28 February 2019
EMA/CHMP/851480/2018
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## DECTOVA

International non-proprietary name: zanamivir

Procedure No. EMEA/H/C/004102/0000

## Note

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

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# List of abbreviations

| | |
|---|---|
| ADR | Adverse drug reaction |
| AE | Adverse event |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| AUC | Area under the curve |
| AUC(0-□) | Area under the concentration-time curve over the dosing interval |
| ARDS | Acute respiratory distress syndrome |
| BAL | Broncoalveolar lavage |
| BID | Twice daily |
| CDC | Centers for Disease Control and Prevention |
| CDER | Center for Drug Evaluation and Research |
| CFU | Colony Forming Units |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence interval |
| CL | Clearance |
| Cmax | Maximum observed concentration |
| CPP | Critical process parameter |
| CQA | Critical Quality Attribute |
| CrCl | Creatinine clearance |
| CRF | Case report form |
| CRS | Chemical Reference Substance (official standard) |
| C □ | Pre-dose (trough) concentration at the end of the dosing interval |
| COPD | Chronic obstructive pulmonary disease |
| CNS | Central nervous system |
| CPSR | Clinical Pharmacology Study Report |
| CRF | Case report form |
| CSR | Clinical study report |
| Ctrough | Trough concentration |
| CUP | Compassionate use programme |
| CYP | Cytochrome P450 |
| ECDC | European Centre for Disease Prevention and Control |
| ECMO | Extra corporeal membrane oxygenation |
| EEA | European Economic Area |
| ELF | Epithelial lining fluid |
| EP | European Pharmacopoeia |
| EU | European Union |
| EU RMP | European Risk Management Plan |
| FDA | Food and Drug Administration |
| GC | Gas Chromatography |
| GMP | Good Manufacturing Practice |
| GSK | GlaxoSmithKline |
| HA | Haemagglutinin |
| HPLC | High performance liquid chromatography |
| IC50 | 50% inhibitory concentration |

| | |
|---|---|
| IC90 | 90% inhibitory concentration |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ICU | Intensive care unit |
| ILI | Influenza like illness |
| IP | Investigational product |
| IPC | In-process control |
| IPP | Influenza positive population |
| IPR | Influenza positive oseltamivir resistant |
| IR | Infrared |
| IV | Intravenous |
| KF | Karl Fischer titration |
| LRT | Lower respiratory tract |
| MAA | Marketing authorisation application |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MPA | Medical Products Agency |
| MV | Mechanical ventilation |
| NA | Neuraminidase |
| NAI | Neuraminidase inhibitor |
| NANA | N-Acetyl-D-Neuraminic Acid |
| NAM | N-acetyl-D-mannosamine |
| NDA | New Drug Application |
| NMR | Nuclear Magnetic Resonance |
| NOAEL | No observed adverse effect level |
| NP | Nasopharyngeal |
| PAR | Proven Acceptable Range |
| PBRER | Periodic Benefit Risk Evaluation Report |
| PCR | Polymerase chain reaction |
| PD | Pharmacodynamic |
| PDE | Permitted Daily Exposure |
| Ph. Eur. | European Pharmacopoeia |
| Pgp | P-glycoprotein |
| PHE | Public Health England |
| PK | Pharmacokinetic |
| PVDF | polyvinylidene fluoride |
| QbD | Quality by design |
| QP | Qualified person |
| qPCR | Quantitative polymerase chain reaction |
| QTPP | Quality target product profile |
| RNA | Ribonucleic acid |
| SAE | Serious adverse event |
| SEAIDCRN | Southeast Asia Infectious Diseases Clinical Research Network |
| SC | Subcutaneous |
| SD | Standard deviation |
| SmPC | Summary of Product Characteristics |
| SMQ | Standardized MedDRA Query |
| SOC | System organ class |
| S/R | Switch/rescue |
| TID | Three times daily |

| | |
|---|---|
| TTC | Threshold of toxicological concern |
| TTCR | Time to clinical response |
| UK | United Kingdom |
| ULN | Upper limit of normal |
| US | United States |
| UV | Ultraviolet |
| Vdss or Vss | Volume of distribution at steady state |
| WFI | Water for injection |
| WHO | World Health Organization |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant GlaxoSmithKline Trading Services Limited submitted on 21 November 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for DECTOVA, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 November 2014. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The applicant applied for the following indication:

Dectova is indicated for the treatment of influenza A or B virus infection in hospitalised adult and paediatric patients (⩾6 months):

- when circulating influenza virus is resistant to other approved anti-influenza medications, or resistance develops while on anti-influenza treatment, and/or
- who cannot take anti-influenza medications via other routes of administration

**The legal basis for this application refers to:**

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

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

## *Information on Paediatric requirements*

Pursuant to Article 7 Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0212/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0212/2017 was not yet completed as some measures were deferred.

## *Information relating to orphan market exclusivity*

### Similarity

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

## *Applicant's request(s) for consideration*

### Marketing authorisation under exceptional circumstances

The applicant requested consideration of its application for a marketing authorisation under exceptional circumstances in accordance with Article 14(8) of the above mentioned Regulation.

## New active Substance status

The applicant indicated the active substance zanamivir contained in the above medicinal product to be considered as a known active substance.

## *Scientific advice*

The applicant received Scientific advice from the CHMP:

| Scientific advice | date | Area |
|---|---|---|
| EMEA/H/SA/1586/1/2010/III | 22 June 2010 | non-clinical and clinical |
| EMEA/H/SA/1586/1/FU/2012/PED/II | 24 May 2012 | clinical |
| EMEA/H/SA/1586/1/FU/2/2014/III | 22 May 2014 | non-clinical and clinical |
| EMEA/H/SA/1586/1/FU/3/2016/III | 10 November 2016 | non-clinical and clinical |

In the 2010 EMA/FDA Parallel scientific advice, the following topics were addressed

The adequacy of the non-clinical studies to support the IV use of zanamivir

The proposed clinical pharmacology program

The design of the Phase III study, randomised, multi-center, double-blind, double-dummy study to evaluate the efficacy and safety of 600 mg of intravenous zanamivir twice daily compared to 150 mg of oral oseltamivir twice daily in the treatment of hospitalised adults and adolescents with influenza.

More specifically:

- The dose regimen for IV zanamir
- The use of oral oseltamivir at 150mg BID dosing as an active control
- The proposal to demonstrate superiority over oral oseltamivir and the statistical analysis plan
- The use of a virological and a clinical endpoint as co-primary
- The proposal for secondary endpoints
- The exclusion of pregnant or lactating women
- The exclusion of children <13 years of age and the proposal to obtain more safety, PK and activity data from an ongoing Phase II study in children before enrolling them in a large scale clinical trials or proposing an extrapolation plan
- The adequacy of this single pivotal trial to support approval

The clinical safety database to support a MAA for IV zanamivir

In the 2012 EMA scientific advice, the following topics were addressed

The extrapolation concept and plan to extend efficacy results of IV zanamivir observed in hospitalised adults and older adolescents with influenza, to hospitalised paediatric patients with influenza including neonates

The adequacy of the extrapolation approach, supported by data from retrospective chart reviews of paediatric patients treated with IV zanamivir via compassionate use, to support registration of a paediatric indication

In the 2014 EMA scientific advice, the following topics were addressed

The adequacy of the non-clinical studies to support the IV use of zanamivir, challenging some of the advice given in 2010

The changes in the pivotal trial since the 2010 advice. Now designed as a randomised, double-blind, double-dummy Phase III to demonstrate superiority of IV zanamivir 300mg BID or 600mg BID over the comparator oseltamivir 75mg BID

The applicant's take on the emerging body of observational data on the use of oral oseltamivir for the treatment of hospitalised patients with influenza pointing to its effectiveness in this population, specifically with regard to a mortality benefit, and the associated challenges in showing superiority of IV zanamivir over oral oseltamivir in the Phase III.

The conduct of a second interim analysis to include a futility analysis with the hypothesis that if oseltamivir is indeed efficacious, then IV zanamivir may be unlikely to be superior to an efficacious treatment

The applicant's opinion that failure to demonstrate superiority over oral Oseltamivir may not indicate lack of efficacy but instead may point to similar efficacy of two treatments

The key analyses that will help define a favourable benefit-risk profile to support an MAA for IV zanamivir

- Primary endpoint (time to clinical response) and a key secondary endpoint (time to respiratory status improvement) in a key secondary analysis
- Key Subgroup analyses
- Non-inferiority on mortality as a new secondary analysis

The possibility to grant a MA in pre-specified subpopulations, where a clear benefit is shown, even if an advantage is not observed in the overall study population when compared to oseltamivir

In the 2016 EMA scientific advice, the following topics were addressed

The use of animal models to support efficacy against resistant influenza viruses

The possibility to bridge efficacy from inhalation route to IV route

The evidence base to support approval of zanamivir 600 mg BID IV for treatment of influenza

The possibility to investigate alternative regulatory routes (i.e. conditional marketing authorisation or exceptional circumstances) for approval given that the pivotal Phase III study did not meet its pre-specified primary endpoint (time to clinical response)

The post-authorisation study to evaluate the clinical effectiveness of treatment with IV Zanamivir in subjects hospitalised in ICU with drug-resistant influenza

The risk minimisation activities to identify, characterise and prevent or minimise risks relating to the use of IV zanamivir

## *1.2. Steps taken for the assessment of the product*

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

Rapporteur: Svein Rune Andersen Co-Rapporteur: Nithyanandan Nagercoil

| | |
|---|---|
| The application was received by the EMA on | 21 November 2017 |
| The procedure started on | 28 December 2017 |
| The Rapporteur's first Assessment Report was circulated to all CHMP members on | 19 March 2018 |
| The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on | 16 March 2018 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on | 4 April 2018 |
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on | 26 April 2018 |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | 9 Nov 2018 |
| The following GCP inspection were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product: | |
| – A GCP inspection at two investigator sites located in India and Norway and at the Sponsor site in UK were performed between April to May 2018. The outcome of the inspection carried out was issued on | 19 June 2018 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on | 24 September 2018 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 4 October 2018 |
| The CHMP agreed on the list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on | 18 October 2018 |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 12 November 2018 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on | 28 November 2018 |
| The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on | N/A |
| The CHMP agreed on the second list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on | 13 December 2018 |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 14 January 2019 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the second List of Outstanding Issues to all CHMP members on | 16 January 2019 |

| | |
|---|---|
| SAG experts were convened to address questions raised by the CHMP on<br><br>The CHMP considered the views of the SAG as presented in the minutes of this meeting. | 21 January 2019 |
| The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on | N/A |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Dectova on | 28 February 2019 |

# 2. Scientific discussion

## *2.1. Problem statement*

### 2.1.1. Disease or condition

Influenza is an acute viral infection that spreads easily from person to person in any age group and that can cause serious complications in certain risk groups. In addition to seasonal epidemics, influenza pandemics can occur when a new influenza virus subtype emerges or when an animal influenza virus begins to spread among humans [*Source:* WHO/Europe influenza control and other respiratory pathogens].

### 2.1.2. Epidemiology

According to the European Centre for Disease Prevention and Control (ECDC), seasonal influenza causes illness in 5–10% of the European population each year. Individuals of all age groups are affected, but rates of illness are highest among young children. During most influenza seasons, rates of serious illness and death are highest among children <2 years, individuals >65 years, and individuals at increased risk for complications from influenza due to chronic illnesses. Studies conducted during the 2009 influenza A(H1N1) pandemic indicate that morbidly obese persons (BMI ≥40) and pregnant women are also at greater risk for developing severe influenza disease. In addition, there are certain occupational groups at increased risk of acquiring zoonotic influenza, e.g. poultry and swine industry workers [Expert opinion on neuraminidase inhibitors for the prevention and treatment of influenza – review of recent systematic reviews and meta-analyses. Stockholm: ECDC; 2017].

Severe influenza disease may evolve following seasonal, zoonotic or pandemic influenza, and is often associated with high viral load. An acute influenza infection may be complicated by otitis media, sinusitis, viral and bacterial pneumonia, acute lung injury, myocarditis, pericarditis, septicaemia, encephalitis, and/or death. In addition, influenza disease may trigger worsening of chronic medical conditions present before acquiring the influenza infection, especially underlying cardiopulmonary conditions and diabetes, and increase the risk of complications such as cardiovascular events like myocardial infarction and stroke.

Influenza viruses constantly change through two main mechanisms:

• antigenic drift which is characterised by point mutations leading to minor and gradual antigenic changes in the surface haemagglutinin (HA) and neuraminidase (NA) proteins

• antigenic shift caused by reassortment between human, avian and swine viruses and characterised by major antigenic changes in which a new HA with or without a new NA subtype is introduced into the human population.

These changes, particularly those resulting from antigenic shift, can result in influenza strains that are immunologically distinct from the previously circulating strains, resulting in high infection rates in the immunologically naïve population, and may lead to the emergence of novel geographically localised influenza epidemics or pandemics.

**Table 1. Emergence of novel localised influenza infections/epidemics and pandemics in the 20th and 21st centuries***

| Emergence (year) | Influenza subtype | Estimated global mortality |
|---|---|---|
| 2014 | A(H7N9)avian | >180 persons |
| 2009 | A(H1N1)pdm09 | 123 000–203 000 (in 2009) |
| 2003 | A(H7N7)avian | 1 person |
| 1997 | A(H5N1)avian | >400 persons |
| 1977 | A(H1N1) | unknown |
| 1976 | A(H1N1)swine | 1 person |
| 1968 | A(H3N2) | 1 million |
| 1957 | A(H2N2) | 1.5million |
| 1918 | A(H1N1) | >50million |

* Excluding sporadic cases of zoonotic influenza by H3N2v, H5N8, H9N2, H10N8

*Source:* ECDC- Expert opinion on neuraminidase inhibitors for the prevention and treatment of influenza, 2017

More severe illness and young adult age distribution are consistent features of pandemic influenza, and are linked to more severe lower respiratory tract involvement. Influenza viral pneumonia is more frequent in pandemics compared to seasonal epidemics, and more common in children and young adults compared to older patients, most likely related to lack of specific immunity to the newly circulating pandemic strain in those age groups.

The well-documented morbidity and mortality from the 2009 influenza pandemic, and the emergence of two avian influenza viruses infecting humans in recent years, A/H5N1 (WHO 2008) and A/H7N9, serve to emphasise the continuing threat that influenza poses to public health as a result of emergence of new viral strains infecting populations with limited herd immunity.

Changes in one or more influenza virus virulence determinants such as hemagglutinin (HA),viral RNA polymerase complex (PA, PB1, PB2), nucleoprotein (NP), neuraminidase (NA), and non-structural protein 1 (NS1) by either mutation (antigenic drift) or reassortment (antigenic shift) drive changes in virulence of influenza A viruses. Another important element in influenza virulence is tropism for lower respiratory tract epithelium, with the HA of pandemic strains such as 2009 A/H1N1pdm and emerging avian influenza viruses such as H7N9 and H5N1 showing receptor binding specificity for $\alpha$(2-3) sialylated glycans that are expressed on bronchial epithelium.

Current epidemiology data are available for Europe from the European Centre for Disease Prevention and Control (ECDC). For the 2016/2017 influenza season, of all detected influenza virus, 94% are attributed to influenza A and 6% to influenza B. Of the influenza A virus detections, 98% are attributed to H3N2. Influenza B viruses were mostly of the B/Yamagata lineage. Nine countries reported a total of 7526 laboratory-confirmed hospitalised influenza cases during the 2016–2017 influenza season. Excess mortality was mainly observed in people aged 65 years or older but was also considerable among 40–64-year-olds. There was little antiviral resistance to neuraminidase inhibitors detected (<1%).

The number of people affected varies from year to year among countries, making it hard to predict the annual number of deaths or economic impact. ECDC estimates that on average nearly 40 000 people die prematurely each year from influenza in European Union/European Economic Area (EU/EEA) countries.

### 2.1.3. Biologic features

Influenza virus is a member of the orthomyxovirus family and causes an acute viral disease of the respiratory tract. Influenza is characterised bronchoscopically by diffuse inflammation and oedema of the larynx, trachea, and bronchi; mucosal biopsies show lymphocytic and histiocytic inflammatory infiltrate and desquamation.

### 2.1.4. Clinical presentation

Influenza virus infection can result in either acute uncomplicated illness or complicated/severe illness requiring medical supportive measures as defined by the WHO and other public health authorities.

**Uncomplicated influenza population:** Most patients with influenza virus infection will experience a self-resolving illness which usually presents abruptly with constitutional and respiratory signs and symptoms, including fever, myalgia, headache, malaise, cough, sore throat, and nasal congestion. Typically, symptoms last for 7 to 10 days and improve without significant morbidity.

**Complicated / severe / hospitalised influenza:** As complicated/severe influenza is defined by the need for hospital admission for clinical management, the terms complicated, severe and hospitalised influenza are used interchangeably. Complicated influenza is defined by the need for hospitalisation for clinical management, symptoms and signs of lower respiratory tract infection, central nervous system involvement, severe dehydration, presenting secondary complications or exacerbation of underlying chronic disease. Risk factors include pregnancy, age > 65 years or < 5 years, chronic medical diseases such as diabetes, kidney, liver, neurological, lung and cardiac disease, compromised immune system and morbid obesity.

Severe influenza predominantly involves localisation of virus to the LRT with resultant complications. These complications include viral pneumonia, respiratory failure, ARDS, as well as exacerbation of underlying lung diseases (e.g. asthma, chronic obstructive pulmonary disease) involving the bronchi and small airways. According to the WHO Consultation on Clinical Aspects of Pandemic H1N1 2009 Influenza, pathologic findings at death among hospitalised patients with pandemic H1N1 showed pulmonary histologic findings dominated by diffuse alveolar damage. Bacterial pneumonia, usually caused by *Staphylococcus aureus* (often methicillin resistant), *Streptococcus pneumonia*, *Streptococcus pyogenes* and other bacteria, were diagnosed in 20 to 24% of ICU patients and found in 26 to 38% of patients who died during the 2009/2010 pandemic. Patients with severe immunosuppression were at increased risk for protracted viral replication and pneumonia. Cases of neurologic manifestations, myocarditis, myositis and rhabdomyolysis with some fulminant cases were also reported.

### 2.1.5. Management

There remain very limited options for treatment of influenza, with only two classes of approved antiviral medicines: the adamantanes (amantadine and rimantadine) and the neuraminidase inhibitors (NAIs) (zanamivir, oseltamivir, peramivir, laninamivir). High level of resistance in influenza A strains has changed treatment guidelines and the use of adamantanes is no longer recommended.

The NAIs zanamivir and oseltamivir were introduced in the late 1990s and act by inhibiting viral cleavage of sialic acid from the cell surface glycoconjugates of infected cells, preventing viral spread in the respiratory tract. Neuraminidase inhibitors have antiviral activity against all subtypes of influenza A and influenza B strains. IV peramivir has recently been approved for the treatment of influenza in a small number of countries based on studies of single infusion treatment in outpatients with uncomplicated influenza. A marketing authorisation application (MAA) was submitted in the European Union (EU) for IV peramivir in early 2017. Laninamivir, an inhaled NAI is approved in a limited number of countries.

All EU Member States recommend neuraminidase inhibitors (NAIs), in combination with clinical supportive care, for treatment of severe, complicated or progressive illness, or for patients at high risk of complications, irrespective of vaccination status. NAI use is recommended as treatment or prophylaxis for residents of nursing homes or other long-term care facilities at risk of severe disease. A minority of EU/EEA Member States recommend use as treatment or prophylaxis for outpatients who may have a higher risk of severe outcomes of influenza (young children, elderly or individuals of any age with underlying chronic illnesses).

Many EU/EEA Member States maintain a stockpile of influenza antivirals as capsules or powder for use during influenza pandemics.

According to ECDC, in general, influenza viruses have been susceptible to the two NAIs available for treatment in the EU/EEA over the past ten years. However, during the 2007–2008 influenza season, an oseltamivir-resistant influenza A(H1N1) strain emerged in Europe and was later detected throughout the world. This virus strain remained susceptible to zanamivir. Fortunately, this resistant strain has not circulated worldwide since the 2009 influenza A(H1N1) pandemic virus became dominant. Based on an analysis of 11 387 influenza viruses circulating globally in 2012–2013, the proportion of A(H1N1)pdm09, A(H3N2), B/Victoria-or B/Yamagata-lineage viruses with reduced or highly reduced susceptibility was low (1%, 0.4%, 1% and 0.3%, respectively) to one or more of the NAIs tested (oseltamivir, zanamivir, peramivir and laninamivir). Even in parts of Asia, e.g. Japan, where use of antivirals has been significantly greater than in the EU/EEA Member States, the level of antiviral resistance is low.

