alleviated more rapidly for patients in the peramivir group compared with the OSE group (median hours = 75.6 hours versus 99.8 hours). The probability of alleviation of influenza symptoms was higher in the peramivir group compared with the OSE group at all but 1 time interval (>180 to 192 hours) after dosing. This difference was larger in the earlier time windows; by 156 hours after initial dosing, the probability of alleviation of symptoms was relatively similar in the 2 treatment groups.

In terms of virology endpoints, overall, a total of 68 patients had positive virus titres at baseline. Positive viral titres persisted for slightly more than half of these patients (37 (56%) of 66 patients with available titres) at Day 3, which was reduced to 3% in these 66 patients by Day 7. By Day 14, viral shedding was not reported for any patients. On Day 3, a lower percentage of patients in the peramivir group (51%) compared with the oseltamivir group (77%) had positive viral titres. By Day 7, the groups were similar (4% in the peramivir group and 0 patients in the oseltamivir group). Among patients who received peramivir, there were no notable differences within each treatment group among the 3 older age cohorts in the reduction of viral shedding over time. No patients 28 days to < 2 years of age who received peramivir had positive influenza virus titres at baseline. Overall, median log10 $TCID_{50}$/mL value was 4.50 at baseline. Overall influenza virus titres were reduced to a median log10 $TCID_{50}$/mL value of 0.75 by Day 3 and to 0.50 by Day 7.

The PK analysis demonstrates that a single IV peramivir 600 mg for children 13 to 18 years or 12 mg/kg for children 2 to 12 years produced PK parameters (plasma concentration and truncated $AUC_{0\text{-}3h}$) that were comparable with those in adults. The resolution of influenza signs and symptoms and viral shedding for paediatric patients treated with peramivir was consistent with that observed in placebo-controlled studies in peramivir treated adults with influenza. There is minimal efficacy data in children <2 years.

Study 0918T0633 (un-controlled open-label study in Japan)

This was a Phase III, multicentre, un-controlled open-label study of IV peramivir in paediatric subjects with acute uncomplicated influenza. Peramivir IV was given at 10 mg/kg, once daily. On Day 2 and thereafter, repeated once daily dose was allowed if the subject's temperature was ≥ 38.0°C. Male and female subjects, 28 days or older but <16 years of age, were eligible. For infants < 1 year old, only those whose birth weights had been ≥ 2500g were eligible. Subjects must have had a fever (> 38°C); a positive RAT; and, if the subject was ≥ 7 years of age, at least 1 moderate to severe respiratory symptom of influenza infection. In addition, symptom duration must have been ≤ 48 hours. Efficacy evaluations included self-assessments of temperature, severity of influenza symptoms, and evaluation of activities of daily living. This study enrolled 117 subjects and 97.4% completed the study. A total of 3 patients discontinued. The youngest patients were between ≥ 28 days to < 1 year old (n= 4). A total of 115 patients were included in the ITTI Population. The primary endpoint was the duration of influenza measured by the time to disappearance of influenza symptoms. For 63 evaluable patients between the ages of 6 to < 16 years, the median time to alleviation of influenza symptoms was 30.5 hours (95% CI: 22.6, 45.8). The median time to alleviation of influenza symptoms was 25.5 and 45.6 hours in patients ≥ 6 to < 12 years and ≥ 12 to < 16 years old, respectively. For all patients, the median time to resolution of fever was 20.4 hours (95% CI: 19.1, 20.9) and ranged from 19.7 to 20.8 hours. The study has shown good response to peramivir in relation to symptoms.

Safety

Overall, the safety of peramivir has been evaluated in clinical studies involving 2,155 subjects with influenza, with daily doses ranging from 75 mg to 600 mg administered over 1 to 10 days of treatment. In these randomised, controlled studies, peramivir has been generally safe and well-tolerated. In clinical studies, a single 600 mg infusion of peramivir in adults had similar safety and tolerability to a single 300 mg dose, the approved dosage in Japan. Additionally, the safety and tolerability profiles of a single 600 mg infusion of peramivir were similar in Japanese/Southeast Asian subjects and North American subjects.