There is an unmet need for additional treatments of seasonal, avian and pandemic influenza, especially in critically ill hospitalised patients and risk groups including immunocompromised subjects. Dectova being administered by intravenous infusion may be a valuable supplement to the existing treatments, especially when strains that are resistant to other antivirals are circulating.

## *About the product*

Zanamivir 10 mg/ml solution for infusion (referred throughout as IV Zanamivir) is an aqueous formulation that was developed originally to support the nonclinical safety assessment and Phase 1 clinical studies of RELENZA inhalation powder. In 2005 the US Food and Drug Administration (FDA) approached GlaxoSmithKline (GSK) to initiate a development programme of the aqueous formulation of Zanamivir for treatment of severe influenza in response to the highly pathogenic H5N1 avian threat and concern over oseltamivir resistance. This formulation could be administered by nebulisation or IV administration. While there was interest in both methods of administration, public health agencies were most supportive of the need for an IV formulation. This development programme was fully initiated subsequent to the onset of the 2009 influenza A H1N1 pandemic amid mounting recognition of the compelling public health basis for development of parenteral anti-influenza medications. Furthermore, there was also a need for a NAI with the ability to treat hospitalised patients with influenza viruses resistant to oseltamivir or peramivir following seasonal H1N1 oseltamivir resistance observed from 2007-2009.

In parallel to the clinical development programme, GSK initiated a global Compassionate Use Programme (CUP) in May 2009 at the request of the FDA and public health agencies. In February 2010, the Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on the compassionate use of IV Zanamivir in accordance with Article 83 of regulation (EC) 726/2004. To date over 3,000 patients have been treated in the CUP.

Zanamivir hydrate 10 mg/ml solution for infusion (IV Zanamivir hydrate) is a clear, colourless, single use sterile preparation containing 10 mg/ml Zanamivir hydrate. Tonicity is adjusted with sodium chloride. No buffers or preservatives are included in the formulation.

Zanamivir hydrate does not undergo biotransformation and is eliminated as unchanged drug by renal excretion. The recommended dose of IV zanamivir for adults (age ≥ 18 years) with normal renal function (creatinine clearance greater or equal to 80 ml/min) is 600 mg given twice daily. Adolescents, children and infants with normal renal function should receive a weight-based dose. The recommended initial treatment course is for 5 days. Physicians should consider extending the initial 5-day treatment course for up to 5 additional days if ongoing viral shedding is detected or if clinical symptoms warrant further treatment.

At time of submission of the Marketing Authorisation Application, the proposed indication was treatment of influenza A or B virus infection in hospitalised adult and paediatric patients (≥6 months); when circulating influenza virus is resistant to other approved anti-influenza medications, or resistance develops while on anti-influenza treatment, and/or who cannot take anti-influenza medications via other routes of administration.

### *Type of Application and aspects on development*

The applicant requested consideration of its application for a Marketing Authorisation under exceptional circumstances in accordance with Article 14(8) of the above mentioned Regulation for a proposed restricted indication based on the following:

- Influenza virus that is resistant to other approved anti-influenza medications occurs so rarely that it is not feasible to conduct clinical studies in this patient population
- Currently, there is a significant gap in the scientific knowledge of a commercially available test for real-time identification of influenza resistance
- It is not feasible to conduct controlled clinical studies in a patient population who can only be administered anti-influenza medication via the IV route as there are no anti-influenza IV medications approved for hospitalised patients in the European Union
- Unethical to conduct a placebo-controlled study in this extremely sick patient population

The applicant was of the opinion that by restricting the indicated patient population to a population that is not currently served by available anti-influenza therapies, the marketing authorisation application falls within the scope of the exceptional circumstances legislation.

## *2.2. Quality aspects*

### 2.2.1. Introduction

The finished product is presented as clear, colourless, sterile solution for infusion containing 10 mg/ml of zanamivir (as hydrate) in a single use vial without preservative. Each vial contains 200 mg of zanamivir (as hydrate) in 20 ml solution for infusion.

Other ingredients are: sodium chloride and water for injections (WFI).

The product is available in 26 ml clear vial (type I glass) with a stopper (coated chlorobutyl rubber), an over-seal (aluminium) and a plastic flip-off cap.

## 2.2.2. Active Substance

### *General information*

Full documentation for the active substance has been provided. The active substance has a monograph in the Ph. Eur.

The active substance is the same as the substance previously approved for applicant's product Relenza inhalation powderexcept that in the present application the substance is not micronised, the limit for any other impurities has been tightened and a limit for endotoxins has been added to the present active substance specification, and the retest period has been increased. The removal of the micronisation step is considered acceptable given the use of dissolved active substance in Dectova. Relenza was first approved nationally in Sweden 1999 and has subsequently been approved in most EEA countries (except from CY and LI) through mutual recognition procedure SE/H/0180.

The active substance is zanamivir hydrate. Zanamivir is the INN of the anhydrous substance which according to Ph. Eur. has the chemical name (2*R*,3*R*,4*S*)-3-(acetylamino)-4-carbamimidoylamino-2-[(1*R*,2*R*)-1,2,3-trihydroxypropyl]-3,4-dihydro-2*H*-pyran-6-carboxylic acid. The hydrate has the molecular formula $C_{12}H_{20}N_4O_7$, x $H_20$ and the structure shown below:

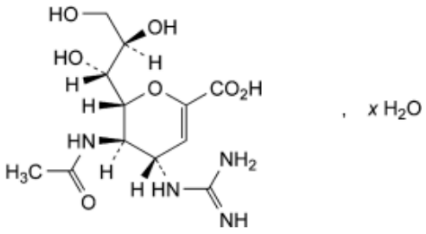



**Figure 1: active substance structure**

The molecular mass for the anhydrous substance is 332.3. It is a chiral substance with five stereogenic carbons which arise from the proposed starting material. Stereoisomerism is controlled by specific optical rotation in the starting material and the active substance. Absolute configuration of the stereochemical centres is indicated in the chemical name.

The chemical structure of zanamivir hydrate was confirmed by elemental analysis, IR spectroscopy, UV spectroscopy, $^{1}H$ and $^{13}C$ NMR spectroscopy, mass spectrometry, and single crystal X-ray diffraction.

The active substance is a white to off-white hygroscopic powder. At room temperature aqueous solubility is approximately 16 mg/ml and solubility in saline (intravenous formulation) approximately 18 mg/ml. Aqueous solubility increases somewhat towards lower and higher pH values. It is amphoteric and is partially ionised over the whole pH range. The measured $pK_a$ for the acid group is 2.4 and for the guanidine moiety 12.9. Zanamivir reversibly adsorbs water.

Two hydrate forms of the active substance have been identified; a non-stoichiometric hydrate (hydrate 1) and a stoichiometric hydrate (hydrate 2). Hydrate 1 is the solid state form consistently produced by the proposed synthetic route and is the selected form for the manufacture of Dectova.

### *Manufacture, characterisation and process controls*

The active substance is manufactured using a 5 chemical synthesis steps. The QP declarations provided for the active substance manufacturers are acceptable.

The manufacturing process may be performed by two routes, C and D. These are the same as those registered for zanamivir in Relenza inhalation powder. Route D was developed to avoid the use of azide chemistry.

Both routes consist of 5 chemical transformations with isolated intermediates using commercially available raw materials with acceptable specifications, followed by hydrate conversion in the last step. Purified water used in the final steps complies with note for guidance on quality of water for pharmaceutical use.

No rework for the intermediates has been established.

Critical operations have been identified Investigation of critical process parameters ranges have been described. In-process control tests are specified. Specifications are provided for all intermediates.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin. Control of impurities in specifications for starting material, reagents and intermediates was also discussed. Routes C and D have been assessed for mutagenic impurities in accordance with ICH M7. A summary of the mutagenic impurities associated with routes C and D and their control strategies has been provided.

Three mutagenic impurities which are not included in the Ph. Eur. monograph have been identified. These are controlled in active substance intermediates and the limits applied have been justified by purge studies. EP impurity F is controlled at active substance level.

The finished product is administered as a maximum daily dose of 1.2 g and has a dosing regimen of less than 1 month. Therefore, the TTC for individual mutagenic impurities is 120 mcg/day, which corresponds to a TTC-based acceptable limit of 100 mcg/g for any individual mutagenic impurity.

The control strategies and data presented from spiking and purging studies conclude that there is negligible risk of mutagenic impurities in the active substance exceeding the TTC-based acceptable limit and demonstrates that the levels of mutagenic impurities potentially present in zanamivir active substance are well controlled. Furthermore it has been confirmed that active substance from routes C and D will not be mixed and therefore not all the impurities will be present simultaneously in any single batch of the finished product at a given time.

With regards to the manufacturing process development, as indicated above, the active substance was approved for the product Relenza through the mutual recognition procedure SE/H/0180. The active substance for Dectova is manufactured by the same routes although the final micronisation step is not performed. Description of development studies including information on change in manufacturing sites, manufacturing scale and manufacturing process approved for the product Relenza through variations have been presented.

The materials of the container closure system of the active substance comply with EU Commission Regulation No. 10/2011 for food contact use and Ph. Eur. 3.1.3.

## *Specification*

The active substance specification is in accordance with the Ph. Eur. monograph with some additional tests. The specification is based on the active substance critical quality attributes (CQA). The specification includes tests for identity (Ph. Eur.), specific optical rotation (Ph. Eur.), related substances (HPLC), loss on drying (Ph. Eur.), sulfated ash (Ph. Eur.), assay (HPLC, Ph. Eur.), acetate content (GC), water content (KF) and bacterial endotoxins (Ph. Eur.).

Residual solvents are limited in the specification in line with ICH Q3C.

The absence of specific tests for heavy metals in the specification for zanamivir active substance has been discussed and justified.

The analytical methods used have been adequately described. In-house analytical methods for residual solvents by GC, related substances by HPLC and water content by Karl Fisher have been described and validated in accordance with ICH guidelines. Comparable batch results, obtained by the Ph. Eur. zanamivir hydrate method and the in-house method for related substances, for three batches have been presented.

Working standards are used for quantification which have been compared to the Ph. CRS standards.

Complying batch data has been provided for both active substance manufactured by route Cand active substance manufactured by route D . The results are within the specifications and consistent from batch to batch.

### *Stability*

Stability data from commercial scale batches of active substance from the proposed manufacturers stored in a container closure system representative of that proposed for use in routine bulk storage and transport for up to 108 months (3 batches from route C) and 36 months (3 batches from route D) under long term conditions (30 ºC / 65% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) (3 batches from each route) according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on one batch.

The following parameters were tested: description, assay, impurities and water. The analytical methods used were the same as for release and were stability indicating. No significant changes were observed for any of the tested parameters under long term, accelerated and photo stability studies.

Forced degradation studies to verify the suitability of the HPLC method for zanamivir content and related impurities have been performed. The conditions used were heating in aqueous solution, heating in acid, heating in base and exposure to light. No evidence of interference of impurity peaks with the active substance peak was observed.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 108 months when stored up to 30 °C in the proposed container.

## 2.2.3. Finished Medicinal Product

### *Description of the product and pharmaceutical development*

The proposed commercial product is a clear, colourless single use solution for infusion preparation containing zanamivir (as hydrate) 10 mg/ml. Each single-use vial contains 20 ml of solution, containing 200 mg zanamivir. The product may be diluted prior to infusion.

The excipients are sodium chloride for tonicity adjustment and water for injections. Both excipients are of Ph. Eur. quality. The formulation is not buffered or preserved. All excipients are well known pharmaceutical ingredients. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The vials are clear Ph.Eur. type 1 glass with a coated chlorobutyl type I rubber stopper, aluminium overseal and flip-off cap.

A science and risk based approach, applying Quality by Design (QbD) and quality risk management according to ICH Q8, Q9 and Q10, was used for the development of the finished product. A Quality Target Product Profile (QTPP) was developed to define the desired quality characteristics of the finished product, i.e. a 10 mg/ml intravenous solution for infusion, containing a total of 200 mg of zanamivir, supporting dose titration for paediatric patients or those with renal impairment. The QTPP further defined the product as being suitable for direct infusion or for dilution in normal saline for IV infusion. The product was to comprise materials with the required functional characteristics and to meet pharmacopoeial and other relevant quality standards, including sterility, over the proposed shelf-life. The container closure was to provide adequate protection to the product and allow for terminal sterilisation. The proposed shelf-life was to take into account the seasonal use of the product.

The finished product CQAs were identified and formed the basis of the specification. They included: description, identity, content, drug related impurities, sterility, bacterial endotoxins, particulate contamination, pH, osmolality and extractable volume. An understanding of the impact of the attributes of the active substance, excipients, container closure system and in process materials, and parameters of the manufacturing process on the quality of the finished product was established.

As indicated in the active substance section, the active substance zanamivir hydrate is a slightly hygroscopic powder, which is slightly soluble in water. Its solubility in saline at room temperature is approximately 18 mg/ml. The pH and osmolality of the solution are both within physiologically acceptable ranges and make the formulation suitable for its intended route of administration.

Further investigation of pH solution stability showed that there was no trend in pH, active substance content or related impurities across the range of storage conditions, supporting the development of a non-buffered solution of zanamivir hydrate in the proposed sodium chloride concentration across the investigated concentration range. The impact of varying levels of sodium chloride and drug content on osmolality was investigated. This, together withthe manufacturing process and to minimise risk of *in-vivo* precipitation, a solution concentration of 10 mg/ml that is not close to the active substance solubility limit was selected for the product.

Whilst the active substance is a hydrate able to absorb/desorb water as environmental humidity changes, experimental work demonstrated that there is minimal risk to the CQA of drug content during dispensing in normal environmental operational conditions.

Compatibility of the active substance with the excipients was confirmed by the stability studies performed during development and on the primary stability batches. These studies demonstrated the acceptable chemical and physical stability of the finished product

The manufacturing process was developed in parallel with the formulation studies. The manufacturing process and control strategy for the product were defined based on risk assessment, applicant's manufacturing experience and knowledge gained during product development.

The manufacturing process is simple involving preparation of a bulk solution of zanamivir dissolved in water for injections with sodium chloride in order to ensure the correct osmolality. The bulk solution after double filtration is filled into sterilised vials. The filled vials are then autoclaved (Ph. Eur. conditions).

Thermal stability of Zanamivir hydrate solution was investigated and it concluded that the solution is physical and chemically stable when exposed to/stored at elevated temperatures. In addition, terminal sterilisation in an autoclave under conditions exceeding those specified in the Ph. Eur had no negative impact on physical and chemical stability.

Compatibility of the formulation with the filters was demonstrated.

The formulation of the product intended for marketing is the same as the formulation used in Phase II and phase III clinical trials.

The control strategy for the different steps of the manufacturing process (e.g. bulk solution preparation, filling, terminal sterilization, primary packaging) have been described.

The suitability of the glass vial was assessed Glass delamination was also investigated. No delamination particulates were observed in solution after  greater than 60 months ofstorag at the conditions tested. Moreover, levels of glass extracts in solution were lowor not detected, supporting a lack of container-formulation interaction.The rubber stoppers comply with Ph. Eur. 3.2.9 type I closures. Rubber closures for containers for aqueous parenteral preparations, for powders and for freeze-dried powders and USP<87> Biological Reactivity Tests. Suitability of the selected stopper was demonstrated during product development underboth long term and accelerated storage conditions. Compliance with Ph.Eur. 3.2.9 for fragmentation and penetrability was evaluated for both “as manufactured” and “aged” stoppers. Compatibility of the rubber stoppers was further verified through extractable and leachable testing.

Risk assessments and experimental studies were used to establish the risk of patient exposure to leachables. Extractable studies were conducted to determine the risk associated with the stopper material. Vials from severalbatches of finished product were stored inverted -to maximise contact with the stopper- for up to 60 months at 30°C/75% RH (the long term storage condition) and for up to 12 months at 40°C/75% RH. The results demonstrate that the volatile, semi-volatile and non-volatile leachables are at or below the reporting thresholddefined following the recommendations in ICH M7 for exposure periods less than or equal to one month. No leachables were detected at a level that would represent a risk to patients dosed with the product. Therefore, it is concluded that leachables present a negligible risk to patient safety.

Input material used for the manufacture of the product (excipients and bulk drug substance) have microbial controls where applicable (i.e. for the WFI) and endotoxin controls (for the active substance, sodium chloride and WFI) in place. Bioburden of the bulk solution is determined before sterile filtration into vials, followed by terminal sterilisation. Microbial control of the formulation occurs at various stages of the process and is monitored throughout the shelf-life of the product. The finished product is a single use product and does not contain any antimicrobial preservatives. Product sterility is assured by controls on the excipients, active substance, primary packaging components, equipment and the processing environment, by product terminal sterilisation and through online and finished product testing. Stability studies include sterility testing to ensure integrity over the shelf life of the product. Microbial immersion has been used to demonstrate integrity of the container closure system after filling and terminal sterilisation. As shown in the next section, the finished product specification includes tests for bacterial endotoxins and sterility (Ph. Eur. 2.6.1).

Container closure integrity testing was used to demonstrate that the container closure system (glass vial/stopper/overseal) is robust through the processes used to combine the individual components. A microbiological challenge study was performed to demonstrate the integrity of the seal between the vial/stopper/overseal following subjection to autoclaving using the routine sterilisation cycle. At the end of the incubation period all challenged vials remained clear with no contamination, thus demonstrating maintenance of the sterility of the vial contents and integrity of the vial/stopper/overseal interface.

The product may be administered by intravenous infusion as supplied i.e. at 10 mg/ml or diluted, to no less than 0.2 mg/ml, in 0.9% w/v sodium chloride. The compatibility of the formulation with intravenous solutions and medications other than 0.9 % w/v sodium chloride is not known.

## *Manufacture of the product and process controls*

The manufacturing process has been developed to reproducibly deliver the finished product critical quality attributes of description, identity, content, drug-related impurities, sterility, bacterial endotoxins, particulate contamination, pH, osmolality and extractable volume.

The manufacturing process consists of five main steps: primary pack preparation, bulk solution preparation, filtering and filling, terminal sterilisation and inspection.

Holding times are proposed at different stages of manufacture. The proposed holding times have been justified on the basis that the active substance and finished product are chemically stable. Microbial validation results further support the proposed holding times.

All critical process parameters (CPPs) together with in-process materials CQAs and in-process controls (IPC) have been identified. Process parameters and IPC are adequately set to control the process leading to consistent quality.

No design space or proven acceptable Ranges (PAR) are proposed for the commercial product. The manufacturing process is based on target values and set points for process parameters supported by batch data from the commercial site of manufacture.

The process is considered to be a standard manufacturing process. Major steps of the manufacturing process have been validated by a number of studies. Process validation was performed on three consecutive production scale batches which were manufactured at the commercial site at production scale, using the manufacturing process and controls as defined in in the dossier. The applicant proposed an additional validation exercise to complete an aspect related to inspection of the sterilised vials which will be completed prior to commercial supply of the drug product in accordance with the process validation scheme presented. This is acceptable.

Overall, it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

## *Product specification*

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: description (visual), identification (HPLC, UV), assay (HPLC), related substances (HPLC), extractable volume (Ph. Eur.), particulate contamination (Ph. Eur.), pH (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.).

The test for related substances has been omitted from the release specification. This is acceptable since all synthetic process impurities, which are not degradation products are controlled in the active substance specification in accordance with ICH Q6A, and the impurity profile of the finished product is that of the active substance, no degradation products are formed during the commercial manufacturing process.

Osmolality is not tested on the finished product. This is considered acceptable based on the development work. The control strategy for osmolality for Dectova includes several elements and has been adequately justified. A risk assessment for elemental impurities was carried out in line with ICH Q3D, which concluded that no tests for elemental impurities were required.

The omission of a test for elemental impurities has also been justified. A risk assessment was conducted in accordance with option 2b of the ICH guideline Q3D guideline for elemental impurities to evaluate the potential for elemental impurities to be present in zanamivir hydrate. The risk assessment included the Class 1 elemental impurities (cadmium, lead, arsenic and mercury), the Class 2A elemental impurities (cobalt, vanadium and nickel), an intentionally added Class 2B elemental impurity from the active substance , the Class 3 elemental impurities recommended for consideration for a parenteral formulation (lithium, antimony, and copper), and intentionally added Class 3 elemental impurity from the container closure system. The risk assessment considered the contribution from the drug substance, manufacturing equipment, excipients and the container closure system. No elemental impurities were identified as having the potential to be present at a level of greater than 30% of the Permitted Daily Exposure (PDE) limit for parenteral administration, using Option 2b defined in ICH Q3D. The risk assessment for Dectova

is appropriate to control elemental impurities in the product to within safe levels below 30 % of the proposed ICH Q3D PDE.

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

Adequate information has been provided for reference standards and materials. Batch analysis data has been presented for batches of the proposed batch size and the results show consistency. The container closure system complies with relevant pharmacopoeia criteria.

Batch analysis results are provided for 6 production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

## *Stability of the product*

Stability data from three commercial scale batches of finished product manufactured with active substance made by route C stored for up to 60 months under 5 °C/Ambient and long term conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Supportive stability data on finished product batches manufactured by route D (48 months under long term and 6 months under accelerated conditions) were also submitted. The batches of Dectova are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing, a 26 ml Type I clear glass vial and sealed with a coated chlorobutyl stopper and secured with an aluminium overseal with a removable plastic flip-off cap. These batches were stored in the upright orientation and one of these batches was also stored in the inverted orientation.

The long term storage condition of 30°C/75% RH was used. No significant changes were observed in description, zanamivir content, drug-related impurities content, particulate contamination, pH and sterility in any of the conditions tested. All results complied with the proposed commercial specification. The results demonstrate the chemical and physical stability of the product at all storage conditions.

In addition, stability stress testing was performed under the following testing conditions: 50°C/ambient (1 and 3 months) upright (2 batches), freeze/thaw cycle (-20°C/30°C) upright (2 batches) and photostability (1 batch). The results demonstrate the chemical and physical stability of Dectova at all storage conditions. No significant changes were observed in description, zanamivir content, drug-related impurities content, particulate contamination and pH. All results complied with the proposed commercial specification.

Forced degradation studies for Dectova exposing the product to high temperature and UV-Vis light exposure were conducted to identify the main degradation products formed. Zanamivir hydrate in Dectova was stable under both conditions, None of the degradation products reported were observed to form above the identification threshold (>0.2%) specified in ICH Q3B in the primary stability studies. Mass balance was achieved for all stressed samples. The results demonstrate the stability indicating nature of the proposed HPLC method for zanamivir content and drug-related impurities.

In-use stability of zanamivir hydrate solution for infusion following dilution in a representative infusion bag of 0.9% w/v sodium chloride, at concentrations of 0.2 mg/ml and 10 mg/ml was also evaluated. These concentrations correspond to the lowest and highest doses expected to be administered. Samples were analysed after storage in a representative infusion bag under refrigeration (2ºC to 8ºC) and at room temperature 6 days. No significant changes were observed inthe tests performed.The results demonstrate the chemical stability of Dectova when stored for up to 6 days at 2ºC to 8ºC and room temperature.

Based on available stability data, the proposed shelf-life of 5 years without restrictions for storage conditions as stated in the SmPC (section 6.3) is acceptable.

Chemical in use stability has been demonstrated for 24 hours at 2ºC to 8ºC and room temperature. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 ºC, unless dilution has taken place in controlled and validated aseptic conditions.

### *Adventitious agents*

No excipients derived from animal or human origin have been used.

## 2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The active substance, zanamivir hydrate, is a known active substance with a Ph. Eur. monograph which has already been approved for the product Relenza inhalation powder from the same applicant. The information presented in this submission has been declared to be essentially the same as that registered for Relenza. Minor differences have been highlighted and are considered acceptable.

The formulation is a simple solution containing the active substance (200mg zanamivir in 20ml/vial, giving a final concentration of 10mg/ml), a tonicity adjusting agent and a solvent. The product is a single use parenteral preparation for intravenous delivery sterilised by terminal sterilisation (autoclaving). The manufacturing process is simple involving preparation of a bulk solution of zanamivir dissolved in water for injections with sodium chloride in order to ensure the correct osmolality. The bulk solution after double filtration is filled into sterilised vials. The filled vials are then autoclaved (Ph Eur conditions).

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

## 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

## 2.2.6. Recommendations for future quality development

None

## *2.3. Non-clinical aspects*

## 2.3.1. Introduction

Zanamivir was evaluated in a series of *in vitro* and *in vivo* studies to characterise the virology of zanamivir and to determine its activity against influenza virus A and B virus replication, with respect to treatment and prophylaxis of influenza. Nonclinical virology studies were performed 20 years ago to support the inhaled zanamivir program to investigate the primary pharmacodynamic actions with respect to the treatment and prophylaxis of influenza. These studies determined the receptor specificity of zanamivir *in*

*vitro* and its effects on isolated influenza A and B viruses. The effects of zanamivir were investigated *in vivo* using the ferret, as influenza infection of the respiratory tract results in symptoms that resemble closely the disease in humans. Studies that are more recent were carried out to investigate the antiviral activity of IV Zanamivir. The plasma elimination half-life of zanamivir in ferrets and mice is 40 and 11 minutes, respectively, and is therefore too short to study IV Zanamivir (Stittelaar, 2008). The antiviral activity of IV Zanamivir was therefore studied in cynomolgus monkeys. No specific secondary pharmacodynamic studies have been conducted.

It is noted that in the CHMP Scientific Advice issued on 24 June 2010 (EMEA/H/SA/1586/1/2010/III) a question relating to the Toxico-Pharmacological development was raised by the applicant. It was asked if the supplied package of non-clinical studies was sufficient to support the full clinical development of IV zanamivir. CHMP's answer stated that the package was sufficient, although a definitive decision on the adequacy of the data would only be made on full assessment of the final non-clinical dossier. It also stated that the following additional points might be taken into consideration:

*"Regarding safety pharmacology studies, consideration should be given to the low number of animals which have been used to identify undesirable pharmacodynamic properties of zanamivir that may be relevant for human safety. Therefore, this may be sufficient for the assessment of safety pharmacology of IV zanamivir as long as the important functional endpoints as overt central and peripheral effects, cardiovascular and respiratory effects and pharmacodynamic drug interactions will have been assessed in repeated-dose toxicity studies following IV administration. This issue is considered important to be clarified in the dossier."*

The important functional endpoints outlined in the CHMP advice have not been assessed in repeat dose toxicity studies. The applicant´s justification that the absence of overtly adverse findings in both safety pharmacology and repeat-dose toxicology studies, together with an absence of findings in clinical use gives reassurance of the safety of zanamivir in clinical usage, is acceptable.

## 2.3.2. Pharmacology

### *Primary pharmacodynamic studies*

#### *In vitro*

Inhibition of influenza virus neuraminidase (NA) was examined in several studies with $IC_{50}$ values varying from 0.64 nM and 7.9 nM against the NAs of a range of laboratory adapted and clinical isolates of influenza A and influenza B viruses. It was shown activity against influenza A/H1N1pdm09 viruses, with and without the H275Y substitution, the most common oseltamivir NA substitution (IC50, 0.29 and 0.37 nM respectively).

Zanamivir did inhibit influenza virus NAs derived from nonhuman mammals and birds (N1 to N9) with IC50 values between 2.2 and 30.1 nM. Different clades of influenza A/H5N1 viruses are sensitive to zanamivir with $IC_{50}$ values in the range of 1.21 to 1.96 nM as are A/H5N1 viruses containing the H275Y substitution (the most common substitution giving resistance to Oseltamivir) ($IC_{50}$ 2.4-2.5 nM).

Zanamivir is also active against the H7N9 avian influenza virus ($IC_{50}$ 0.74 nM) that has infected humans since 2013 (Zhang, 2014). Oseltamivir and peramivir treatment in patients infected with H7N9 readily selects a variant with the NA R292K substitution that is resistant to oseltamivir ($IC_{50}$ >1000 nM) and has reduced susceptibility to peramivir ($IC_{50}$ 96.5 nM) and zanamivir ($IC_{50}$ 12.4 nM).

In mammalian cells *in vitro*, it was shown activity against a range of laboratory adapted and clinical isolates of influenza A and influenza B viruses. This included all 9 avian NA subtypes. $IC_{50}$ range was 0.005 to 16 µM; mean 1.5 µM.

Zanamivir did not have any antiviral activity against herpes simplex virus, varicella zoster virus, cytomegalovirus, human rhinovirus and human parainfluenza virus *in vitro*, or activity against Plasmodium falciparum, at all concentrations tested up to the maximum of 1000 µM.

Activity against human immunodeficiency virus (HIV) in inhibition of HIV-1 syncytia formation and inhibition of p24 antigen synthesis assays with $IC_{50}$ = 15 to 22 µM) was 10 to 10,000-fold less than that seen with influenza A and B viruses. It was 100 to 200 times less than the antiviral activity of azidothymidine against HIV-1. Zanamivir activity is not impaired by substances that are frequently used to treat influenza symptoms, for example ibuprofen, oxymetazoline and co-amoxiclav.

Zanamivir had low cytotoxicity compared to comparators (e.g. ribavirin) and $CCIC_{50}$ values were > 1mM for each of the 4 cell lines that were tested MRC-5, PANC-1, 161-BR and MDCK. No uptake into MOCK cells in vitro was found, indicating that the antiviral activity of zanamivir was extracellular.

***In vivo***

Zanamivir was shown to be effective when administered either therapeutically or prophylactically in both the mouse and ferret models of influenza.

Zanamivir did not protect chickens (administrated intratracheally) against systemic infection with highly pathogenic avian influenza viruses introduced into the trachea. This is because the drug acts locally in the respiratory tract and has limited effect against a systemic infection.

In a macaque challenge study, it was demonstrated that at doses of 10 and 20 mg/kg, there were reductions in viral load in monkeys (> 10 times in 50 % of the animals). The sample sizes were small and there was considerable variability of viral load and gross pathology within groups.

**Drug resistance**

Resistance to zanamivir has been investigated *in vitro*, *in vivo*, and in humans following treatment and in surveillance studies in viruses isolated from untreated humans. Some resistance in the presence of zanamivir have been identified *in vitro* and *in vivo* (ferrets) but the clinical importance of the resistant genotypes is not established. More details on drug resistance are presented in the clinical part of the assessment report.

## *Secondary pharmacodynamic studies*

Specific secondary pharmacodynamic studies have not been conducted with zanamivir. Zanamivir was a weak inhibitor of human lysosomal NA and NA from other organisms. Zanamivir was shown to be a weak inhibitor of the human lysosomal sialidase with $IC_{50}$ values in the range 0.93-1.0 mM (Report 92/083). It was shown that zanamivir inhibits the sialidase of influenza A and B viruses more than that of parainfluenza virus, three bacteria and sheep liver.

## *Safety pharmacology programme*

Safety pharmacology studies have been performed in rats, dogs and cats to evaluate the potential effects of zanamivir on the central and peripheral nervous systems, cardiovascular and respiratory systems as well as potential adverse pharmacodynamic effects in the mouse. Increased arterial blood pressure at IV doses of 10 and 30 mg/kg was observed in cats, but was not reproduced in dogs or in clinical data and the clinical relevance is likely to be low.

No *in vitro* study was performed to evaluate the cardiovascular system. The lack of *in vitro* studies can be accepted based on the *in vivo* study results and human ECG data are available from two studies, including a QT study and no effect of zanamivir was observed when given IV up to 1200 mg.

Cardiovascular function was examined in cats, dogs, and no effect on blood pressure, heart rate, ECG or PT or QT intervals were discovered in dogs that were given zanamivir as single IV doses up to 30 mg/kg or by IV infusion at 90 mg/kg/day. In a five week study with dogs given zanamivir IV there were no treatment effects related to the cardiovascular system

### *Pharmacodynamic drug interactions*

In a study in mice effects on pentobarbitone-induced loss of righting reflex (sleep time), it was observed an increase in sleeping time at 100 mg/kg administration of zanamivir.

## 2.3.3. Pharmacokinetics

#### Method of analysis

The methods and limits of quantification were adequate with regard to specificity and sensitivity to support the kinetic analyses of zanamivir.

#### Absorption

Absorption from the lungs after inhalation (IH) administration to mouse, rat and dog had a $T_{max}$ value in general up to 1.5 hours after the end of the IH period or sooner. Poor absorption was seen after oral administration based on low oral bioavailability in rats and dogs, probably due to low permeability.

Following IV administration, zanamivir was rapidly cleared from the plasma with half-lives ranging from 0.26 hours (rats) to 2.7 hours (monkeys). Renal clearance seen in rats and dogs were 7.8 and 2.8 mL/min/kg respectively and was 90 % of the plasma clearance. This is expected since zanamivir is primarily excreted via urine. In general, high clearance and low volume of distribution was observed.

Repeat IV studies in rats (non-pregnant and pregnant) and dogs for up to 5 weeks, showed a dose-proportional increase in exposure to Zanamivir. No notable gender difference in exposure was observed in rats or dogs. Systemic exposure was observed in female rabbits after IV administration of zanamivir.

Zanamivir was administrated by IH in rats up to 26 weeks of duration and up to 52 weeks in dogs, with no noteworthy change of parameters by repeated administration. A dose proportional increase in exposure was observed, with little difference between the sexes. The same pattern was observed after IH dosing of zanamivir in the carcinogenicity studies in mice and rats (104 weeks) with no difference in exposure between males and females or due to repeated administration and systemic exposure increasing with increasing dose. Similar systemic exposure to zanamivir was demonstrated in pregnant and non-pregnant rabbits. Systemic exposure was demonstrated following subcutaneous (SC) administration of zanamivir.

#### Distribution

***In vitro***

It was observed that zanamivir was bound to plasma proteins and to erythrocytes from rats and dogs and rats to a low degree, less than 10 % (quite similar to the situation in man). Drug interactions due to protein displacement are therefore not likely to occur in humans. It was shown that zanamivir is not a substrate for human P-gp, and that it has a low passive permeability (measured in MDCKII-MDR1 cells in the presence of 2 µM GF120918A (a potent inhibitor of P-gp).

It was also shown that zanamivir did not inhibit renal transporter-mediated uptake, since less than 50 % inhibition of uptake was measured via all tested transporters (hOAT1, hOAT2, hOAT3, hOAT4, hOCT1, hOCT2, hOCT2-A, hOCT3 and hURAT1).

***In vivo***

In a study in rats, zanamivir was given IV and it was shown distribution, but not to CNS. It was shown that with the exception of bladder, kidney, and lung, the tissue concentrations were generally below those present in blood. The highest concentrations were seen in the bladder and kidney, with zanamivir rapidly clearing from most tissues, consistent with urine being the most important way of excretion.

Zanamivir had a low volume of distribution in rats, dogs and monkeys with values from 0.2 to 0.3 L/kg, less than the intercellular fluid volume, indicating limited distribution into tissues. Low levels were still present 168 h post-dosing in the gastrointestinal tract and in the eyes of pigmented rats. However, no increased binding of drug-related material was found in any other melanin containing tissues.

Low levels of zanamivir were found to cross the placenta (0.04% and 0.02% of the administered dose reaching the foetus 0.5 hours post dose on Days 12 and 19 in rats) following IV administration to rats and rabbits of 10 mg/kg. In lactating rats, the drug concentration was higher in the milk than in the plasma, indicating some exposure of drug-related material in the milk to suckling pups. Zanamivir was detected in bronchoalveolar lavage fluid (BAL) with a BAL/plasma ratio of up to 0.161 at 1 hour following dosing in a single IV study in rats given 10 mg/kg. In male cynomolgus monkeys, it was confirmed that zanamivir distributed into the pulmonary compartment at concentrations greater than the $IC_{50}$ for H5N1 throughout the 12-hour dosing interval.

**Metabolism**

There was no metabolism observed in vitro after incubation with rat lung microsomes or rat lung supernatant preparations. Zanamivir was not metabolised in rats, dogs, pregnant rats or pregnant rabbits after IV administration of 10 mg/kg $^{14}$C-Zanamivir.

**Excretion**

Excretion of zanamivir was investigated in rats, pregnant rabbits and dogs. Almost all of the radiolabelled zanamivir was excreted in urine, mostly in the first 24 hours. 91-100 % was excreted in urine in rats and between 80-95 % was excreted in urine in dogs. Faecal excretion was low and was less than 3% in male rats and 0.2-0.8 % in male dogs. Excretion was also primarily in urine in female rats (84.1 % of administered dose), pregnant rats (95 % of the administered dose) and pregnant rabbits (64 % following a single IV dose of 10 mg/kg with total recovery of 83 %).

**Drug interactions**

Zanamivir is not metabolised and there is low risk of drug interactions due to inhibition or induction of drug metabolising enzymes by co-administered drugs. In an *in vitro* study, no changes to the uptake of glucose, urate or Gly-Sar were observed following incubation with zanamivir indicating no interactions of zanamivir in the reabsorption process in renal tubules.

## 2.3.4. Toxicology

### *Single dose toxicity*

Single dose acute toxicity studies were performed in the mouse or rat by the intravenous and oral routes of administration, and additionally in the rat by inhalation. Studies showed a low potential for acute toxicity of zanamivir by the intravenous, inhalation or oral route. Doses used were limited by the solubility in sodium chloride. Target organ toxicity was not seen following IV administration of zanamivir of 90 mg/kg to mice, rats or following oral doses in mice or rats. In a study with mice following intravenous administration of 90 mg/kg zanamivir, one mouse was killed for humane reasons due to low posture and loss of co-ordination, indicating CNS effects.

## *Repeat dose toxicity*

Repeat dose toxicity studies were performed in rats and dogs using IV, IH and or intranasal (IN) route of administration.

IV studies were performed in rats and dogs up to 5 weeks duration. In rats, the continuous (24-hour) IV infusion of Zanamivir for 48 hours at a dose level of 13824 mg/kg/day produced renal damage in one rat. The continuous IV infusion in rats of zanamivir at dose concentration up to 6912 mg/kg/day for 14 consecutive days was associated with vacuolar degeneration in the kidneys and increased prominence of the sinusoidal macrophages in the lymph nodes. In another 14 –days IV infusion study in rats, reduced body weight gain was observed in females at 1728 mg/kg/day and a dose-related (reversible) vacuolation of the proximal convoluted tubules in the renal cortex in males and females at 864 and 1728 mg/kg/day, which was considered to represent hydropic change in the cortical tubule cells. No toxic treatment related effects were seen in the 5-week IV administration study in rats.

In a 5-week inhalation study in rats, reduced neutrophil counts were observed in males and a temporary disturbance of urinary output and urinary electrolyte concentration was observed in female rats.

In rats and dogs, the AUC data from IV pivotal studies resulted in margins of 0.75 to 16 for zanamivir (observed at NOAEL).

## *Genotoxicity*

Overall, zanamivir was not considered genotoxic when tested in a battery of *in vitro* an *in vivo* tests.

## *Carcinogenicity*

Carcinogenic studies were only performed in mice and rats by inhalation route and revealed no tumorigenic findings related to long-term inhalation carcinogenicity studies.

## *Reproduction Toxicity*

Zanamivir did not affect fertility or reproductive performance in male or female rats and rabbits. Some behavioural effects were observed in F1 generation males in a fertility study with IV doses of zanamivir up to, 90 mg/kg/day. Physical and functional developmental effects consisting of a reduction of mean performance times in the rotarod test, a slight reduction in forelimb grip strength and a slight reduction in the level of arousal were reported in males derived from the group given 90 mg/kg/day in the fertility study. A possible effect was apparent also at 9 mg/kg/day.

Following administration of 80 mg/kg TID SC in rats, there were slightly higher incidences of some minor alterations and variants that indicated a delay in development.

In an organogenesis study in rabbits, the incidence of malformations (post implantation loss) seemed elevated in treated groups.

Subcutaneous (SC) repeat administration tests were performed in young rats and via inhalation in juvenile dogs. There were no adverse treatment-related effects on juvenile rats or dogs related to zanamivir administration subcutaneously or via inhalation.

## *Local Tolerance*

No dermal irritancy, ocular irritancy or skin sensitisation potential was observed in the performed studies investigating local tolerance.

### *Other toxicity studies*

**Impurities**

The impurities was considered as safe and qualified up to the set specifications.

**Antigenicity**

No antigenic potential was revealed when zanamivir given by intraperitoneal or SC administration followed by IV challenge in an antigenicity study in guinea pigs.

**Immunotoxicity**

The immunotoxic potential of zanamivir in rats was investigated following daily SC administration at doses of 9 and 80 mg/kg/day for 28 days and no adverse effects indicating immunotoxicity was detected.

**Phototoxicity**

Zanamivir does not absorb light in the 290 to 700 nm wavelength range therefore, there is no concern with regard to photosafety in patients and photosafety testing was not warranted, according to ICH S10.

## 2.3.5. Ecotoxicity / environmental risk assessment

The zanamivir PECSW refined value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. Therefore, zanamivir is not expected to pose a risk to the environment.

A Phase II Tier A assessment is not required for Dectova.

## 2.3.6. Discussion on non-clinical aspects

Zanamivir was shown as a weak inhibitor of the human lysosomal neuraminidase and the neuraminidase from several other organisms. It is therefore unlikely to affect other pharmacologically relevant targets and it can be accepted that no specific secondary pharmacodynamic studies have been conducted with zanamivir.