The most common TEAEs observed in clinical trials included diarrhoea, decreased neutrophil count, and increased blood glucose. These were similar to events observed in subjects administered oseltamivir or placebo and were generally consistent with the acute illness and underlying concomitant medical conditions of study subjects. Elevated blood glucose is more common in the elderly.

Safety signals were not detected in special analyses designed to evaluate the safety of peramivir in neuropsychiatric events, rash, hypersensitivity, renal function, haematological abnormalities, infusion site reactions, orthostatic hypotension, hepatic function, haemorrhagic colitis, and muscle effects. Although nephrotoxicity was noted in male rabbits in non-clinical safety studies, detailed investigations of renal function and urinary protein excretion in clinical trials have shown no evidence of nephrotoxicity in human subjects.

There was no evidence of an effect of peramivir on cardiac conduction. An adequate, thorough QT study was negative. IV peramivir administrations at doses of 600 mg and 1200 mg (supra-therapeutic) were not associated with QTc prolongation or other repolarisation abnormalities.

Laboratory findings were generally consistent with influenza illness. Enzyme elevations (for example, CK) in the studies using peramivir IM were associated with the formulation and route of administration.

In evaluations of subpopulations, no relevant safety findings were observed. Elderly subjects and Hispanic ethnicity subjects each represented only 2% of the total enrolled in acute uncomplicated influenza studies. However, there is no evidence to suggest that efficacy or safety of peramivir will be compromised in the elderly or Hispanic or other ethnic subgroups. Elevated blood glucose was more common in the elderly and this would need to be monitored, particularly in diabetics. Although conclusions may be limited as some of these populations were relatively small, there were no apparent differences in reported events based on gender, age, race, ethnicity, renal dysfunction, pre-existing hepatotoxicity, or pre-existing respiratory disease.

As of 30 September 2015, peramivir has also been administered to approximately 1,600,000 influenza patients following the 13 January 2010 approval in Japan. Three post marketing safety surveillance studies have been conducted with 2 reporting final conclusions. No safety signals arose from these observational studies. The spontaneous AE reports did not show any new risks that were not previously seen with other NAIs. Given the large number of patients exposed to peramivir in the post marketing setting, the reporting rate for all events is low. There have been safety signals from the Japanese post marketing data, such as shock, anaphylaxis, and haemorrhagic colitis, analysis has indicated that these AEs are unlikely to be risks from peramivir treatment, but are likely coming from the underling influenza illness, concomitant medications, or comorbidities. Two events remain safety signals and these AEs (neuropsychiatric events severe rashes such as Stevens-Johnsons disease and erythema multiform) were considered significant enough to warrant informing prescribers and patients through appropriate statements in the PI.

In May 2016, anaphylaxis was identified by the FDA as new safety information in patients receiving peramivir. Anaphylaxis was therefore added to the contraindications, warnings, and precautions and post-marketing experience section of the US package insert. Anaphylaxis has also been included the Contraindications / Precautions / post-marketing experience sections of the proposed Australia PI.

Risk management plan

The submitted RMP is considered as generally acceptable; however a minor outstanding recommendation for the nonclinical part of the safety specification should be addressed: to include a brief explanation of the renal/urothelial changes of uncertain clinical relevance in the 'key safety findings (from nonclinical studies)' in the nonclinical part of the safety specification of the EU-RMP.

The suggested wording for condition of registration is as follows:

> *Implement the peramivir (Alpivab/Rapivab) EU-RMP version 0.2 dated 11 August 2017 (DLP 31 March 2017) and ASA version 2.0 dated October 2017 and any future updates as a condition of registration.*

The RMP evaluator informed the delegate that the dosage advice in relation hospitalised patients has been amended by the sponsor (in their Section 31 response) to the followings:

> *Hospitalised Patients*
>
> *For patients hospitalised with influenza infection, daily dosing is recommended for a period of up to 5 days. During the 2009-2010 H1N1 pandemic, patients were dosed once daily for a period of up to 10 days.*

The above change will need reconsideration following the ACM advice.

Risk-benefit analysis

Delegate's considerations

Adult patients with acute uncomplicated influenza

As discussed, the results of pivotal study 0722T0621 confirmed the efficacy of both 300 mg and 600 mg of peramivir for the treatment of adult patients with acute uncomplicated influenza. The primary endpoint of TTAS has previously been established as suitable for randomised controlled studies in acute uncomplicated influenza, as noted in the FDA guideline (Guidance for Industry. Influenza: Developing Drugs for Treatment and/or Prophylaxis). The integrated efficacy analyses from the 4 placebo controlled studies (one IV and 3 IM studies) showed that peramivir therapy has a generally consistent benefit in both clinical and virologic endpoints. Among subjects who received peramivir, the median TTAS was 114.1 hours for subjects in the 150 mg group, 84.1 hours for subjects in the 300 mg group, and 79.4 hours for subjects in the 600 mg group. The median TTAS was 107.4 hours for subjects who received placebo. The overall median TTAS for subjects who received peramivir was 87.6 hours, which represents a significant improvement compared with placebo (107.4 hours). Similar trends were seen in the individual studies. Studies which compared peramivir to OSE or SOC (Study 0815T0631, BCX1812-301, and BCX1812-201) found equivalence. Two studies comparing 600 mg with 300 mg favoured 600 mg but did not reach statistical significance (Studies 0816T0632 and BCX1812-303).

The primary endpoint of TTAS is presented by virus subtype for the pooled ITTI population of the placebo controlled studies (Studies 0722T0621, BCX1812-211/311, and BCX1812-212). The results for A/H1N1 and A/H3N2 were highly similar to the results for the overall ITTI study population. In the A/H1N1 group, the median time to alleviation of symptoms was numerically better than placebo for subjects who received peramivir (-19.8 hours). The results for A/H3N2 group showed a stronger benefit of peramivir overall than was seen for influenza A/H1N1, with a significant improvement compared with placebo (-31.2 hours). Although the H275Y variant of influenza A/H1N1 has reduced susceptibility to peramivir, treatment with peramivir was numerically superior to placebo (-15.7 hours).

Among subjects with influenza B, there was no improvement in time to alleviation of symptoms with peramivir compared with placebo.

Paediatric patients with acute uncomplicated influenza

The results from Study BCX1812-305 indicate that influenza symptoms were alleviated more rapidly for patients in the peramivir group compared with the OSE group (median hours = 75.6 hours versus 99.8 hours). There were no notable differences by age and no apparent age-related trends in the time to alleviation of symptoms. In addition, data for virology endpoints and time to resumption of usual activities were similar in these two studies. Both studies had a very low rate of influenza-related complications. Additional experience in 1,199 children in the post-marketing studies in Japan supports the safety of peramivir injection for paediatric use.

Hospitalised patients with acute influenza

Study BCX1812-301 did not demonstrate a significant difference between placebo + SOC and peramivir 600 mg + SOC for the primary endpoint of time to clinical resolution. Study BCX1812-201 and Study BCX1812-303 did not show any significant differences between the treatment groups.

No analyses were done across the studies in hospitalised patients, as these studies had different design parameters, different inclusion criteria, and different treatment dosages. In Study BCX1812-201, subjects were dosed with 200 mg or 400 mg IV peramivir in comparison to oral OSE. By contrast, in BCX1812-301, subjects were dosed with 600 mg (or 10 mg/kg for 12-18 year olds or 12 mg/kg for 6 to 12 year olds) peramivir in comparison to placebo (plus standard of care). Study BCX1812-303 had markedly different inclusion/exclusion criteria because the study ran primarily during the 2009 to 2010 H1N1 pandemic, inclusion criteria were intentionally broad, resulting in many critically ill subjects being enrolled. Clinical data from these studies were often confounded by underlying comorbidities and concomitant medications.