Increased arterial blood pressure (lasting less than 4 minutes) at IV doses of 10 mg/kg and 30 mg/kg was observed in a study on cardiovascular and respiratory function in cats. This was however not reproduced in dogs (single IV dose of up to 30 mg/kg or in the repeat dose toxicity IV studies), and the clinical relevance of the finding in cats is likely to be low.

A tendency for prolonging of the sleeping time was observed in mice administered Zanamivir of 100 mg/kg. However, studies of effects of various P-450 isoenzymes (below) showed that there were no effects of Zanamivir on metabolic pathways mediated by cytochrome P450 (CYP) enzymes in human liver microsomes *in vitro* or in expression levels of hepatic CYP enzymes *in vivo* in the rat. It is not expected that zanamivir will affect the hepatic clearance of compounds metabolized by CYP enzymes, which may be administered concomitantly.

In Ames test, statistically significant increases in revertant colonies were observed in some strains with or without S9, but the results were small and not reproducible. In a plate incorporation assay, positive results were obtained with some strains in the absence or presence of S9 that were not dose-related or reproducible. In the mouse lymphoma assay, there were also positive results that were not reproducible or performed according to current guidelines. In conclusion, zanamivir was not considered genotoxic.

It is noted that in study, the route of administration is oral. The guideline for OECD474 (Mammalian Erythrocyte Micronucleus Test) states the anticipated route of human exposure should be considered when designing an assay. The impurity is controlled to less than 0.01% in the zanamivir drug substance

and was studied in a mammalian erythrocyte micronucleus test for worker-safety reasons and not conducted specifically in support of IV zanamivir. As such, the applicant's choice of route of administration is considered justified for this study.

It can be accepted that no carcinogenicity studies were performed with the IV route of administration.

Based on the absence of neoplastic findings in the inhalation carcinogenicity studies, indication of carcinogenic potential in the IV repeat-dose studies and no positive genotoxicity results, zanamivir is considered not to pose a carcinogenic risk in the proposed IV short-term clinical use.

In a fertility and reproductive study with IV doses given to rats (male and female) up to 90 mg/kg/day, behavioural effects were observed in F1 generation males. This was for example a reduction in mean performance times in the accelerating rotarod test or reduction in forelimb grip strength was seen. These effects were however not observed in other studies (including the pre and post-natal study) with same dose levels, and the biological relevance appears low.

In an organogenesis study in rabbits, the incidence of malformations (post-implantation loss) seemed elevated in treated groups. However, the majority of these were multiple, confined to a few litters and minor background anomalies were not increased consistent with a spontaneous pattern. Overall the distribution as well as pattern of anomalies and malformations among foetuses in different groups was indicative of a spontaneous aetiology

Higher incidence of some minor variants and alterations was observed after administration of zanamivir SC, at doses up to 240 mg/kg/day in pregnant rats. Incomplete ossification of skull bones and sacral vertebral arches, slightly kinked ribs, slightly dilated ureter and elongated innominate artery, was observed, but without statistical significance. Since the findings often occur spontaneously in the Wistar Han rat they are considered to be either associated with a delay in skeletal development or minor changes.

Zanamivir is not considered teratogen in animals, but was shown to cross the placenta. Zanamivir was secreted in low amounts in milk in rats.

### 2.3.7. Conclusion on the non-clinical aspects

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, or toxicity to reproduction and development, with the exception of a rat embryofoetal development study (subcutaneous administration). In the rat embryofoetal study, there was an increase in the incidence rates of a variety of minor skeletal and visceral alterations, most of which remained within the background rates of the historical occurrence in the strain studied.

The CHMP considers that from a non-clinical point of view, no issues remain which would preclude granting of a Marketing Authorisation.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

#### *GCP*

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

The applicant has provided a statement to the effect that clinical trials conducted outside the Community

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

- Tabular overview of clinical studies

**Table 2. Clinical reports providing efficacy information for IV Zanamivir**

| **Efficacy and Safety Studies: Controlled Clinical Studies Pertinent to the Claimed Indication** | | | | | |
|---|---|---|---|---|---|
| **Study Identifier** | **Study Objective(s** | **Study Design** | **Treatment Details** | **Total Number of Subjects** | **Primary endpoint** |
| NAI114373 | Efficacy, | Randomized, double-blind, double dummy, parallell group | IV Zanamivir 300 mg BID, IV Zanamivir 600 mg BID, oral oseltamivir 75 mg BID (with adjustments for age and weight [adolescents only], and renal function); Duration: 5 to 10 days | 615 (205 active control) | To assess the efficacy of treatment with 600 mg of intravenous (IV) Zanamivir twice daily compared to 75 mg of oral oseltamivir twice daily, and 600 mg IV Zanamivir twice daily compared to 300 mg IV Zanamivir twice daily on time to clinical response (TTCR). |
| **Efficacy and Safety Studies: Uncontrolled Clinical Studies** | | | | | |
| NAI113678 Adult Cohort | Safety, PK | Open label, multiple dose | IV Zanamivir 600 mg BID with adjustments for renal function Duration: 5 to 10 days | 130 | To assess the safety and tolerability of intravenous (IV) Zanamivir in the treatment of hospitalized adult, adolescent and paediatric subjects with influenza infection. |
| NAI113678 Paediatric Cohort | Safety, PK | Open label, multiple dose | IV Zanamivir 600 mg BID (with adjustments for age and weight [paediatrics and adolescents only] and renal function) Duration: 5 to 10 days | 71 | |
| NAI115215 | Safety, and clinical response | Open label, multiple dose | IV Zanamivir 600 mg BID (adjusted for age and weight [adolescents only] and renal function). Duration: 5 to 10 days | 21 | To assess the safety and tolerability of 600 mg of IV Zanamivir twice daily in the treatment of hospitalized subjects with influenza infection. |

## 2.4.2. Pharmacokinetics

Zanamivir hydrate sterile 10 mg/ml solution for infusion in 0.9% NaCl (IV zanamivir) is an aqueous formulation that was developed originally to support the nonclinical safety assessment and Phase I clinical studies of Relenza (zanamivir) inhalation powder. Five legacy studies that included the aqueous formulation are now used to support the current MAA in addition to several more recent Phase I studies specifically conducted to support development of IV zanamivir. The clinical pharmacology programme for IV zanamivir with PK data includes eleven Phase I studies, one BE study, and two clinical studies in adults and children hospitalised with influenza. Population PK analyses of zanamivir following IV administration were performed in combined populations of healthy subjects, and paediatric and adults with influenza, with various degrees of renal impairment enrolled across eight Phase I to III studies. In addition, *in vitro* studies using human biomaterial to investigate DDI potential and extent of plasma protein binding have been presented. The proposed posology is 600 mg BID in adults ≥ 18 years and weight-based dose in children below 18 years.

| **Healthy subject PK and initial tolerability study reports** |
|---|
| C92-083: A study to investigate the safety, tolerability and pharmacokinetics of single intravenous doses of GR121167X in man |
| NAIB1008: A study to evaluate the safety, tolerability and pharmacokinetics of GG167 administered intravenously and orally to healthy volunteers |
| NAIB1009: A study to evaluate the safety, tolerability and pharmacokinetics of zanamivir administered intravenously as repeated doses |
| NAI106784: Phase I, open-label study to evaluate steady-state serum and pulmonary pharmacokinetics following intravenous administration of zanamivir in healthy adult subjects |
| **Intrinsic factor study reports** |
| C94-051/C95-014 (NAIB1003): A study to investigate the pharmacokinetics of GG167 in subjects with impaired renal function |
| NAI108127: An open-label, non-randomized, single-dose study to evaluate serum zanamivir pharmacokinetics following intravenous administration to human subjects with renal impairment compared to subjects without renal impairment |
| NAI115070: A double blind, placebo controlled, randomized, dose ascending, single and multiple dose study to investigate the safety and pharmacokinetics following intravenous administration of GR121167 in healthy Japanese males |
| NAI117104: A randomized, double blinded, parallel study to evaluate the pharmacokinetics of zanamivir after single and repeated dose infusion administration in healthy Chinese adults |
| **Extrinsic factor study report** |
| NAI112977 (SEA003): An open-label crossover study to evaluate potential pharmacokinetic interactions between oral oseltamivir and intravenous zanamivir in healthy Thai adults |
| **Population PK report** |
| Population Pharmacokinetic and Exposure-Response Analysis of Zanamivir Following Intravenous Administration in Adult Healthy Subjects and Hospitalized Subjects with Influenza Infection (NAIB1009, NAI108127, NAI112977, NAI114346, NAI115070, NAI117104, NAI113678 and NAI114373) |

The formulation containing zanamivir 10 mg/mL in 0.9% sodium chloride presented in 26 ml Type I glass vials that was used in some clinical studies (including Phase III) is the same as the intended commercial product. Acceptable PK, analytical and statistical methods have been used.

*popPK:* Population PK and PKPD model analysis have been performed to inform the clinical pharmacological development of zanamivir. The results generated from the popPK analyses were used to characterise the zanamivir disposition, while simulations and the PKPD model were used to support dosing recommendations in adults and children 6 months to <18 years. Simulations of 300 mg and 600

mg BID and QD regimens for zanamivir IV, analysed by age and renal function, have been presented as well as estimates of percentages with steady state concentrations throughout the dosing interval above the $IC_{50}$ and $IC_{90}$ values (see PD section). The model was based on data from studies with extensive (healthy subjects) and sparse (influenza patients) PK sampling covering a range of doses (100-1200 mg) given as IV infusion over 30 minutes. The data were best described by a simple two-compartment IV infusion model. The inter-compartmental clearance (Q) and volume of distribution (V1, V2) were positively correlated with body weight.

### *Absorption*

The current product is an aqueous formulation intended for infusion only. Mean oral bioavailability was 2% (range 1-4%), with or without glucose. A BE study was conducted to support the use of blinded, over-encapsulated Tamiflu capsules as the active comparator in the pivotal study **NAI114373**.

### *Distribution*

Binding of $^{14}$C-zanamivir to human plasma proteins and red blood cells was found to be ≤10% over the investigated concentration range (0.05, 0.5, 10 µg/ml). Following IV administration, zanamivir concentrations in serum decline in a bi-exponential manner, with a rapid initial distribution phase. In the popPK analysis the $Vd_{ss}$ was estimated to be 18.8 L for a typical adult subjects, and was not affected by infection with influenza virus. Following IV 600 mg BID zanamivir, the median trough concentrations in epithelial lining fluid were 47-66% compared to orally inhaled zanamivir 10 mg BID (the approved posology for Relenza) in healthy individuals. Urea-corrected drug concentrations of zanamivir could be detected in throat gargles and/or nasal washes at 1h following IV administration of 50 mg to 600 mg single doses zanamivir, and at 4h and 12h following IV administration of 600 mg BID zanamivir. A high inter-subject variability was observed.

### *Elimination*

No mass balance study has been conducted. No metabolites have been reported in nonclinical studies, and predominantly renal elimination of unchanged drug was observed in the investigated species. Following IV administration, zanamivir concentrations in human serum decline in a bi-exponential manner, with a half-life of approximately 2-3 hours. The individual studies as well as the popPK analysis indicate that zanamivir undergoes extensive renal elimination. More than 90% of zanamivir is excreted unchanged in urine. Total and renal clearance correlated well with CrCL. Mean clearance (CL) following IV administration ranged between 90 to 111 ml/min across doses of 1-16 mg, and renal clearance ($CL_R$) of unchanged drug ranged between 93 to 130 ml/min across doses of 50-600 mg. In a popPK analysis the typical value of zanamivir clearance (CL) was estimated to be 113.67 ml/min in healthy adults.

The potential consequences of possible genetic polymorphism have not been discussed.

### *Dose proportionality and time dependencies*

Zanamivir serum concentrations ($C_{max}$ and AUC) appear to be dose-proportional over the investigated dose range (single dose 1 to 1200 mg) in healthy individuals. $C_{max}$ ranged from 2263 (50 mg) to 43371 ng/ml (600 mg). $C_{max}$ after initial dose (300 or 600 mg) was approximately proportional to dose regardless of renal function. Negligible accumulation (accumulation ratio 1.05) based on $AUC_T$ was observed following zanamivir 600 mg IV BID for five days.

### *Intra- and inter-individual variability*

Across doses, inter-individual variability in serum concentrations in **NAI106784** was low. In **NAI117104** the inter-subject CV% for all the PK parameter estimates ranged from 13.9% to 24.5% on Day 1 (300 mg single dose) and 8.7% to 15.6% on Day 8 (end of 300 mg q12h IV dosing). After 600 mg q12h the inter-subject CV% for all the PK parameter estimates ranged from 17.0% to 25.4% on Day 1 and 7.0% to 23.5% on Day 8. High inter-subject variability in zanamivir PK exposure were observed within the target population following repeated administration of zanamivir 600 mg IV BID. In the popPK analysis inter-individual variability on CL in patients (69.4%) was 3 times higher than in healthy subjects with similar renal function. IIV on V1 was 34.8%. Intra-subject variability has not been reported.

### *Pharmacokinetics in target population*

The proposed posology includes a 600 mg loading dose (irrespective of renal function), followed by reductions in maintenance dose when CrCL is < 80 ml/min with prolonged administration of the second dose. Zanamivir is expected to be removed by CRRT, and the zanamivir dose is selected based on CRRT clearance ($CL_{CRRT}$ in ml/min) in individual CRRT patients in place of calculated CLCr. For patients on intermittent haemodialysis/peritoneal dialysis, the zanamivir dose as determined by CLCr is given after completion of the dialysis session. The proposed dose recommendations were used in clinical studies.

Zanamivir PK parameters in target patients following IV administration by 30 minute infusion of doses adjusted for age, weight and renal function were overall similar with those observed in Phase I studies, however variability was higher. After an initial dose of 600 mg zanamivir in adults, AUC increased 1.4- to 11-fold with decreasing CLCr. Comparable $C_{max}$ was observed in individuals irrespective of renal function as expected considering the initial 600 mg loading dose and the 30 minutes infusion period. After repeated doses of zanamivir (600 mg BID dosing schedule adjusted for renal function) in adults, $C_{max}$ decreased with decreasing renal function, but AUC was comparable with exception of the <30 ml/min cohorts: lower AUC in subjects with CLCr <15 mL/min and two-fold higher AUC in patients with CLCr 15 to <30 ml/min.

Mean exposures (AUC) in patients 6 months to <18 years with normal renal function ranged from 64.5 to 107 h*µg/ml as compared to adult exposure of 82.9 to 90.3 µg*h/ml following 600 mg single and BID dosing. Few patients were included within each age and renal cohort, only seven children in this study (**NAI113678**) were aged <1 year.

In the popPK analysis CL in hospitalised patients was found to be 24% lower (5.16 L/hr [85.9 ml/min]) as compared with healthy subjects (6.82 L/hr [113.67 ml/min] for a typical subject of 70 kg), and was further reduced by ~26-54%, ~54-72% and ~72-86% in patients with mild (CrCl 50-79 ml/min), moderate (30-49 ml/min) and severe renal impairment (15-29 ml/min), respectively and by > 86% for ESRD (<15 ml/min). Half-life increased to 3.88 hours, 5.79 hours and 12.8 hours in mild, moderate and severe renal impaired subjects respectively, compared to 2.44 hours in subjects with normal renal function).

### *Special populations*

In a dedicated renal impairment study, zanamivir AUC and $t_{1/2}$ increased and CL and CLr decreased with decreasing renal function, while as expected after a single dose $C_{max}$, $t_{max}$, and Vz appeared to be similar across the renal function groups. Zanamivir AUC (0-∞) was approximately 56%, 153%, and 427% greater in subjects with mild, moderate, and severe renal impairment, respectively, compared with subjects in the normal renal function group. Corresponding increases in $t_{1/2}$ were observed. Zanamivir total and renal clearance were both highly correlated with CLCr ($r2 > 0.87$, $p<0.0001$).

The effect of liver impairment on zanamivir PK has not been assessed. However, zanamivir is not metabolised, therefore no effect of hepatic impairment is expected.

No dedicated PK study investigating the effect of gender on zanamivir PK has been performed. The popPK analysis did not support a co-variate effect on the PK, and justifies the omission for a dedicated PK study in this regard. This is accepted by CHMP.

PK in healthy Caucasians compared to PK in Thai, Chinese and Japanese healthy subjects appears to be overall similar. Exposures (AUC and $C_{max}$) following 600 mg BID dosing in healthy East-Asians were up to 35% higher as compared to exposures in healthy Caucasians. In a popPK analysis race was not shown to impact on zanamivir CL, although there was a trend for a slightly higher CL in the Asian population.

No dedicated PK study investigating the effect of weight on zanamivir PK has been performed. Since the Vdss is consistent with extracellular volume no effect of obesity is expected. Weight was not included as a covariate in the popPK analysis.

No dedicated PK study in elderly has been performed. Available PK data in elderly patients were obtained in the supportive and pivotal studies **NAI113678** and **NAI114373**. In the popPK analysis, age was found to be correlated with CLCr but had no significant effect on zanamivir pharmacokinetics

### *Pharmacokinetic interaction studies*

*In vitro*, zanamivir was shown to have no inhibitory effect on the metabolism of the probe substrates for CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4 by human liver microsomes over the investigated concentration range 0.1 to 500 µM (0.033 µg/ml to 166 µg/ml). No direct or metabolism dependent inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4 and no induction of CYP1A2 or 2B6 was observed at concentrations up to 10 mM zanamivir (*i.e.* >50-fold free Cmax following repeat dosing of 600 mg IV BID zanamivir). Weak induction of CYP3A4 was observed with concentrations up to 2 mM zanamivir, and a more marked induction of CYP3A4 mRNA, of up to 7 fold (mean ~20% positive control) was observed with 10 mM zanamivir.

Zanamivir 10 µM (3.32 µg/ml) was not a substrate for Pgp and had low passive membrane permeability. Zanamivir 1 mM (332.3µg/ml) produced less than 50% inhibition of uptake via all the tested transporters, hOAT1, hOAT2, hOAT3, hOAT4, hOCT1, hOCT2, hOCT2-A, hOCT3 and hURAT1. No inhibition of the investigated transporters (BCRP, MDR1/Pgp, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3 and OCT2) was observed at zanamivir concentrations 0.01µM to 10 mM.

In an *in vivo* DDI study investigating the impact of zanamivir on oseltamivir PK, $C_{max}$ and AUC of oseltamivir and oseltamivir carboxylate were not significantly different when oseltamivir was given separately or together with zanamivir. Zanamivir CL was shown to be similar, however no formal BE testing of zanamivir PK with or without oseltamivir was performed.

## 2.4.3. Pharmacodynamics

### *Mechanism of action*

Zanamivir is an inhibitor of influenza virus neuraminidase, an enzyme that releases viral particles from the plasma membrane of infected cells and promotes virus spread in the respiratory tract.

## *Primary and Secondary pharmacology*

**Primary pharmacodynamics**

**Challenge study NAIA 1010: Evaluation of the Safety and Efficacy of Zanamivir administered intravenously as repeated doses to healthy male volunteers inoculated with Influenza A Texas/91 (H1N1) Virus**

***Study Design***

This was a double-blind, placebo-controlled, single-centre parallel study in 16 healthy male serologically susceptible (HI antibody titer of ≤1:8 to the challenge strain) subjects to evaluate the effect of zanamivir administered intravenously in preventing illness and reducing viral replication following inoculation with influenza A virus. Subjects were dosed as inpatients twice daily for 5 days starting at 4 hours prior to the scheduled viral inoculation.

Sixteen healthy male volunteers aged 18 to 35 years were enrolled in the study. Eight subjects in the placebo group and seven in the zanamivir group were evaluable in the efficacy analyses. One subject in the zanamivir group shed virus different from the inoculated influenza A/Texas/91 and was excluded from the evaluable population for efficacy assessment. The age distribution was similar among treatments, with a median age of 24 years in both treatment groups. The majority were Caucasian (88% in each treatment arm).

***Treatment Administration***

Sixteen serologically susceptible male subjects were randomized to receive zanamivir 600mg or placebo intravenously over 30 minutes at approximately 8 am and 8 pm for a total of 10 doses in a blind fashion starting 4 hours prior to viral inoculation on Day 0.

Influenza A/Texas/91 (H1N1) virus suspension ($10^5 TCID_{50}$) was administered intranasally to each subject on Day 0 at approximately noon. The inoculum was administered intranasally (0.25ml per nostril) with the subject in a supine position and the neck hyperextended. Back titration indicated the strength of Influenza A/Texas/91 (H1N1) virus administered to each individual was approximately $10^{5.7} TCID_{50}$

***Efficacy Results***

A subject was considered infected if there was a positive culture for the inoculated virus in nasal washings, and/or at least four-fold increase in convalescent HI antibody compared with pre-inoculation.