In addition to the above studies in hospitalised patients, the sponsor has provided a number of published reports of efficacy analysis in severely ill hospitalised patients. The safety data with repeated doses from the hospitalised studies appears similar to that in the trials of acute uncomplicated influenza.

Proposed action

Overall, the submitted data support the use of single IV dose of peramivir for the treatment of acute uncomplicated influenza in adult and children older than 2 years of age. The clinical data is limited in the treatment of influenza B due to the low enrolment of patients infected with influenza B. However, nonclinical data have showed potent activity of peramivir against influenza B.

For the treatment of hospitalised patients with acute serious influenza, the efficacy of peramivir has not been established in the submitted studies.

In terms of safety, many of the common treatment-emergent AEs had similar occurrence in both placebo and other treatment groups, suggesting that they may relate to the underlying influenza and co-morbidities. Anaphylaxis and severe cutaneous reactions have been reported in post marketing setting. Abnormal behaviour is more commonly reported in children than adults. Other side effects include LFT abnormalities, neutropenia; glucose elevation. Development of resistance is always a concern with antiviral agents.

As a long acting agent with a rapid absorption and its IV route of administration, peramivir has its advantages. Because of its IV route, peramivir injection would be a suitable clinical choice in influenza patients who are unable to tolerate oral or inhaled therapy. Relevant

clinical situations would include inability to comply with oral or inhaled medications, such as patients with a history of poor compliance, patients who suffer from gastrointestinal diseases that could impair drug absorption, patients who are unable to use or contraindicated for inhaled medications.

The Delegate recommends the approval of peramivir for the revised indication below:

> *Rapivab is indicated for the treatment of acute uncomplicated influenza in adults and children 2 years and older who have been symptomatic for no more than two days.*

Summary of issues

The pivotal study in adult patients with acute uncomplicated influenza (Study 0722T0621) demonstrated the superior efficacy of IV peramivir (both 300 mg and 600 mg) compared to placebo for the primary endpoint of TTRS (time to alleviation of symptoms). The integrated efficacy analyses from the 4 placebo controlled studies also support the conclusion from Study 0722T0621.

In the oseltamivir-controlled study in paediatric patients with acute uncomplicated influenza (BCX1812-305), Influenza symptoms were alleviated more rapidly for patients in the peramivir group compared with those in oseltamivir group. The PK analysis in this study showed that a single IV peramivir 600 mg for children 13 to 18 years or 12 mg/kg for children 2 to 12 years produced the PK parameters that were comparable with that observed in adults receiving a single 600 mg dose.

Study BCX1812-301 was conducted in 398 subjects (adults and paediatrics) with serious influenza requiring hospitalisation. In this study, subjects were randomised to receive peramivir 600 mg daily for 5 days plus standard of care versus standard of care plus placebo within 72 hours of start of symptoms. The primary endpoint was the time to clinical resolution. Peramivir plus standard of care did not improve median time to clinical resolution compared with standard of care alone. Safety of repeated doses of peramivir appears to be acceptable but the efficacy in this population has not been established in the submitted studies.

Pre ACM assessment

The Delegate has no reason to say, at this time, that Rapivab (peramivir) should not be approved for the revised indication below:

> *Rapivab is indicated for the treatment of acute uncomplicated influenza in adults and children 2 years and older who have been symptomatic for no more than two days.*

The condition of registration is as follows:

- Implement the peramivir (Alpivab/Rapivab) EU-RMP version 0.2 dated 11 August 2017 (DLP 31 March 2017) and ASA version 2.0 dated October 2017 and any future updates as a condition of registration.