Convalescent antibody titres for all subjects were collected 3 to 4 weeks post-inoculation.

All subjects in the placebo group shed virus and all seroconverted. No subjects in the zanamivir group shed virus; one subject in the zanamivir group had seroconversion without shedding virus.

Influenza-like symptoms were obtained by self-administered questionnaire. Symptoms were scored as follows: 0=none; 1=mild; 2=moderate; 3=severe. All subjects in the placebo group and 86% of subjects in the zanamivir group had at least one symptom after inoculation.

There was a statistically significant difference in the incidence of upper respiratory infection, myalgia, and fatigue, and statistically significant differences between groups in overall means (0.01 versus 0.37 in placebo) of daily upper respiratory infection scores (where severity of each symptom was recorded on a scale from 0 to 3, where 0=absent, 1=mild, 2=moderate, and 3=severe). There were also statistically

significant differences between groups in proportions of subjects (29% versus 100% in placebo) with upper respiratory infection symptoms after viral inoculation.

There was a statistically significant difference in the number of subjects with fever (1 subject in the zanamivir group compared with 7 subjects in placebo). The one subject in the zanamivir group with fever had a slight temperature (37.0° C) for half a day on Day 2.

Mean nasal discharge weight was lower in the zanamivir group compared with the placebo group from Day 0 to 7.

There were no statistical or clinical differences between treatment groups in IL-6 or TNF-$\alpha$ plasma levels.

***Efficacy Conclusions***

The results from NAIA1010 indicate that IV zanamivir had significant prophylactic effect against an experimental challenge with influenza A. This was demonstrated by a low infection rate (14% vs. 100% positive serology in the placebo group), isolation by viral culture of virus (0% vs. 100% in the placebo group), as well as reductions in fever (14% vs. 88% in the placebo group), upper respiratory tract illness (0% versus 100% in the placebo group) and total symptom scores (1 vs. 44 median score in the placebo group).

**Virology**

Virology data from the clinical studies **NAI114373** and **NAI113678** are presented in the efficacy section for each of the studies.

**Zanamivir and drug resistance**

Resistance to oseltamivir is well documented, the most common NA resistance substitution being H275Y. The structure of zanamivir is similar to the natural substrate which is likely to contribute to the high barrier to resistance; the majority of oseltamivir resistant viruses remain sensitive to zanamivir.

NA susceptibility and development of drug resistance in influenza viruses continues to be monitored through a number of surveillance initiatives and *ad hoc* studies. The World Health Organization (WHO) collates data from WHO National Influenza Centres and WHO Collaborating Centres, through the Global Influenza Surveillance and Response System (GISRS). Data from Europe (EU/EEA) is collated by the coordinators of Community Network of Reference Laboratories for Human Influenza in Europe (CNRL) under the aegis of the ECDC.

Two basic mechanisms of resistance have been described: one involves changes in the HA and the other changes in the NA. Amino acid changes at or near the receptor binding site decrease the affinity of the HA for sialic acid. These variants have a decreased dependence on NA for release from infected cells *in vitro*. The role of the HA in resistance to zanamivir and other NA inhibitors *in vivo* is not fully understood. The second mechanism of resistance involves amino acid substitutions in the NA that confer reduced affinity of the NA binding site for zanamivir and result in reduced inhibition of NA enzyme activity by the drug.

The most frequent variants selected *in vitro* have amino acid changes at position 119 from glutamic acid to glycine (E119G) or aspartic acid (E119D) or alanine (E119A). Using an H4N2 turkey virus, another resistant virus with an arginine to lysine substitution at residue 292 (R292K), which appeared after several passages in increasing concentrations of zanamivir, has been reported. Both the Glu119 mutant and the Lys292 mutants have reduced NA activity. Passage of influenza A (H1N1) and A/H5N1 in the

presence of zanamivir produced resistant viruses with a large portion of the NA deleted between amino acids 92 and 362 and a substitution at D198N respectively. *In vitro* passage of influenza A/H1N1pdm09 virus in the presence of zanamivir selected a virus with N146S NA and G158E HA substitutions that only reduced drug susceptibility by 2-fold in enzyme assays. The clinical importance of the resistant genotypes which have been selected from in vitro experiments has not been established.

The NA substitution Q136K has been detected during passage of H1N1 viruses in zanamivir. Resistant viruses harbouring the Q136L NA substitution have been selected in ferrets infected with influenza A/H5N1 following treatment with zanamivir and confer high level resistance to zanamivir. The Q136K substitution has previously only been seen in cultured virus and the selection of Q136L in ferrets demonstrates that substitutions at this position in the NA can persist and may be transmittable. The Q136K/L substitution has only been isolated from a small number of immunocompromised patients treated with zanamivir has reduced replicative capacity and therefore is presently not thought to be a public health threat.

*Study* ***NAI114373***

The applicant has provided data on two H3N2 viruses recovered from 2 subjects treated with 300 mg BID group with N294N/S and T325I substitutions. To ascertain the effect of neuraminidase (NA) substitutions N294S and T325I on susceptibility to zanamivir a reverse genetics project was carried out by Viroclinics Biosciences. The N294S and T325I substitutions were created in the genetic background of the influenza A/H3N2 virus A/Tokyo/Ut-Sk-1/07. The recombinant viruses were tested for susceptibility to the neuraminidase inhibitors oseltamivir and zanamivir. The H3N2 virus with the N294S substitution and the parent virus had similar fold changes in susceptibility to zanamivir and oseltamivir relative to the reference strain (zanamivir fold change = 2.44; oseltamivir fold change = 0.95), which is within the normal level of inhibition as defined by World Health Organization (WHO) criteria. However, the N294S substitution in this NA background may impact viral fitness as the virus could not be propagated in a second passage in tissue culture. It was concluded that the N294S amino acid substitution does not confer resistance to either zanamivir or oseltamivir in this NA background.

Several cell culture passages of the T325I recombinant virus have been attempted, but virus of a sufficient titre to perform a susceptibility assay could not be obtained. Therefore, the T325I substitution appears to reduce fitness of the virus; this substitution may confer zanamivir resistance, although conclusive data could not be obtained as the virus could not be cultured. In addition, the NA 325 residue is a position of variability, as substitutions at this position in other subtypes have conferred reductions in susceptibility to neuraminidase inhibitors.

***Case reports of resistance observed in the clinic after treatment with Zanamivir***

Resistance analysis carried out in clinical studies of inhaled zanamivir and information on resistance reported in the literature to both inhaled and intravenous zanamivir are summarized. All case reports describing IV Zanamivir were from participation in the CUP (Compassionate Use Program).

As of June 2017 there have been nine reported cases of zanamivir resistant viruses isolated from **immunocompromised** patients:

**Table 3.**

| NA Substitution | Type/Subtype | Treatment | Reference |
|---|---|---|---|
| R152K | B | Nebulised Zanamivir | Gubareva, 1998a |
| I223R | H1N1pdm09 | Oseltamivir, IV Zanamivir | van der Vries, 2010 |
| I223R | H1N1pdm09 | Oseltamivir, Inhaled Zanamivir[1] | Rousset, 2010 |
| I223R | H1N1pdm09 | Oseltamivir, IV Zanamivir | Nguyen, 2010 |
| I223R | H1N1pdm09 | Oseltamivir, Inhaled Zanamivir[1] | Grund, 2015 |
| E119V, Q136K, R292K, DEL245-248 | H3N2 | Oseltamivir, Inhaled Zanamivir[1], IV Zanamivir | Eshaghi, 2014 |
| E119D | H1N1pdm09 | Oseltamivir, IV Zanamivir | L'Huillier, 2015 |
| E119G | H1N1pdm09 | Oseltamivir, IV Zanamivir | Tamura, 2015 |
| H275Y, I223R, E119G | H1N1pdm09 | Oseltamivir, Inhaled Zanamivir[1], IV Zanamivir | Trebbien, 2017 |

1 Inhaled dry powder 10mg BID

The change in sensitivity is shown below.

**Table 4. NA Resistance Substitutions Previously Observed in the Clinic After Treatment with NAIs**

| Subtype/strain | Selection with | N2 numbering | N1 numbering | B numbering | FC OSV | FC ZAN | FC PMV | Reference |
|---|---|---|---|---|---|---|---|---|
| A/H1N1pdm09 | OSV,ZAN-IC | E119D | E119D | E117D | R (25) | R (827) | R (286) | L'Huillier, 2015; Yates, 2016 |
| A/H1N1pdm09 | OSV,ZAN-IC | E119G | E119G | E117G | S | R (1300) | R (167) | Tamura, 2015 |
| A/H3N2 | OSV-IC | E119V | E119V | E117V | R (>50) | R(4-25) | S | Okomo-Adhiambo, 2010 |
| B | ZAN-IC | R152K | R152K | R150K | R (12-76) | R (9-150) | R (400) | Gubareva, 1998a |
| B | OSV-IC | D198N | D199N | D197N | R (9) | R (9) | DS (4.8) | Mishin, 2005 |
| A/H1N1pdm09 | OSV, ZAN-IC | I222R | I223R | I221R | R (40) | R (10) | R (35) | van der Vries, 2010; Rousset, 2010; Nguyen, 2010a, Grund, 2015 |
| B | OSV-IC | I222T | I223T | I221T | R (13) | S (2.1) | Not known | Hatakeyama, 2007 |
| A/H3N2 | OSV-IC | 246-248 deletion | 247-249 deletion | 245-247 deletion | R (20) | R (9) | Not known | Memoli, 2010b |
| A/H1N1pdm09 | OSV | H274Y | H275Y | H273Y | R (398) | S | R (138) | Englund, 2009; Nguyen, 2010b |
| A/H5N1 | OSV | H274Y | H275Y | H273Y | R (1272) | S | Not known | Le, 2005 |
| A/H1N1pdm09 | PMV-IC | H274Y | H275Y | H273Y | R (200) | S | R (50) | Memoli, 2010a |
| A/H3N2 | OSV | R292K | R293K | R292K | R (>8000) | R (4-25) | Not known | Cohen-Daniel, 2009 |
| A/H7N9 | OSV, PMV | R292K | R293K | R292K | R (100) | R (30) | Not known | Hu, 2013 |
| A/H3N2 | OSV | N294S | N295S | N294S | R( 300) | S | Not known | Kiso, 2004 |
| A/H1N1 | OSV | N294S | N295S | N294S | R (12-15) | S (4.8) | Not known | Saad, 2007; Le, 2005; Carr, 2011 |
| B | OSV | G402S | G398S | G405S | R (3.9*) | R (7) | Not known | Hatakeyama, 2007 |

FC Fold Change of IC50 relative to reference virus; OSV, oseltamivir; ZAN, Zanamivir; PMV, peramivir; IC, immunocompromised.

The NAIs which have been granted marketing authorisations (zanamivir, oseltamivir, peramivir and laninamivir) target the same region, the active site of the NA molecule, and therefore it may be expected that the four drugs would show high levels of cross-resistance. However, because the four molecules bind in different ways within the active site, not all substitutions show cross-resistance and the levels of resistance observed are different. These differences could be important in immunocompromised patients and when resistant virus is in circulation. Zanamivir 's structure is closely related to the natural substrate of NA and this contributes to the high barrier to resistance. Resistance to zanamivir following treatment is rare but resistance following oseltamivir treatment is in the order of about 1% (Neuraminidase Inhibitor Susceptibility Network, 2011). The caveat is that oseltamivir is used to treat influenza infection much more often than

zanamivir. The majority of oseltamivir resistant viruses, the most common being H275Y variants, are sensitive to zanamivir and therefore patients with these resistant viruses can be treated with zanamivir.

There have been nine case reports in the scientific literature of treatment emergent resistant viruses with known resistance substitutions isolated from immunocompromised patients who received IV zanamivir via the CUP and one from an immunocompromised adult from study NAI113678 (E119D), who died on the study. Influenza infections in immunocompromised patients have been shown to have prolonged viral replication despite antiviral therapy, and therefore an increased risk of antiviral resistance emergence and persistent illness.

There is some evidence that selection of resistance during IV zanamivir treatment is slightly higher than treatment with inhaled zanamivir. Two treatment emergent NA resistance substitutions, E119D and E119G, were detected in post Baseline samples in study NAI113678, the latter from an immunocompetent paediatric subject. By contrast, prior to the 2009 pandemic, only one resistant influenza B virus has been reported during treatment with inhaled (nebulised) zanamivir in an immunocompromised patient. The higher baseline viral loads and prolonged duration of shedding in hospitalised patients may account for the slightly higher frequency of resistance selection in subjects receiving IV zanamivir, although they are still rare occurrences.

Zanamivir is active against the majority of oseltamivir resistant viruses including those with the most common oseltamivir resistant substitution, H275Y. In 2008/2009 viruses harbouring the H275Y substitution acquired compensatory substitutions that enabled the viruses to readily transmit and rapidly became the predominant influenza A H1N1 virus circulating globally. Although similar events have not occurred with the current circulating influenza A/H1N1pdm09 virus there have been clusters of transmittable viruses with the H275Y substitution. If widespread resistance to oseltamivir and peramivir were to occur, the only available treatment option active against H275Y viruses might be zanamivir.

**Secondary pharmacodynamics.**

**Study Number: NAI114346**: **A Phase I, Randomized, Placebo-Controlled, Four-Way Crossover Study to Evaluate the Effect of Intravenous Zanamivir on Cardiac Conduction as Assessed by 12-lead Electrocardiogram with Moxifloxacin as a Positive Control in Healthy Volunteers.**

*Study period:*

Initiation Date: 19 May 2011, Completion Date: 02 August 2011

*Objectives:*

*Primary*

• To demonstrate a lack of QT prolongation from single IV dose of zanamivir 600 mg and 1200 mg (standard dose and supra-therapeutic dose) as determined by the baseline-adjusted, maximum time-matched QTcF effect compared to placebo.

*Criteria for evaluation:*

Primary

• Change from baseline in QTcF for zanamivir.

Secondary

• Change from baseline in QTcB, QTci, QT, and HR.

• Pharmacokinetic parameters of AUC(0-t), AUC(0-∞), Cmax, tmax, CL, Vz, and t½ from serum zanamivir concentration-time data and (if needed) AUC(0-t), AUC(0-∞), Cmax, tmax, CL/F, Vz/F, and t½ from plasma moxifloxacin concentration-time data.

• Safety and tolerability of zanamivir as assessed by change from baseline in 12-lead ECGs, vital signs (blood pressure and heart rate), AEs, and toxicity grading of clinical laboratory tests.

*Subject Disposition and Demographics***:** A total of 40 subjects were enrolled into this study. Two subjects withdrew from the study after Period 1: one subject due to investigator discretion and another subject did not return for Period 2 and was lost to follow-up.

There were more males (63%) than females (38%) and the mean age of the subjects was 30 years. Most subjects were either Caucasians (60%) or of African American/African heritage (28%).

On Day 1 of each period, IV zanamivir or placebo for zanamivir was administered in blinded fashion as 30-min IV infusions. Oral moxifloxacin (positive control) or placebo for moxifloxacin was also administered in a single blind fashion at the same time the IV dose was started.

Each subject participated in the study for approximately 9 weeks i.e., 30 day screening period, 4-week treatment period, and a 5-7 day follow-up period. There were four treatment sequences with a 5-7 day washout between treatments.

Twelve-lead electrocardiogram (ECGs) including continuous Holter monitoring, clinical laboratory safety tests, vital sign measurements, physical examinations, adverse event (AE) reports, and PK samples were collected throughout the study. In each treatment period, a Holter monitor was used to measure cardiac conduction from pre-dose on the morning of Day 1 until the morning of Day 2 with the recording card being changed pre-dose on Day 1. Triplicate ECG readings

were extracted from the Holter monitor data for analysis on Day 1 at three timepoints pre-dose (-1.5, -1.0 and -0.5 hours pre-dose) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6.5, 8.5, 12, and 24-hours post-dose.

A follow-up visit was conducted 5-7 days after administration of the last dose of study medication in treatment period 4.

*Results*

**Table 5. Summary of Selected PK parameters from 600 mg and 1200 mg IV Zanamivir[1] (ZMV PK Summary Population)**

| Treatment | N | AUC(0-∞) (µg·hr/mL) | AUC(0-t) (µg·hr/mL) | Cmax (µg/mL) | CL (L/hr) | Vss (L) | Vz (L) | t½ (hr) |
|---|---|---|---|---|---|---|---|---|
| A | 38 | 92.9 (15) | 91.4 (15) | 39.4 (16) | 6.46 (15) | 16.9 (16) | 18.9 (17) | 2.02 (13) |
| B | 38 | 187 (16) | 184 (16) | 78.7 (16) | 6.43 (16) | 16.9 (17) | 19.0 (19) | 2.05 (12) |

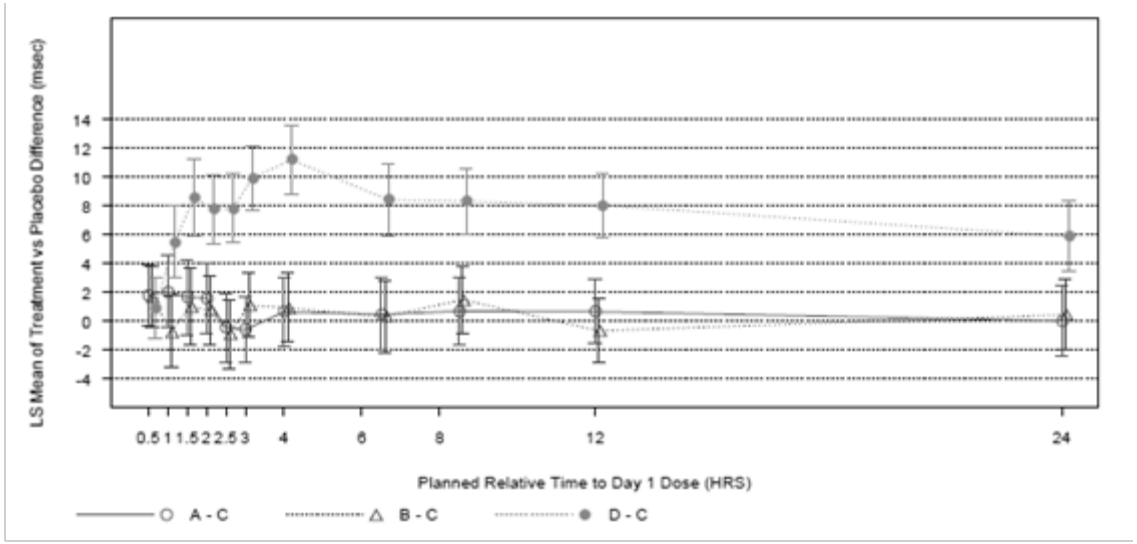
[1] Values denote geometric mean (CVb%)

Treatments:

A: Single dose IV Zanamivir 600 mg over 30 minutes + oral moxifloxacin placebo.
B: Single dose IV Zanamivir 1200 mg over 30 minutes + oral moxifloxacin placebo.

For both dose levels, mean values for CL, volumes of distribution and t½ are essentially the same, indicating dose independence. Inter-subject variability was low for all PK parameters, as characterized by CVb% values ranging from 12-19%. Statistical results from regression analysis of dose proportionality by the power model ($y = \alpha * \text{Dose}^{\beta}$) indicate that Cmax and AUC(0-∞) were proportional to IV zanamivir dose.

**Figure 2. Plot of Least Squares Mean of Zanamivir and Moxifloxacin Treatment Difference from Placebo for QTcF Change from Baseline (90% CIs) (PD Summary Population)**




Treatments:
A = Single dose IV Zanamivir 600 mg + oral moxifloxacin placebo
B = Single dose IV Zanamivir 1200 mg + oral moxifloxacin placebo
C = Single dose IV Zanamivir placebo + oral moxifloxacin placebo
D = Single dose IV Zanamivir placebo + oral moxifloxacin 400 mg.

No 12-lead ECG findings of clinical significance were reported for any subject during the study.

**Table 6. Predicted Mean and 90% CI of Double Delta QTcF and Delta QTcF at Geometric Mean Cmax from 1200 mg IV Zanamivir (PK/PD Population)**

| Cmax (μg/mL) | Mean Predicted (msec) | 90% CI |
|---|---|---|
| 78.7 | ΔΔQTcF 1.123 | (-0.414, 2.661) |

| | | |
|---|---|---|
| | ΔQTcF 2.261 | (0.955, 3.566) |

Based on the results above, the upper limit of the 90% CI for ΔΔQTcF (correcting for baseline and placebo) and ΔQTcF (correcting for baseline only) is 2.661 msec and 3.566 msec, respectively, which suggests that Zanamivir will not have an effect on ΔΔQTcF and ΔQTcF at a peak concentration that is approximately two-fold greater than the expected Cmax from the highest dose (600 mg) evaluated in ongoing Phase II and Phase III clinical studies and currently considered as the standard clinical dose.