Request for ACM advice

The committee is requested to provide advice on the following specific issues:

1. Does the committee consider that the submitted data support the use of single IV dose of peramivir for adult patients with acute uncomplicated influenza?

2. Does the committee consider that the submitted data support the use of single IV dose of peramivir for paediatric patients 2 years and older with acute uncomplicated influenza?
3. Does the committee agree that the submitted data did not establish the efficacy of repeated doses of IV peramivir for the treatment of hospitalised patients with acute serious influenza, and therefore the statement below should not be included in the Dosage and Administration section of the PI:

   Hospitalised Patients

   For patients hospitalised with influenza infection, daily dosing is recommended for a period of up to 5 days. During the 2009-2010 H1N1 pandemic, patients were dosed once daily for a period of up to 10 days.
4. Does the committee consider that the indication should be revised as below:

   Rapivab is indicated for the treatment of acute uncomplicated influenza in adults and children 2 years and older who have been symptomatic for no more than two days.

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

The sponsor appreciates the opportunity to respond to the TGA's Request for ACM advice and welcomes the Delegate's pre-ACM preliminary assessment that there are no reasons precluding approval of Rapivab (peramivir) for treatment of influenza in adults and children 2 years and older who have been symptomatic for no more than two days.

Major issue (revised indication)

(Q1) Does the committee consider that the submitted data support the use of single IV dose of peramivir for adult patients with acute uncomplicated influenza?(Q4) Does the committee consider that the indication should be revised as below:

> *Rapivab is indicated for the treatment of acute uncomplicated influenza in adults and children 2 years and older who have been symptomatic for no more than two days.*

The sponsor questions the Delegate's suggestion to restrict the indication to treatment of acute uncomplicated influenza and asserts that the indication sought (below) is appropriate and supported by evidence:

> *Rapivab is indicated for the treatment of infections due to influenza A and B viruses in adults and children 2 years and older. Treatment should commence as soon as possible, but no later than 2 days after the onset of the initial symptoms of infection.*

The indication sought by the sponsor is consistent with that of other NAIs approved by TGA. The approved indication for both oseltamivir (Tamiflu) and zanamivir (Relenza) is the 'treatment of infections due to Influenza A and B viruses in adults and children'. The applicant has applied for the same indication, based on the similarity of the level and type of evidence provided for oseltamivir and zanamivir to support the indication. No clinical studies to demonstrate efficacy in hospitalised patients were required for approval of this indication for either oseltamivir or zanamivir.

The Delegate's suggestion to restrict the indication appears to be based on the statement that:

> *Safety of repeated doses of peramivir appear to be acceptable but the efficacy in the hospitalized population has not been established in the submitted studies.*

This is inconsistent with the conclusion of the TGA clinical evaluator who states:

> *Peramivir injection would be a suitable clinical choice in patients hospitalised with acute serious or potentially life-threatening influenza.*

As a class of drug, NAIs have been demonstrated to reduce mortality and disease burden in severely ill patients hospitalised with influenza infection. In the peramivir clinical program, there were several studies conducted in subjects who were hospitalised with influenza. Whilst the clinical studies in hospitalised adult and paediatric patients for peramivir did not demonstrate superiority over standard treatments, evidence supports non-inferiority to oseltamivir in hospitalised influenza-infected patients. Evidence from the use of peramivir in a pandemic setting also supports clinical improvement and reduced mortality in critically ill patients, including in children.

Similar evidence for the benefit of peramivir in adults and children was observed during the 2009 H1N1 pandemic, where the product was provided under an Emergency Use Authorization in the U.S.A (the first Emergency Use Authorization issued by the US FDA for an unapproved drug). Early treatment with peramivir during the pandemic was associated with clinical improvement and low rates of mortality in critically ill, hospitalised patients. Therefore, the sponsor believes that the totality of scientific evidence available for peramivir is equivalent to, if not more than that available for the currently TGA registered NAIs and thus supports its use in patients hospitalised with influenza infection.

The Delegate is suggesting an indication that is aligned with U.S. FDA guidance for development of NAI, a guidance which has not been adopted in Australia. The sponsor believes that the term ''acute uncomplicated influenza'' is not useful in the context of Australian clinical practice, and has the potential to confuse clinicians when making decisions to treat patients with influenza infection.

To the best of the sponsor's knowledge there are no local guidelines which reference the clinical syndrome of 'acute uncomplicated influenza' in treatment algorithms or recommendations. When asked to explain the term 'acute uncomplicated influenza', infectious diseases and respiratory physicians have produced varied and inconsistent definitions. There is a formal pathology-based definition for 'acute uncomplicated influenza': It is characterised bronchoscopically by diffuse inflammation and oedema of the airways, mucosal biopsies with lymphocytic and histiocytic inflammatory infiltrate and desquamation and limited tissue damage and secondary infections.

However, in clinical practice, treatment decisions are based on diagnostic and clinical parameters rather than histo-pathology criteria. The Antibiotic Therapeutic Guidelines 2014 state that regardless of the duration of the symptoms, treatment should be offered based on clinical criteria that is, to individuals with established complications or to patients requiring admission to hospital for management of influenza. Similarly, the CDC in the USA recommend the use of antiviral treatments, including peramivir, in patients with confirmed or suspected influenza who are hospitalised; have severe, complicated or progressive illness; or are at higher risk of influenza complications.

At present, there remains an unmet medical need for a parenteral NAI to treat patients with influenza infection. In the ICU setting in particular, there is a critical need for an NAI that is suitable for treatment of patients who are intubated, have impaired consciousness or are suffering encephalitis as a complication of influenza infection. The IV route of administration is also the preferred option in non-critically ill patients who cannot tolerate or absorb oral or enterically administered oseltamivir because of suspected or known gastric stasis, malabsorption, gastrointestinal bleeding or have had gastric surgical procedures.

Some public health guidances in the UK and USA recommend the use of IV zanamivir if there is poor response to oseltamivir, or if there is poor gastrointestinal absorption.

However, IV zanamivir is not approved and is not readily available in Australia. There is limited safety and efficacy data on the use of IV zanamivir in hospitalised patients. In contrast, as acknowledged by the Delegate, there are no safety limitations associated with multiple days of dosing of peramivir. Controlled studies in hospitalised patients showed that administration of up to a total of 6000 mg peramivir over a 10 day period did not demonstrate adverse events related to dose or total exposure.

In summary, the sponsor believes that the indication sought for peramivir is appropriate and unambiguous in the context of clinical decision-making for treating patients with influenza infection for the following reasons:

- The evidence provided for the registration of peramivir is comparable to NAIs already approved in Australia.
- The indication sought is consistent with that approved by the TGA for other neuraminidase inhibitors.
- Peramivir has been demonstrated to be non-inferior to oseltamivir in studies of hospitalised influenza-infected patients.
- The benefit of using peramivir in critically ill patients in a pandemic setting has been shown.
- There is an unmet medical need for intravenous neuraminidase inhibitors for the treatment of influenza.
- Safety of IV peramivir has been demonstrated following repeat dosing of up to 10 days.

Other issues (Dosage and Administration)

- *(Q3) Does the committee agree that the submitted data did not establish the efficacy of repeated doses of IV peramivir for the treatment of hospitalised patients with acute serious influenza, and therefore the statement below should not be included in the Dosage and Administration section of the PI:*

  Hospitalised Patients

  For patients hospitalised with influenza infection, daily dosing is recommended for a period of up to 5 days. During the 2009-2010 H1N1 pandemic, patients were dosed once daily for a period of up to 10 days.

The sponsor believes that evidence for the efficacy of IV peramivir in the treatment of hospitalised patients with influenza has been provided, as outlined in the previous section of this response.