*Conclusions:*

• Single therapeutic (600 mg) and supra-therapeutic (1200 mg) doses of IV zanamivir were well-tolerated in this study of healthy subjects.

• Zanamivir pharmacokinetics from IV administration demonstrated low inter-subject variability (12-19%) and was dose proportional from the 600 mg and 1200 mg doses.

• The study was sensitive enough to detect the effect of moxifloxacin, the positive control on QTcF, confirming that this study was valid for assessing the effects of IV zanamivir on cardiac repolarization.

· IV zanamivir had no effect on cardiac repolarization at either the anticipated therapeutic dose (600 mg) or supra-therapeutic (1200 mg) dose.

*DER relationships*

No exposure-response relationship was established in single studies or by PKPD model analysis of clinical response data. Simulations predicted that the percentage of subjects that have the entire dosing interval above *in vitro* $IC_{50}$ and $IC_{90}$ values (influenza virus A and B) were >95.5 and >97% following 300 mg BID and 600 mg BID, respectively. Frequency of dosing appeared to be more important than amount given in a single dose (300 or 600 mg) with respect to keeping the exposure in subjects with influenza above *in vitro* $IC_{50}$ and $IC_{90}$ values for the A and B viruses, consistent with the PK characteristics of zanamivir.

## 2.4.4. Discussion on clinical pharmacology

**Pharmacokinetics**

*popPK:* The model is considered to be of moderate regulatory impact as it is used to support dose recommendations in adult patients with impaired renal function and in paediatric/adolescent patients with normal or impaired renal function. Appropriate, standard methods have been used and the results are adequately presented. In general, the dataset includes wide ranges of covariates although the majority of subjects were Caucasians, and PK data obtained from children, patients with ESRD, ECMO or renal replacement therapy are limited. The ranges of covariates have been presented and all have been screened for potential relationship with the etas (η).

Several issues were addressed at Day121 to further substantiate the suitability of the model, which pertains to the following:

The BLQ observations, which accounted for approximately 8.5% of available data, mainly occurred at pre-dose (~72%). The BLQ observations are thus not likely to impact on model performance, and exclusion of the BLQ observations from the model dataset is acceptable.

Weight was not included as a covariate, but was included in the calculation of CLCr. The effect of WT on CL was estimated to be only 0.137 with poor precision (RSE = 42%) and effects of CrCl and WT on CL were considerably correlated (>0.7). This suggested that CrCl plays a more dominant role in describing CL than WT, thus weight was dropped from the model. It is noted that the proposed posology is to some extent weight based and this results in lighter subjects receiving lower doses than would be predicted based on allometry alone. Therefore, the risk is to efficacy rather than safety.

By inspection of the pcVPCs, the model appears to describe the observed data reasonably well. Although data are sparse for some subgroups, it is agreed that in general the model appears to be fit-for-purpose and could be used to make dose recommendations in renally impaired adults and children. The final model building dataset included PK data from 7, 7 and 12 pediatric subjects aged 6 months to <1 year, 1 to <2 years and 2 to <6 years, respectively.

The applicant places considerable weight on pcVPC plots for efficacy. The PKPD is not well understood, but time above IC50 or IC90 could be important (see PD discussion). It is noted that the goal is to target similar overall exposures rather than trough concentrations. The plots provided show a reasonable prediction of the trough concentrations, although there is an over-prediction in patients (with no specific trend based on age, body weight or renal impairment) which should be considered when proposing dose recommendations. From the safety and efficacy perspective, the adult trough PK data do not raise major concerns. However, there is a concern that in children efficacy may not be maintained.

Simulated initial and steady state exposures (including peak and trough concentrations) for the different age and renal groups were in excess of the IC50 and IC90 values for the influenza B strains (day 180 response). Although the exposure observed in paediatrics with severe renal impairment was lower than that of the adults, the plasma concentration was maintained above the IC50 and IC90 values for the B influenza strains despite the 24-48 hour dose delay between initial dose and BID maintenance dosing. Steady-state were quickly achieved.

Accumulation of drug is seen in subjects with influenza following repeated administration, consistent with the 24% decrease in clearance estimated in subjects infected with influenza in the popPK analysis. The accumulation tend to increase with increase in impairment of renal function.

*Bioequivalence:* Formally, BE to the marketed oseltamivir capsules, was not fully demonstrated for the oseltamivir over-encapsulated formulation.

*Distribution:* The binding of $^{14}$C-zanamivir to human plasma proteins and red blood cells was found to be negligible (≤10%) over the investigated concentration range (0.05, 0.5, 10 µg/ml) and is likely not clinically relevant. The volume of distribution (18.8L) is relatively low, slightly exceeds the volume of extracellular water (~16 L) and is consistent with zanamivir physicochemical characteristics as a polar compound with low protein binding.

The observed trough concentrations indicate that zanamivir concentrations in the upper and lower respiratory epithelium following the proposed posology would be in excess of the highest *in vitro* $IC_{50}$ values and $IC_{90}$ value for influenza virus neuraminidase (range: <1 to 4 ng/ml and range: ~1.7 to 7.8 ng/ml, respectively), and the *in vitro* $IC_{90}$ values for influenza virus Type A (1.8 ng/ml) and influenza B (7.8 ng/mL). However, an interpretation of these PK data in terms of relationship to efficacy against influenza virus in the target population is not possible.

*Metabolism & elimination:* The individual studies as well as the popPK analysis indicate that zanamivir undergoes extensive renal elimination as unchanged drug. It appears that renal excretion is comparable to GFR and that active renal secretion is not likely. Since zanamivir is mainly recovered unchanged in urine in humans, consistently shown in several clinical studies, the lack of a mass balance study is acceptable. The potential consequences of possible genetic polymorphism has not been discussed. Considering the apparent lack of zanamivir metabolism, this is acceptable.

*Dose proportionality & time dependency:* Dose-linear exposure has been demonstrated (1 mg to 1200mg). Zanamivir does not appear to demonstrate time-dependent PK.

*Variability:* There was a higher inter-individual variability in infected patients vs. healthy subjects. For example, in healthy subjects with normal renal function the inter-individual variability (IIV) for plasma zanamivir after BID dosing has been mostly < 15%. However, the popPK model estimated that IIV on CL was 69.4%, which was 3.1 times larger in influenza infected subjects than in healthy subjects with comparable renal function. Also, the data in patients do not suggest linearity in PK between 300 and 600 mg doses. Some of this observed difference in IIV might be due to rapid shifts in renal function during recovery from acute infection. Overall, the differences between healthy subjects and patients are not a concern.

*Target population & impaired renal function:* Renal impairment has a significant effect on zanamivir PK, and dose adjustment is thus required for IV zanamivir administration in patients with decreased renal function. The target population is expected to include a relatively large proportion of patients with pre-existing renal impairment and/or decrease in renal function due to the underlying infection.

The proposed posology includes a 600 mg loading dose (irrespective of renal function), followed by reductions in maintenance dose when CrCL is <80 ml/min with prolonged administration of the second dose. The loading dose approach appears reasonable as single dose $C_{max}$ was unaffected by renal function. Although the DER relationship is not known, it is a well-established principle that treatment should be initiated as early as possible. As a result, the Day 1 exposure will be higher compared to the following treatment days.

There is no scientific rationale for the infusion time of 30 minutes, which results in a high $C_{max}$, when the applicant's aim is to achieve target trough concentrations. The serum and ELF levels, especially trough levels, have simply been compared to concentrations determined to be required for neuraminidase inhibition and for *in-vitro* virus neutralisation. There is no concern regarding the safety of this infusion time in terms of local tolerance or AEs that could be related to $C_{max}$.

The renal impairment study did not enrol subjects with ESRD requiring dialysis, and only four subjects were included per cohort which is considered to be too few. Only one subject in the severe renal impairment cohort had CLCr <20 ml/min. The investigated dose was only 100 mg, despite scientific advice (2006) where it was suggested to use a dose as close as possible to the dose to be evaluated in the

clinical studies (*i.e.* 600 mg). A renal impairment study performed in accordance to the EMA guideline (EMA/CHMP/83874/2014) would have provided further data on which to base the dose recommendations in patients with renal impairment.

In study **NAI113678**, paediatric subjects received an age-adjusted, weight-based dose intended to provide comparable systemic exposures to 600 mg BID in adults. Paediatric/adolescent subjects with renal impairment received an adjusted maintenance dose of IV zanamivir based on calculated CLcr consistent with the dosing strategy in renally impaired adults. Paediatric/adolescent subjects received an initial dose of 14 mg/kg or 12 mg/kg (not to exceed 600 mg) regardless of renal function, followed first by a delay and then a twice daily maintenance dose according to their effective renal function.

Haemodialysis and peritoneal dialysis are likely to remove zanamivir from the circulation. Zanamivir is also expected to be removed by CRRT and it seems appropriate that the dose should be selected using the appropriate CRRT clearance for the patient. Although the PK appeared similar compared to subjects not receiving such supportive measures, data are available for only a limited number of subjects on CRRT and no definite conclusions can be drawn. Additionally, there are limited data on patients on dialysis.

Subject 1191 in **NAI113678** had very high plasma concentrations, which is most likely explained by a sampling error where blood was drawn from the infusion arm.

*Gender*: The popPK analysis did not support a co-variate effect on the PK and no dose adjustment accounting for gender is recommended.

*Race:* In a popPK analysis race was not shown to impact on zanamivir CL, however the dataset consisted of predominantly Caucasians. No dose adjustment according to race is proposed which is found acceptable.

*Impaired liver function:* The effect of liver impairment on zanamivir PK has not been assessed which is acceptable considering the low protein binding and predominant renal elimination of zanamivir.

*Weight*: Creatinine clearance appears to play a more dominant role in describing CL than WT, and weight was not included as a covariate in the popPK model (see above).

*Elderly:* No dedicated PK study in the elderly was performed. The popPK analysis did not support a co-variate effect on the PK and no dose adjustment is required based on age.

*DDI:* Zanamivir is primarily renally eliminated and no metabolites have been identified. The absence of studies investigating zanamivir as a CYP enzyme substrate is thus acceptable.

The CYP inhibition and induction interaction potential at clinically relevant concentrations is low. Likewise, the transporter inhibition potential of zanamivir is low. Zanamivir is not a substrate of human drug transporters. Based on a SIMCYP Physiologically Based Pharmacokinetic (PBPK) model, the risk of CYP3A4 induction at clinically relevant concentrations is considered to be low. The current PBPK model and qualification data set for this application can therefore be considered acceptable to indicate a low risk of CYP3A4 induction with zanamivir 600 mg IV BID and the proposed SmPC wording (SmPC 4.5 and 5.2) is agreed. It is also considered that the clinical risk is reduced by the short-term administration of zanamivir and its proposed use in a hospitalised setting where potential drug interactions can be monitored.

The *in vivo* DDI study investigating the impact of zanamivir on oseltamivir PK was performed in healthy Thai subjects, which may not be representative to the Caucasian population. However, published literature indicates that renal transporters OAT1 and OAT2 have low potential for genetic and functional diversity.

No other *in vivo* studies investigating the DDI potential when zanamivir is combined with other commonly used medications (*e.g.* paracetamol) have been performed.

**Primary pharmacology**

Study **NAIA 1010** was a double-blind, placebo-controlled, parallel study in 16 healthy male serologically susceptible (HI antibody titer of ≤1:8 to the challenge strain) subjects to evaluate the effect of zanamivir administered intravenously in preventing illness and reducing viral replication following inoculation with influenza A virus. The infection rate was the main endpoint, but a number of other evaluations were performed, including clinical symptoms, serum hemagglutination inhibition antibody, nasal discharge and cytokines (IL-6 and TNF-α).

This challenge study in healthy volunteers represent a proof of concept for the ability to zanamivir to prevent influenza A infection, virus replication and disease symptoms when IV zanamivir is administered 4 hours prior to virus inoculation. This was an experimental placebo-controlled challenge study in 16 healthy males, not influenza patients. Also, IV zanamivir was given prior to inoculation with influenza virus, so the relevance to the indication applied for is minor.

**Clinical Virology / Resistance**

See discussion on clinical efficacy for more details on virology from the clinical studies.

The most commonly occurring influenza virus oseltamivir resistance substitution (H275Y) confers high level resistance to oseltamivir (and moderate level resistance to peramivir), but remains sensitive to zanamivir. In 2007-2009 viruses harbouring the H275Y substitution became widespread and within one year comprised nearly 100% of circulating influenza A/H1N1 viruses. There was a low incidence of H275Y during the Phase III study (NAI114373) so it was not possible to demonstrate clinical efficacy of IV zanamivir in this population.

In the setting of widespread resistance to oseltamivir or peramivir, zanamivir may be the only available treatment option for patients with influenza.

Many patients identified with oseltamivir resistant virus are also immunocompromised and thus at high risk of severe illness and complications of influenza, as well as a longer duration of severe illness due to a reduced ability to clear virus. Published reports from the IV zanamivir Compassionate Use Program highlight a number of these cases for whom IV zanamivir was requested due to the current lack of adequate treatment options.

Resistance to zanamivir during treatment is rare reflecting its high barrier to resistance. Resistance to zanamivir was not observed in more than 14,000 subjects participating in treatment and prophylaxis clinical studies evaluating the inhaled zanamivir formulation, although the first report of resistance was in an immunocompromised child in 1998. In the IV zanamivir clinical studies, 1 resistance substitution was detected in an immunocompromised adult (N=130) and 1 in an immunocompetent child in study NAI113678 (N=71), who received prior oseltamivir treatment. In NAI114373, 1 potential resistance substitution was detected on Day 2 in an immunocompetent subject in the 300 mg arm (N=163) and none were detected in the 600 mg arm (N=162).

**Secondary pharmacology**

A phase I, randomised, placebo-controlled, four-way crossover study was performed to evaluate the effect of intravenous zanamivir on cardiac conduction as assessed by 12-lead electrocardiogram with moxifloxacin as a positive control in healthy volunteers.

Zanamivir pharmacokinetics from IV administration demonstrated low inter-subject variability (12-19%) and was dose proportional from the 600 mg and 1200 mg doses.

The study was sensitive enough to detect the effect of moxifloxacin, the positive control on QTcF, confirming that this study was valid for assessing the effects of IV zanamivir on cardiac repolarization.

IV zanamivir had no effect on cardiac repolarisation at either the anticipated therapeutic dose (600 mg) or supra-therapeutic (1200 mg) dose.

**DER relationships**

With only one dose level (and dose adjustments according to renal function) in study **NAI113678**, the variability in exposure was not sufficient to elucidate a PKPD relationship. Additionally, the investigated doses of 300mg and 600 mg (study **NAI114373** and PKPD model) are potentially at the flat higher end of the PKPD curve.

The applicant has in a response explained why it is considered that comparing plasma and Epithelial Lining Fluid (ELF) exposures with IC values is a valid approach to justifying the clinical dose. Pharmacokinetic studies of zanamivir have demonstrated drug penetration into the pulmonary compartment following intravenous (IV) administration of 600 mg zanamivir and have established the ELF drug trough concentrations as 419 ng/ml. It has also been shown that following IV administration of zanamivir 600 mg dose BID, drug concentrations in ELF are 73% of serum drug concentrations. During influenza infection, viral replication takes place in the pulmonary compartment which is the same site ELF drug concentrations are measured and is therefore the appropriate site to measure drug concentrations for efficacy. ELF 12-hour concentrations (trough) were comparable following twice daily administration of oral inhaled zanamivir 10 mg (the approved dose) and twice daily administration of IV zanamivir 600 mg.

There is currently lack of a clearly defined pharmacokinetic (PK)/pharmacodynamic (PD) parameter linked to virologic (and clinical) efficacy for inhaled zanamivir or IV zanamivir. In an experimental *in vitro* hollow-fiber infection model utilizing oseltamivir sensitive and oseltamivir-resistant viruses, investigators at the Center for Biodefense and Emerging Infections at the Center for Medical Sciences predicted AUC/half maximal effective concentration (EC50) as the PD index for IV zanamivir 600 mg if dosed every 8 hours, which is the same predicted PD marker for other NAI in this model. However, when dosed at 600 mg every 12 hours, the Time >EC50 was the PD index that best predicted suppression of viral replication. Zanamivir drug concentrations above viral IC50 values provided sustained viral suppression, reducing peak viral titres by approximately 4 log10 PFU/ml and reducing the probability of resistance selection. Therefore, a single PK/PD index may not be sufficient to describe optimal therapeutic regimens for all patient groups.

The applicant stressed that several prior applications for various antiviral agents have also focussed on trough levels being maintained over *in vitro* values derived from enzyme and/or viral inhibition studies. At this stage it seems unlikely that it would be fruitful to pursue this matter. The relationship between serum and ELF concentrations and the IC50 or IC90 values has been well described and do suggest that the selected dose would be adequate to exert the described antiviral effect.

## 2.4.5. Conclusions on clinical pharmacology

Considering the relatively simple PK of zanamivir, the clinical pharmacological investigation programme is overall acceptable.

The challenge study in healthy volunteers represents a proof of concept for the ability of zanamivir to prevent influenza A infection, virus replication and disease symptoms when IV Zanamivir is administered 4 hours prior to virus inoculation. This was an experimental placebo-controlled challenge study in 16 healthy males, not influenza patients. Also, IV zanamivir was given prior to inoculation with influenza virus, so the relevance to the indication applied for is minor.

The most commonly occurring influenza virus oseltamivir resistance substitution (H275Y) confers high level resistance to oseltamivir (and moderate level resistance to peramivir), but remains sensitive to zanamivir. There was a low incidence of H275Y during the Phase III study (NAI114373) so it was not possible to demonstrate clinical efficacy of IV zanamivir in this population. In the setting of widespread resistance to oseltamivir or peramivir, zanamivir may be the only available treatment option for patients with influenza.

It should be noted that section 5.1 of the SmPC has been revised to add a section on resistance:

*Resistance*

*Resistance selection during zanamivir treatment is rare. Reduced susceptibility to zanamivir is associated with mutations that result in amino acid changes in the viral neuraminidase or viral hemagglutinin or both. Neuraminidase substitutions conferring reduced susceptibility to zanamivir have emerged during treatment with zanamivir in human viruses and those with zoonotic potential: E119D, E119G, I223R, R368G, G370D, N434S (A/H1N1); N294S, T325I (A/H3N2); R150K (B); R292K (A/H7N9). The neuraminidase substitution Q136K (A/H1N1 and A/H3N2), confers high level resistance to zanamivir but is selected during adaptation to cell culture and not during treatment.*

*The clinical impact of reduced susceptibility in these viruses is unknown, and the effects of specific substitutions on virus susceptibility to zanamivir may be strain-dependent.*

A phase I placebo-controlled QT study was sensitive enough to detect the effect of moxifloxacin, the positive control on QTcF, confirming that this study was valid for assessing the effects of IV zanamivir on cardiac repolarization. IV zanamivir had no effect on cardiac repolarisation at either the anticipated therapeutic dose (600 mg) or supra-therapeutic (1200 mg) dose.

In vitro studies indicate that zanamivir is not an inhibitor or substrate of Breast Cancer Resistant Protein (BCRP), P-glycoprotein, Multidrug And Toxin Extrusion protein (MATE)1, MATE2-K, Organic Anion Transporter (OAT)1, OAT3, Organic Anion Transporting Polypeptide (OATP)1B1, OATP1B3 and Organic Cation Transporter (OCT)2 transporters, nor is it an inhibitor of cytochrome P450 (CYP) enzymes CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4.

Zanamivir is not an inducer of CYP1A2 and 2B6 and, although induction of CYP3A4 *in vitro* was observed at 50-fold higher than the clinically relevant concentrations, no interaction with CYP3A4 substrates is expected based on physiologically based pharmacokinetic modelling.

## *2.5. Clinical efficacy*

The following studies or datasets are considered in this section:

**Table 7. Overview of clinical studies**

| **Study reports and related information of controlled clinical studies** |
|---|
| NAI114373: A Phase III international, randomized, double-blind, double-dummy study to evaluate the efficacy and safety of 300 mg or 600 mg of intravenous zanamivir twice daily compared to 75 mg of oral oseltamivir twice daily in the treatment of hospitalized adults and adolescents with influenza |
| **Study reports and related information of uncontrolled clinical studies** |

| |
|---|
| NAI113678: An open-label, multi-centre, single arm study to evaluate the safety and tolerability of intravenous zanamivir in the treatment of hospitalized adult, adolescent and paediatric subjects with confirmed influenza infection - Adult cohort and paediatric cohort reported separately |
| NAI115215: An open-label, multi-centre, single arm study to evaluate the safety and efficacy of intravenous zanamivir in the treatment of hospitalized patients with confirmed influenza infection [Japanese subjects] |
| **Other Clinical Study Reports (including on-going study synopses)** |
| REL113375: Zanamivir aqueous solution for compassionate use in serious influenza illness |
| NAI115008: Zanamivir aqueous solution compassionate use program retrospective chart review |

**NAI114373.** The main study NAI114373 was randomized, double-blind, with three arms comparing 600 mg IV Zanamivir with comparator 75 mg oral oseltamivir and 300 mg IV Zanamivir.

The primary objective was to assess the efficacy of 600 mg of IV Zanamivir twice daily compared to 75 mg of oral oseltamivir twice daily, and 600 mg IV Zanamivir twice daily compared to 300 mg IV Zanamivir twice daily on time to clinical response (TTCR). The patient population was hospitalised adults and adolescents (> 16 years) with influenza.

Due to lack of randomized studies in patients hospitalised for influenza comparing the effect of neuraminidase inhibitors with placebo, a non-inferiority margin to compare Zanamivir with oseltamivir could not be estimated. Therefore, a superiority analysis for the primary endpoint was the only option for a formal statistical comparison.

**NAI113678.** The supportive study was open-label, single arm.

The primary objective was to assess the safety and tolerability of intravenous (IV) Zanamivir in the treatment of hospitalised adult, adolescent and paediatric subjects with influenza infection. Children age categories: 6 months<1 year, 1 to <2 years, 2 to <6 years, 6 to <13 years, 13 to <18 years.

This was mainly a safety study, but virology and clinical endpoints as well as pharmacokinetics were included. The study was initiated in 2009 during the H1N1 pandemic and for the adult population H1N1pdm2009 was the dominating strain. With no control arm, it is not possible to evaluate efficacy based on clinical endpoints. Due to large variability in influenza disease progress and outcome, the use of historical control data is of little value.

**NAI115215:** The primary objective was to assess the safety and tolerability of 600 mg of IV Zanamivir twice daily in the treatment of hospitalised subjects with influenza infection.

The study title includes “to evaluate safety and efficacy”. With no control arm, it is not possible to evaluate efficacy based on clinical endpoints.

**NAI115008:** This was an observational, retrospective, multi-centre, cohort data collection study. The treating physician/delegate reviewed the patient’s chart and recorded data including demographics, medical data, safety variables and treatment outcomes on a paper CRF. Efficacy cannot be evaluated from this study.

## 2.5.1. Dose response studies

The rationale for selecting 600 mg IV zanamivir hydrate BID as the dose for clinical investigation in hospitalised patients with influenza was based on results from nonclinical studies and clinical studies:

- Nonclinical safety and exposure data.
- **NAI106784**: Pharmacokinetic (PK) study in bronchoalveaolar lavage (BAL) following inhaled and IV Zanamivir hydrate administration demonstrating similar pulmonary exposure between the approved 10 mg inhaled Zanamivir hydrate dose and the 600 mg IV Zanamivir hydrate dose.
- **NAIA1010**: An experimental influenza challenge study in healthy volunteers demonstrating the significant clinical prophylactic and antiviral effect of 600 mg IV Zanamivir hydrate BID.
- Compassionate Use Programme (**REL113375**): Zanamivir hydrate (600 mg BID) aqueous solution supply on a compassionate use basis to hospitalised patients with serious influenza illness who have no other treatment options (Ongoing since May 2009 with >3,000 patients treated).

In the clinical development programme for IV Zanamivir hydrate the dosage regimen of 600 mg BID was investigated in both the Phase II (**NAI113678**) and single pivotal Phase III (**NAI114373**) studies. An additional dosing regimen of 300 mg BID was investigated in the single pivotal Phase III study (**NAI114373**) as a result of CHMP scientific advice with lack of formal dose-ranging in the development programme been noted.

## Main study

**NAI 114373:**

**A Phase III international, randomized, double-blind, double-dummy study to evaluate the efficacy and safety of 300 mg or 600 mg of intravenous zanamivir twice daily compared to 75 mg of oral oseltamivir twice daily in the treatment of hospitalized adults and adolescents with influenza**

### *Methods*

### *Study Participants*

**Eligible subjects** were aged at least 16 years with:

Fever [oral temperature ≥38 $^0$C, rectal/core, tympanic ≥38.5 $^0$C or axilla ≥37.4 $^0$C] or history of fever within the prior 24 h or reported feverishness within the prior 48 h

AND at least 2 out of the following 4:

- *Oxygen saturation <95%* on room air by trans-cutaneous method or need for any supplemental oxygenation or ventilatory support or increase in oxygen supplementation requirement of ⩾2 litres for subjects with chronic oxygen dependency; in chronic hypoxia without supplemental oxygen an oxygen saturation ⩾ 3% below the historical baseline oxygen saturation was required
- *Respiration rate >24 breaths per minute* (unless receiving ventilatory support or oxygen supplementation)
- *Heart rate >100 beats per minute*
- *Systolic blood pressure <90 mmHg*

Onset of influenza symptoms was to be within 6 days prior to enrolment with a positive influenza diagnostic test result or strong suspicion of influenza based on local surveillance information.

There was to be sufficient severity of any medical illness that, in the Investigator's judgement, justified hospitalisation of the subject for treatment and supportive care.

The main **exclusion criteria,** in addition to hypersensitivity were:

- Subjects who had taken more than a total of 3 days of approved anti-influenza therapy in the period from onset of symptoms and prior to enrolment.

- Subjects who, in the opinion of the investigator were not likely to survive beyond 48 hours from Baseline.

- Subjects with creatinine clearance ≤ 10 ml/min.

- Subjects who required (ECMO) at Baseline.

- Subjects with liver toxicity or underlying chronic liver disease or history of severe cardiac disease.

This included, but was not limited to subjects who were intubated/ventilated, pregnant, immunocompromised, HIV positive or had renal impairment and subjects who may have received prior licensed anti-influenza medication.

## *Treatments*

**IV Zanamivir hydrate**

Zanamivir hydrate aqueous solution, 10 mg/ml, was supplied as a single use, sterile clear, colorless preparation tonicity adjusted with sodium chloride and presented in 20 ml clear glass vials closed with rubber stoppers. Each vial contained 200 mg Zanamivir hydrate.

Zanamivir hydrate aqueous solution could have been administered as supplied or as an infusion in 0.9% sodium chloride for intravenous administration.

**Placebo to Match IV Zanamivir hydrate**

No vials of placebo to match IV Zanamivir hydrate were provided, instead a normal saline solution of a matched volume was prepared by an unblinded pharmacist at site to act as a placebo to active IV Zanamivir hydrate.

**Oral Oseltamivir**

Oseltamivir (TAMIFLU) was provided as 75 mg capsules (Roche Pharmaceuticals). Product for this study was sourced in the US and was over-encapsulated.

Over-encapsulation of oseltamivir was necessary to maintain the study blind. There were no other manipulation or changes to the capsule or the active powder contained within the capsule. GSK has conducted *in vitro* dissolution testing of marketed oseltamivir capsules in comparison to the over-encapsulated capsules and, as expected, there was a small delay (10-20 minutes) in the time for complete dissolution of the over-encapsulated oseltamivir relative to the standard capsule; however, both forms were fully dissolved within approximately 30 minutes. Oseltamivir is a prodrug that is readily absorbed and extensively converted over approximately 4 hours to the active metabolite, oseltamivir carboxylate, which is responsible for its antiviral activity. GSK has conducted a bioequivalence study evaluating the pharmacokinetic properties of the over-encapsulated oseltamivir 75 mg capsules used as a blinded comparator in this study relative to the commercially available 75 mg capsules. Results from the study demonstrated bioequivalence of the over-encapsulated and commercial capsules [Study NAI115096].

**Placebo to Match Oseltamivir**

Placebo to match oral oseltamivir was supplied as capsules with a common excipient of appropriate quality.

**Dose and Administration**

Subjects were randomized in a 1:1:1 ratio to one of three treatment arms.

| **Arm** | **Dose and Dose Interval**1 | |
|---|---|---|
| Treatment Arm A | 300 mg IV Zanamivir hydrate twice daily | Placebo to match oral oseltamivir twice daily |
| Treatment Arm B | 600 mg IV Zanamivir hydrate twice daily | Placebo to match oral oseltamivir twice daily |
| Treatment Arm C2 | 75 mg oral oseltamivir twice daily | Placebo to match IV Zanamivir hydrate twice daily |

1. Dose adjusted for weight and renal impairment
2. Treatment Arm C could have been discontinued temporarily or permanently in the event of widespread oseltamivir resistance if the protocol defined study design change criteria had been met.

Subjects randomised to IV Zanamivir hydrate received placebo to match oral oseltamivir twice daily. Subjects randomised to oral oseltamivir received a normal saline infusion as a placebo to match IV Zanamivir hydrate.

Where possible, the IV and oral IP were administered at approximately the same time.

Subjects and all site staff were blinded to the study treatment. However, the pharmacist (or an appropriately qualified member of staff not involved in the routine care and management of subjects) was unblinded to allow preparation of study drugs.

**Duration of Treatment**

The duration of randomized treatment was 5 days. However, for a given subject, the initial 5-day treatment course may have been extended for up to 5 additional days if clinical symptoms or patient characteristics as assessed by the investigator warranted further treatment. Alternatively, if the investigator considered that a subject was failing to improve clinically on their randomized treatment, the investigator could choose to initiate the switch/rescue option on Day 6 through Day 10 for up to 5 days. With inclusion of the switch/rescue option, the maximum duration of treatment was up to 14 days.

**Table 8. Initial Dose and Twice Daily Maintenance Dose Regimens of IV Zanamivir hydrate or Placebo for Adult and Adolescent Subjects and Individuals with Renal Impairment**

| **Adults (≥18 years)** | **Initial Dose[1]** | **Maintenance Dose** | | | | |
|---|---|---|---|---|---|---|
| | | **CLcr or CLCRRT (mL/min)** | | | | |
| | | **≥ 80** | **50 to <80** | **30 to <50** | **15 to <30[3]** | **<15 [4]** |
| | 600 mg | 600 mg | 400 mg | 250 mg | 150 mg | 60 mg |
| | 300 mg | 300 mg | 200 mg | 125 mg | 75 mg | 30 mg |
| **Adolescents (16** | **Initial** | **Maintenance Dose** | | | | |

| to <18 years)[2] | Dose[1] | CLcr or CLCRRT (mL/min) | | | | |
|---|---|---|---|---|---|---|
| | | ≥ 80 | 50 to <80 | 30 to <50 | 15 to <30[3] | <15 [4] |
| Weight <50kg | 12 mg/kg | 12 mg/kg | 8 mg/kg | 5 mg/kg | 3 mg/kg | 1.2 mg/kg |
| | 6 mg/kg | 6 mg/kg | 4 mg/kg | 2.5 mg/kg | 1.5 mg/kg | 0.6 mg/kg |
| Weight ≥50kg | 600 mg | 600 mg | 400 mg | 250 mg | 150 mg | 60 mg |
| | 300 mg | 300 mg | 200 mg | 125 mg | 75 mg | 30 mg |

**Key:**

1. The initial dose for each patient was the dose specified for CLcr or CLCRRT ≥80 ml/min.
2. Adolescent subjects with body weight ≥50 kg should have received the same dose as adults with the same degree of renal function. Adult subjects with body weight <50 kg should have received the adult dose.
3. The time interval between initial dose and start of maintenance doses for subjects with CLcr or CLCRRT of 15 to <30 ml/min was 24 hours.
4. The time interval between initial dose and start of maintenance doses for subjects with CLcr or CLCRRT of <15 ml/min was 48 hours.

## *Objectives*

**Primary**

- To assess the efficacy of treatment with 600 mg of IV Zanamivir hydrate twice daily compared to 75 mg of oral oseltamivir twice daily, and 600 mg IV Zanamivir hydrate twice daily compared to 300 mg IV Zanamivir hydrate twice daily on time to clinical response (TTCR).

**Secondary**

- To assess the efficacy of treatment with 600 mg IV Zanamivir hydrate twice daily compared to 75 mg of oral oseltamivir twice daily, and 600 mg IV Zanamivir hydrate twice daily compared to 300 mg IV Zanamivir hydrate twice daily as measured by the combined analysis of TTCR and time to improvement in respiratory status (RS).
- To assess mortality following treatment with 600 mg IV Zanamivir hydrate twice daily compared to 75 mg oral oseltamivir twice daily, and 600 mg IV Zanamivir hydrate twice daily compared to 300 mg IV Zanamivir hydrate twice daily in the treatment of hospitalized adult and adolescent subjects with influenza infection.
- To assess reduction in viral load from nasopharyngeal (NP) swabs (and lower respiratory tract samples, if available) following treatment with 600 mg IV Zanamivir hydrate twice daily compared to 75 mg oral oseltamivir twice daily, and 600 mg IV Zanamivir hydrate twice daily compared to 300 mg IV Zanamivir hydrate twice daily.
- To evaluate clinical measures of influenza illness following treatment with 600 mg IV Zanamivir hydrate twice daily compared to 75 mg oral oseltamivir twice daily, and 600 mg IV Zanamivir hydrate twice daily compared to 300 mg IV Zanamivir hydrate twice daily using a variety of measures including improvement in Katz Activities of Daily Living (ADL) score and ADL activities, improvement in level of activity, duration and severity of influenza symptoms, duration of

hospital stay, duration of Intensive Care Unit (ICU) stay, complications of influenza, associated antibiotic use, modality and duration of invasive and non-invasive ventilator support, duration and quantity of oxygen supplementation and overall and disease specific mortality.

- To assess the safety and tolerability of 600 mg IV Zanamivir hydrate twice daily in comparison to 75 mg oral oseltamivir twice daily, and 600 mg IV Zanamivir hydrate twice daily compared to 300 mg IV Zanamivir hydrate twice daily in the treatment of hospitalized adult and adolescent subjects with influenza infection.
- To assess viral susceptibility and resistance to Zanamivir hydrate and oseltamivir.
- To evaluate Zanamivir hydrate pharmacokinetics (PK) (peak and trough serum concentrations) from 300 mg or 600 mg IV Zanamivir hydrate twice daily in hospitalized adult and adolescent subjects.
- To evaluate time to clinical response and antiviral efficacy in the subset of subjects with influenza virus with reduced susceptibility to oseltamivir and/or presence of H275Y mutation.

## *Outcomes/endpoints*

### *Primary Endpoint*

The primary endpoint was the time to clinical response in subjects with confirmed influenza. Clinical response was defined as *resolution of at least 4 of the 5 signs* described below within the respective resolution criteria, maintained for at least 24 hours, or hospital discharge, whichever occurred first:

| Sign of clinical response | Response criteria |
|---|---|
| Temperature[1] | ≤36.6°C (≤97.9°F) – axilla, or<br>≤37.2°C (≤99°F) – oral, or<br>≤37.7°C (≤99.9°F) – rectal/core[6], tympanic |
| *AND* | |
| Oxygen saturation[2,3,4] | ≥95% (without supplemental oxygen) |
| *AND 2 out of the following 3:* | |
| Respiratory status | 3. Return to pre-morbid oxygen requirement (subjects with chronic oxygen use), OR<br>4. Need for supplemental oxygen (administered by any modality – ventilator, non-invasive ventilation, facemask, facetent, nasal canula, etc) to no need for supplemental oxygen, OR<br>5. Respiratory rate ≤24/min (without supplemental oxygen) |
| Heart rate | ≤100/min |
| Systolic blood pressure[5] | ≥90 mmHg |
| *OR* | |
| Hospital discharge | • Subjects who were discharged from hospital were considered to have met the clinical response endpoint at the time of hospital discharge and were not required to have documented resolution of at least 4 response criteria (i.e. achieved success at the time of discharge if not observed prior to it). |

1. Without the use of antipyretics within 8 hours
2. A subject with a history of chronic hypoxia (without supplemental oxygen) satisfied normalization criteria for oxygen saturation if the value (without supplemental oxygen) was ≤2% from subject's historical oxygen saturation baseline as recorded within 12 months prior to enrolment as documented in the subject's medical records.
3. This requirement was waived for subjects with a history of chronic supplemental oxygen requirement who had a baseline oxygen saturation <95% with supplemental oxygen, within 12 months prior to enrolment as documented in the subject's medical records.

4. Footnote 4 removed in Protocol Amendment 02.
5. Without inotropic support administered within 2 hours.
6. Core temperatures include measurements via a temporal thermometer, indwelling catheters and Swan Ganz catheters

**Note:**
For subjects who achieved 4 out of the 5 vital sign resolution criteria above, maintained for at least 24 hours, it was mandatory that both the temperature and oxygen saturation response criteria were achieved in order for the clinical response endpoint to be met.

***Secondary Efficacy Endpoints***

- The combined analysis of TTCR and time to improvement in RS.
- Mortality rate at Day 14, Day 28 and end of study (all cause and attributable mortality).
- Change from Baseline in Katz ADL score and each ADL activity between treatment arms at Day 5/6, and Day 10/11 and Day 14 if treatment is extended beyond 5 days, and end of study (PT +28 Days).
- Time to return to pre-morbid functional status as measured by the Katz ADL score and each ADL activity.
- Proportion of subjects in each treatment arm who have returned to pre-morbid functional status by the Katz ADL score and each ADL activity at the end of study (PT +28 Days).
- Time to return to pre-morbid level of activity as measured by the 3 point scale [bed rest, limited ambulation or unrestricted].
- Incidence and duration of clinical symptoms of influenza.
- Incidence of complications of influenza and associated antibiotic use.
- Ventilation status: modality and duration of invasive and non-invasive ventilator support, duration and quantity of oxygen supplementation.
- Length of ICU and hospital stays as assessed from 1st day of dosing.
- Time to absence of fever, time to improved respiratory status, oxygen saturation, heart rate and systolic blood pressure (as defined in the clinical response criteria).

**Virologic Endpoints**

- Time to virologic improvement, defined as a 2 log drop in viral load or sustained undetectable viral RNA (on 2 successive occasions) as measured by qPCR from nasopharyngeal samples.
- Time to no detectable viral RNA by qPCR from nasopharyngeal samples.
- Time to no detectable virus as measured by quantitative viral culture from nasopharyngeal samples.
- Change from Baseline in quantitative viral load as measured by qPCR and qVC from nasopharyngeal swabs on Day 3 and Day 5, and Day 8, Day 10 and/or last day of randomized treatment, if randomized treatment is extended beyond 5 days, and S/R Day 5/6 (up to Day 14), if applicable.
- Proportion of subjects in each treatment arm with undetectable viral RNA by qPCR and absence of cultivable virus from nasopharyngeal samples on Day 3 and 5, and Day 8, Day 10 and/or last day of randomized treatment, if randomized treatment is extended beyond 5 days, and S/R Day 5/6 (up to Day 14), if applicable.
- Proportion of subjects in each treatment arm with no detectable viral RNA during treatment by qPCR and absence of cultivable virus in lower respiratory samples, if collected.

- Time to no detectable viral RNA by qPCR and absence of cultivable virus in any obtained sample (upper and lower respiratory samples).
- Viral susceptibility to zanamivir hydrate and oral oseltamivir at Baseline and throughout treatment by NA and HA sequence analysis and NA enzyme inhibition assay. Minority species harbouring resistance associated mutations explored by clonal analysis or ultradeep 454 nucleotide sequencing and will be subject to a separate report.

### *Sample size*

The study was planned to have 160 influenza positive subjects per arm at a two-sided significance level of $\alpha$ =0.05 and power of over 90% under the assumptions of 1.5 days difference between the primary comparisons (i.e., the 600 mg IV zanamivir hydrate arm versus oral oseltamivir arm or the 600 mg IV Zanamivir hydrate arm versus 300 mg IV zanamivir hydrate arm) and standard deviation of 4 days based on TTCR. Therefore, a total of 600 subjects were planned to be enrolled into the study in order to have 480 influenza positive subjects assuming an estimated 80% of subjects were influenza positive. The power was 84% at a two-sided $\alpha$ =0.02 under the same assumptions.

At the final analysis, the primary endpoint of TTCR was tested at a 2-sided $\alpha$ = 0.02 for each of the two pairwise comparisons in IPP. Additionally, these tests were performed at a 2-sided $\alpha$ = 0.0075 in the two pre-specified subgroups. The alpha levels for the statistical tests and comparisons were chosen empirically with the aim of controlling the overall Type 1 error at 5% under multiplicity adjustment. The study had over 90% power and 65% power under the assumption of benefit in the symptom onset ≤4 days subgroup and ICU/Mechanical ventilation subgroup, respectively.