Therefore, the sponsor would like to retain the dosing for hospitalised patients with influenza in the 'Dosage and Administration' section.

Although there is evidence to support the safe use of IV peramivir for up to 10 days, the sponsor takes this opportunity to amend the dosing to 5 days to reflect the dosing regimen used in the pivotal study of hospitalised patients.

Other issues (Paediatric data)

- *(Q2) Does the committee consider that the submitted data support the use of single IV dose of peramivir for paediatric patients 2 years and older with acute uncomplicated influenza?*

The FDA approved the extension of indication to include paediatric patients 2 years and older in September 2017 based on the same data package provided to the TGA. The sponsor would also like to clarify that the paediatric data for children 2 years of age and older was provided to the EMA as supplemental data and has been accepted for evaluation by the EMA.

In regards to the restriction of indication to acute uncomplicated influenza in paediatric patients 2 years and older, the sponsor refers ACM members to comments in the Major issue (revised indication) section of this response and iterates that the term 'acute uncomplicated influenza' is not helpful and is potentially confusing when making treatment decisions for influenza infection in children. The unmet medical need for an intravenous NAI is even greater in children who may have difficulty swallowing or inhaling medication.

Studies assessing the safety and efficacy of repeated dosing of peramivir for treatment of critically ill hospitalised patients infected with influenza included children. Studies BCX1812-301 and BCX1812-303 enrolled children aged 6 years and older and during the 2009 H1N1 pandemic, hospitalised children aged 28 days and older received multiple days dosing of peramivir. The data demonstrate the safety and efficacy of repeated dosing of peramivir in hospitalised children.

Other issues (Quality evaluation)

For the information of the Delegate and ACM, current GMP clearances have now been approved for all manufacturers of the peramivir drug substance and drug product.

Advisory Committee Considerations[13]

The Advisory Committee on Medicines (ACM), taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Rapivab solution for infusion containing 200 mg / 20 mL of peramivir to have an overall positive benefit-risk profile for the indication:

> *Rapivab is indicated for the treatment of acute uncomplicated influenza in adults and children 2 years and older who have been symptomatic for no more than 2 days.*

However, the ACM proposed revised wording of the indication to:

> *Rapivab is indicated for the treatment of infections due to influenza A and B viruses in adults and children 2 years and older who have been symptomatic for no more than two days. Clinical trials have not established the efficacy of repeated doses of peramivir over placebo or other treatments for influenza in hospitalized patients.*

In making this recommendation, the ACM:

- noted that despite the small amount of data with single dose Rapivab in symptom alleviation in individuals predominantly with uncomplicated influenza A there is unlikely to be any difference between the efficacy for Influenza A and Influenza B strains based on the mechanism of action of Rapivab
- noted that the efficacy of repeated doses in a hospital setting has not been demonstrated in clinical trials especially for complicated presentations of influenza.
- noted that the sponsor disagreed with the Delegate's proposed indication which restricts treatment with Rapivab to acute uncomplicated influenza.

[13] The ACM provides independent medical and scientific advice to the Minister for Health and TGA on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The committee is established under Regulation 35 of the *Therapeutic Goods Regulations 1990*. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in 2010. ACM encompasses pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

- was of the view that if the indication is not restricted to 'acute uncomplicated influenza' then information should be included in the wording of the indication that; 'clinical trials have not established the efficacy of repeated doses of peramivir over placebo or other treatments for influenza in hospitalized patients' or similar.
- advised that the dosage information for hospitalised patients should be removed from the dosage and administration section of the PI. This information should be retained elsewhere in the PI (for example in the clinical trials section) because of the high likelihood of use of Rapivab in the hospital setting.
- noted that in the post-market surveillance setting some neuropsychiatric events (for example, abnormal behaviour) were more commonly reported in children vs adults. The committee advised that this information should be included in the PI and that active pharmacovigilance studies specifically in the paediatric population to better characterise the safety profile in this population, especially in younger ages with potentially greater vulnerability to potential brain toxicity, be requested.

Proposed conditions of registration

The ACM agreed with the Delegate on the proposed conditions of registration.

Proposed PI/CMI amendments

The ACM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine information (CMI) and specifically advised on the inclusion of the following:

- The committee agreed with the proposed amendments to the PI and CMI however the final version will need to take account of the final wording of the indication.
- The committee agreed that the dosage and administration section should not include information for daily dosing of hospitalised patients for up to five days, but that the information should be retained (for example in the clinical trials section).
- The committee advised that this information regarding the in the post-market setting the incidence of neuropsychiatric events in the paediatric population should be included in the PI.

Specific advice

The ACM advised the following in response to the delegate's specific questions on the submission:

1. *Does the committee consider that the submitted data support the use of single IV dose of peramivir for adult patients with acute uncomplicated influenza?*

The committee considered that the data supported the use of a single IV dose of Rapivab for adult patients with acute uncomplicated influenza. The data demonstrated shortened symptoms duration versus placebo, and was considered comparable to oseltamivir.

2. *Does the committee consider that the submitted data support the use of single IV dose of peramivir for paediatric patients 2 years and older with acute uncomplicated influenza?*

The committee considered that the submitted data supported the use of the single IV dose of Rapivab for paediatric patients 2 years and older with acute uncomplicated influenza. The single dose of peramivir was equivalent to oseltamivir and appeared to be safe. However the committee recommended implementation post-market pharmacovigilance measures to better characterise the safety profile in the paediatric population.

3. *Does the committee agree that the submitted data did not establish the efficacy of repeated doses of IV Rapivab for the treatment of hospitalised patients with acute*

serious influenza, and therefore the statement below should not be included in the Dosage and Administration section of the PI:

> *Hospitalised Patients*
>
> *For patients hospitalised with influenza infection, daily dosing is recommended for a period of up to 5 days. During the 2009-2010 H1N1 pandemic, patients were dosed once daily for a period of up to 10 days.*

The committee agreed that the submitted data did not establish the efficacy of repeated doses of IV Rapivab for the treatment of hospitalised patients with acute serious influenza. The committee concluded that the data for repeated doses of Rapivab was no different to that of placebo or oseltamivir.

The committee recommended the omission of dosage recommendations for hospitalised patients with acute serious influenza, and that this dosing information should be included elsewhere in the PI (for example in the clinical trials section) including a description of the dosing in hospitalised patient clinical trials (daily for 5 days) with a description of the results and the conclusion that the results of these trials did not establish benefit.

4. *Does the committee consider that the indication should be revised as below:*

> *Rapivab is indicated for the treatment of acute uncomplicated influenza in adults and children 2 years and older who have been symptomatic for no more than two days.*

The committee preferred the option of the indication which includes a description of the limitations of the data for efficacy in repeated doses, with the wording of the indication being preferred by ACM:

> *Rapivab is indicated for the treatment of acute influenza infection in adults and children 2 years and older who have been symptomatic for no more than two days. Clinical trials have not established the efficacy of repeated doses of Rapivab over other treatments for influenza in hospitalized patients.*

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Rapivab (peramivir) 200 mg / 20 mL concentrate for intravenous infusion glass vial indicated for:

> *Rapivab is indicated for the treatment of acute influenza infection in adults and children 2 years and older who have been symptomatic for no more than two days.*
>
> *Clinical trials have not established the efficacy of repeated doses of Rapivab in patients with serious influenza requiring hospitalisation.*

Specific conditions of registration applying to these goods

- Rapivab (peramivir) is to be included in the Black Triangle Scheme. The PI and CMI for Rapivab must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The peramivir EU-Risk Management Plan (EU-RMP), version 0.2, dated 11 August 2017 (data lock point 31 March 2017) and ASA version 2.0 dated October 2017, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Rapivab approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

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