Based on the second interim analysis the influenza positive rate was about 78%, therefore 615 subjects were needed to be enrolled in order to have 480 IPP subjects.

### *Randomisation*

Subjects were assigned to study treatment in accordance with the randomization schedule. Subjects were stratified based on time from onset of symptoms to initiation of treatment into one of two strata (≤4 days and 5 to 6 days) prior to randomization.

Randomization was conducted via a central randomization procedure following confirmation of fulfilment of study entry criteria. Subjects were randomized in a 1:1:1 ratio to study treatment in accordance with the computer generated randomisation schedule. The randomisation schedule, including stratification, was generated using the GSK validated randomization software RANDALL.

GSK used an interactive voice response system, Registration and Medication Ordering System (RAMOS), for registration of subjects. Study site personnel were required to call RAMOS to register each subject participating in the study. Upon randomization, subjects were allocated a treatment number. Oseltamivir/placebo treatment assignment information was provided via RAMOS, and the unblinded pharmacist referred to the randomization schedule for zanamivir hydrate/placebo treatment assignment information.

## *Blinding (masking)*

This was a double-blind, double-dummy study and both subject and study staff were blinded to treatment, however an unblinded pharmacist (or an appropriately qualified member of staff not involved in the routine care and management of subjects) at each study site was unblinded to allow preparation of study drugs.

During the blinded randomized treatment period, subjects received an IV infusion (zanamivir hydrate or placebo) twice daily plus an oral therapy (oseltamivir or placebo) twice daily via the unblinded pharmacist.

- **IV infusion:** An unblinded pharmacist prepared an IV infusion of active zanamivir hydrate (300 mg or 600 mg, adjusted for renal function as appropriate) or a normal saline infusion for each subject twice daily.
- **Oral therapy:** An unblinded pharmacist prepared an oral therapy (oseltamivir or placebo) for each subject twice daily (or once daily dependent on renal function). For subjects who could swallow capsules, the oral therapy was administered as blinded capsules. For subjects who could not swallow capsules, oseltamivir powder/placebo powder was extracted from the capsule and mixed with food, or prepared as a suspension for administration via nasogastric, nasojejunal or gastrostomy tube.

Treatment codes could be unblinded by the investigator or treating physician only in the case of a medical emergency or in the event of a serious medical condition, when knowledge of the investigational product was essential for the clinical management or welfare of the subject. GSK Global Clinical Safety and Pharmacovigilance (GCSP) staff could unblind treatment codes in the event of a serious adverse event (SAE).

## *Statistical methods*

Analysis populations for efficacy

- Intent-To-Treat Exposed Population (ITT-E) = all treated
- Influenza Positive Population (IPP) = ITT-E population with proven influenza (positive PCR, culture or serology test as determined by the central virology laboratory). The IPP was used for the primary efficacy analyses.
- Influenza Positive, Oseltamivir Resistant Population (IPR) = IPP with virus showing reduced susceptibility to oseltamivir and/or presence of H275Y; this was not used due to too few subjects.
- Per Protocol Population (PP) = IPP who had post-baseline data and no important protocol deviations. The PP population was used for sensitivity analysis in the primary efficacy comparisons.

Subpopulations and subgroups

Sub-populations of interest were created as subsets of the ITT-E or IPP populations, including randomisation strata, viral load, demographic category, age and ethnic origin categories and/or geographic locations.

Interim analyses

The first interim analysis was conducted when 150 subjects had completed the study to determine whether one dose of IV zanamivir was more favourable than the other (based on safety, clinical and virologic assessments), whether one or both doses of IV zanamivir were significantly superior to oseltamivir, or whether there were insufficient data to recommend discontinuation of a treatment arm.

The statistical comparisons on the primary efficacy endpoint between the zanamivir and oseltamivir groups were performed at alpha level of 0.001. This interim analysis was carried out by the IDMC in December 2012 and conditional power estimates and confidence intervals at various significance levels were included for IDMC review.

The second interim analysis was conducted when ~450 subjects had completed the study to determine if there was sufficient evidence to justify continuing the study to the target sample size of 600 subjects. This second interim analysis was reviewed by the IDMC in August 2014 and allowed for the option of stopping the study for futility. At the request of the IDMC the median difference in TTCR between 600 mg IV zanamivir and the comparator as well as the associated 95% CI were also provided prior to the IDMC meeting.

The recommendation from both the first and second interim analyses was to continue the study with all three treatment arms. Data from the first and second interim analysis were blinded, except to the IDMC.

Final analyses

The final statistical analysis and comparison were performed via van Elteren extension of the Wilcoxon rank-sum test stratified by the randomisation stratification factor (time from symptom onset). Multiplicity and overall type I error were controlled at approximately 5%. Within each pairwise comparison the fall-back procedure was applied to the following ordered hypothesis tests with the initial pre-specified alpha level: *H1* - Onset ≤4 days subgroup ($\alpha$1=0.0075), *H2* - ICU subgroup (α2=0.0075), *H3* – influenza positive population (α3=0.02).

Time to clinical response

Two strategies were employed in the determination of TTCR regarding premature discontinuation and/or therapy switch prior to reaching the clinical response endpoint, with strategy a) as the primary efficacy analysis, and strategy b) as a sensitivity analysis.

a) Discontinuation/Switch = Failure approach: classified subjects who prematurely discontinued and/or switched therapy prior to clinical response as failure if clinical response had not been achieved. Otherwise, success or failure of TTCR was determined by the data. All failures were assigned a worst value for TTCR (e.g. 99 days).

b) Observed approach: Used all available data to determine a subject's success or failure of TTCR, regardless of premature discontinuation or therapy switch. Missing data were not imputed. As in a), a failure was assigned a worst value to TTCR (e.g. 99 days).

Death was considered a failure and assigned a worst value for both cases but deaths which occurred after clinical response were not considered as failures. Subjects discharged from hospital were considered to have met the clinical response endpoint at the time of discharge if TTCR had not been observed.

Changes in planned analyses

After the first interim analysis, resulting in an increase to the sample size to 600 subjects, a protocol amendment (04) was implemented to introduce a second interim analysis to inform and the statistical analysis framework was updated to allow for consideration of additional evidence beyond the original primary and secondary endpoints.

## *Results*

## Participant flow

**Table 9. Summary of subject disposition (ITT-E Population)**

| | IV Zanamivir hydrate 300 mg | IV Zanamivir hydrate 600 mg | Oseltamivir 75 mg (N=205) | Total (N=615) |
|---|---|---|---|---|
| Completion Status, n (%) | | | | |
| Completed | 175 (87) | 178 (85) | 166 (81) | 519 (84) |
| Prematurely Withdrawn | 26 (13) | 31 (15) | 39 (19) | 96 (16) |
| Primary reason for Withdrawal, n (%) | | | | |
| Adverse Event | 14 (7) | 16 (8) | 12 (6) | 42 (7) |
| Lost to follow-up | 3 (1) | 4 (2) | 9 (4) | 16 (3) |
| Investigator discretion | 3 (1) | 5 (2) | 10 (5) | 18 (3) |
| Withdrew consent | 6 (3) | 6 (3) | 8 (4) | 20 (3) |

## Recruitment

Initiation date: 15.01.2011

Completion date: 18.03.2015

The study duration was approximately 33 days for subjects whose treatment duration was 5 days, up to approximately 38 days for subjects whose randomized treatment duration was extended to a maximum of 10 days, and up to approximately 42 days for subjects whose randomized and switch/rescue (S/R) treatment was extended to a maximum of 14 days. The study consisted of Pre-dose Baseline Assessments (Day 1), During Treatment Assessments (Days 1 to 5/6, up to Day 10/11, and S/R Days 1 to 5/6), and daily Post-Treatment Assessments (PT +1 to +28 Days) while a subject remained hospitalized, or PT Assessments on PT +1 to +5, +9, +12, +16, +23, +28 Days if the subject had been discharged from hospital.

## Conduct of the study

Four amendments to the protocol were made; they either occurred early or involved simple administrative changes that did not affect the conduct of the study. The exception was the last amendment, when 425 had been enrolled. This amendment added a second interim analysis when ~450 subjects had completed the study or when those randomised by the end of the 2013/2014 Northern Hemisphere influenza season (31 March 2014) had completed the study, whichever occurred first. In addition, the statistical analysis framework was updated to add some secondary analyses.

Important protocol deviations were reported for 142 subjects (23%) in the ITT-E population with a similar across treatment groups. The most common were deviations related to treatment and administration which occurred in 10% subjects overall.

## Baseline data

**Table 10. Summary of baseline demographic characteristics (ITT-E Population)**

| | IV Zanamivir hydrate 300 mg | IV Zanamivir hydrate 600 mg | Oseltamivir 75 mg (N=205) | Total (N=615) |
|---|---|---|---|---|
| Age in Years, Median (Min, Max) | 57 (15, 95) | 58 (16, 101) | 57 (18, 94) | 57 (15, 101) |
| Age Category in Years, n (%) | | | | |
| ≥15 to ≤20 | 7 (3) | 3 (1) | 4 (2) | 14 (2) |
| >20 to ≤30 | 20 (10) | 7 (3) | 19 (9) | 46 (7) |
| >30 to ≤40 | 17 (8) | 29 (14) | 29 (14) | 75 (12) |
| >40 to ≤50 | 36 (18) | 38 (18) | 30 (15) | 104 (17) |
| >50 to ≤60 | 36 (18) | 41 (20) | 30 (15) | 107 (17) |
| >60 to ≤70 | 38 (19) | 32 (15) | 40 (20) | 110 (18) |
| >70 to ≤80 | 29 (14) | 40 (19) | 34 (17) | 103 (17) |
| >80 to ≤90 | 17 (8) | 16 (8) | 18 (9) | 51 (8) |
| >90 | 1 (<1) | 3 (1) | 1 (<1) | 5 (<1) |
| Sex, n (%) | | | | |
| Female | 82 (41) | 86 (41) | 117 (57) | 285 (46) |
| Male | 119 (59) | 123 (59) | 88 (43) | 330 (54) |
| Ethnicity, n (%) | | | | |
| Hispanic or Latino | 20 (10) | 14 (7) | 27 (13) | 61 (10) |
| Not Hispanic or Latino | 171 (85) | 193 (92) | 173 (84) | 537 (87) |
| Missing | 10 (5) | 2 (<1) | 5 (2) | 17 (3) |
| Race, n (%) | | | | |
| African American/African | 12 (6) | 4 (2) | 10 (5) | 26 (4) |
| American Indian or Alaskan | 3 (1) | 2 (<1) | 4 (2) | 9 (1) |
| Central or South Asian | 10 (5) | 15 (7) | 13 (6) | 38 (6) |
| East Asian | 12 (6) | 18 (9) | 13 (6) | 43 (7) |
| South East Asian | 6 (3) | 4 (2) | 7 (3) | 17 (3) |
| Hawaiian or other Pacific Islander | 2 (<1) | 1 (<1) | 0 | 3 (<1) |
| White - Arabic/North African | 4 (2) | 3 (1) | 3 (1) | 10 (2) |
| White/Caucasian/European | 150 (75) | 162 (78) | 154 (75) | 466 (76) |
| Unknown | 1 (<1) | 0 | 1 (<1) | 2 (<1) |
| Mixed race | 1 (<1) | 0 | 0 | 1 (<1) |
| Height in cm, Median (Min, Max) | 168 (146, 196) | 167 (142, 196) | 165 (140, 191) | 167 (140, 196) |
| Weight in kg, Median (Min, Max) | 76 (36, 173) | 73 (38, 188) | 75 (30, 200) | 75 (30, 200) |
| Body Mass Index (BMI) in kg/m$^2$, Median (Min, Max) | 26 (16, 53) | 26 (15, 66) | 27 (13, 60) | 27 (13, 66) |
| BMI Category, n (%) | | | | |
| ≤20 | 15 (7) | 25 (12) | 20 (10) | 60 (10) |
| >20 to ≤25 | 68 (34) | 64 (31) | 50 (24) | 182 (30) |
| >25 to ≤30 | 57 (28) | 48 (23) | 68 (33) | 173 (28) |
| >30 to ≤35 | 25 (12) | 35 (17) | 32 (16) | 92 (15) |
| >35 to ≤40 | 24 (12) | 21 (10) | 18 (9) | 63 (10) |
| >40 to ≤45 | 9 (4) | 8 (4) | 7 (3) | 24 (4) |
| >45 | 3 (1) | 7 (3) | 10 (5) | 20 (3) |
| Unknown | 0 | 1 (<1) | 0 | 1 (<1) |
| Tobacco User, n (%) | | | | |
| No | 82 (41) | 96 (46) | 108 (53) | 286 (47) |
| Yes | 117 (58) | 108 (52) | 95 (46) | 320 (52) |
| Unknown | 2 (<1) | 5 (2) | 2 (<1) | 9 (1) |

A total of 468 subjects (76%) had at least one chronic underlying medical condition, the most common (>20% of subjects overall) of which were hypertension, hyperlipidemia, diabetes and chronic obstructive pulmonary disease (COPD).

**Table 11. Summary of Influenza Details at Baseline (ITT-E Population)**

| | IV Zanamivir hydrate 300 mg | IV Zanamivir hydrate 600 mg | Oseltamivir 75 mg (N=205) | Total (N=615) |
|---|---|---|---|---|
| Influenza positive test result by local laboratory, n (%) | 166 (83) | 169 (81) | 156 (76) | 491 (80) |
| Local test result[a], n | 199 | 208 | 204 | 611 |
| Positive by rapid test | 58 (29) | 62 (30) | 60 (29) | 180 (29) |
| Positive by influenza virus antigen test | 21 (10) | 12 (6) | 14 (7) | 47 (8) |
| Positive by PCR | 89 (44) | 94 (45) | 81 (40) | 264 (43) |
| Positive by influenza culture | 13 (6) | 10 (5) | 9 (4) | 32 (5) |
| Negative by rapid antigen test or other laboratory test | 33 (16) | 40 (19) | 50 (24) | 123 (20) |
| Symptoms of influenza[b], n/N (%) | | | | |
| Cough | 157/201 (78) | 168/208 (80) | 169/203 (82) | 494/612 (80) |
| Dyspnoea | 158/201 (79) | 163/209 (78) | 170/205 (83) | 491/615 (80) |
| Feverishness | 154/201 (77) | 167/209 (80) | 152/205 (74) | 473/615 (77) |
| Fatigue | 152/201 (76) | 160/208 (77) | 154/205 (75) | 466/614 (76) |
| Myalgias | 121/201 (60) | 133/209 (64) | 126/204 (61) | 380/614 (62) |
| Nasal symptoms | 111/201 (55) | 123/208 (59) | 112/203 (55) | 346/612 (56) |
| Anorexia | 98/201 (49) | 117/208 (56) | 112/204 (55) | 327/613 (53) |
| Headache | 99/201 (49) | 96/208 (46) | 107/204 (52) | 302/613 (49) |
| Sore throat | 87/201 (43) | 101/208 (48) | 90/204 (44) | 278/613 (45) |
| Nausea | 48/201 (24) | 51/208 (24) | 49/203 (24) | 148/612 (24) |
| Diarrhoea | 36/201 (18) | 30/208 (14) | 28/204 (14) | 94/613 (15) |
| Vomiting | 21/201 (10) | 27/208 (13) | 27/204 (13) | 75/613 (12) |
| Study day of flu-like symptom onset, n | 201 | 209 | 205 | 615 |
| Median (min, max) | -3.0 (-6, 1) | -3.0 (-7, 1) | -3.0 (-6, 1) | -3.0 (-7, 1) |
| Mean (SD) | -3.2 (1.56) | -3.1 (1.70) | -3.1 (1.70) | -3.1 (1.65) |

**Table 12. Summary of Influenza Subtypes (IPP)**

| | IV Zanamivir hydrate 300 mg | IV Zanamivir hydrate 600 mg | Oseltamivir 75 mg (N=163) | Total (N=488) |
|---|---|---|---|---|
| Influenza A, n (%) | | | | |
| A/H1N1pdm09 | 62 (38) | 59 (36) | 62 (38) | 183 (38) |
| A/H3N2 | 74 (45) | 73 (45) | 74 (45) | 221 (45) |
| A/H1N1pdm09 & A/H3N2 co-infection | 1 (<1) | 0 | 0 | 1 (<1) |
| Untyped A | 2 (1) | 2 (1) | 1 (<1) | 5 (1) |
| Influenza B, n (%) | 23 (14) | 24 (15) | 23 (14) | 70 (14) |
| Influenza A & B co-infection, n (%) | | | | |
| A and B | 0 | 0 | 1 (<1) | 1 (<1) |
| A/H1N1pdm09 & B | 0 | 0 | 1(<1) | 1 (<1) |
| A/H3N2 & B | 1 (<1) | 4 (2) | 1 (<1) | 6 (1) |

## Numbers analysed

Of 649 patients screened 21 patients were reported as screen failure and 13 patients as not assigned

**Table 13. Populations Analysed (All Subjects)**

| | IV Zanamivir hydrate 300 | IV Zanamivir hydrate 600 | Oseltamivir 75 mg n (%) | Total |
|---|---|---|---|---|
| All Subjects randomized[a] | 201 | 209 | 205 | 626 |
| ITT-Exposed Population (ITT-E) | 201 (100) | 209 (100) | 205 (100) | 615 (98) |
| Safety Population | 201 (100) | 209 (100) | 205 (100) | 615 (98) |
| Influenza Positive Population (IPP) | 163 (81) | 162 (78) | 163 (80) | 488 (78) |
| Influenza symptom onset ≤4 days subgroup | 127 (63) | 131 (63) | 121 (59) | 379 (61) |
| Influenza symptom onset >4 days subgroup | 36 (18) | 31 (15) | 42 (20) | 109 (17) |
| ICU/Mechanical ventilation subgroup | 68 (34) | 54 (26) | 68 (33) | 190 (30) |
| Per Protocol Population (PP) | 147 (73) | 150 (72) | 154 (75) | 451 (72) |
| PK Population | 180 (90) | 187 (89) | - | 367 (59) |

a. 11 subjects were randomized but had no treatment assignment and did not receive IP.
NOTE: Percentage of subjects per population is based on all subjects randomized.

The standard doses of IV Zanamivir hydrate (300 mg and 600 mg twice daily) and oseltamivir (75 mg twice daily) were adjusted in subjects with renal impairment.

**Table 14. Summary of Exposure to Blinded Zanamivir hydrate and Oseltamivir (ITT-E Population)**

| | IV Zanamivir hydrate 300 mg | IV Zanamivir hydrate 600 mg | Oseltamivir 75 mg (N= 205) |
|---|---|---|---|
| Cumulative Duration (Days) | | | |
| n | 199 | 208 | 204 |
| Mean [SD] | 5.92 [1.854] | 5.93 [1.738] | 5.58 [1.891] |
| Median [Min, Max] | 6 [1, 11] | 6 [1, 11] | 6 [1, 11] |
| Daily Dose (mg) | | | |
| n | 201 | 208 | 204 |
| Mean [SD] | 453 [128] | 919 [251] | 135 [20] |
| Median [Min, Max] | 500 [141, 600] | 1000 [84, 1200] | 146 [75, 150] |
| Total Cumulative Dose (mg) | | | |
| n | 201 | 208 | 204 |
| Mean [SD] | 2521 [1152] | 5113 [2192] | 729 [277] |
| Median [Min, Max] | 2800 [300, 6000] | 5450 [420, 12000] | 750 [75, 1500] |

If the investigator considered that a subject was failing to improve clinically on their randomized double-blind treatment, the investigator could choose to initiate the switch/rescue option (open label 600 mg IV Zanamivir hydrate) on Day 6 through Day 10 for up to 5 days. A total of 20 subjects in the ITT-E population received open-label IV Zanamivir hydrate via the switch/rescue option (5 subjects in the 300 mg IV Zanamivir hydrate arm, 4 subjects in the 600 mg IV Zanamivir hydrate arm and 11 subjects in the oseltamivir arm). Seventeen subjects who received switch/rescue therapy were in the IPP (5 subjects in

the 300 mg IV Zanamivir hydrate arm, 3 in the 600 mg IV Zanamivir hydrate arm, and 9 in the oseltamivir arm.

## Outcomes and estimation

### Primary endpoint

There were no significant differences in time to clinical response across treatment comparisons in the overall IPP or in either of the two pre-specified subgroups, or in the additional *post-hoc* analyses. A 0.48 day difference was seen between the 600 mg IV zanamivir hydrate arm and the oseltamivir arm in the overall IPP.

**Table 15. Summary of Observed Clinical Response (IPP)**

| | IV Zanamivir hydrate 300 mg | IV Zanamivir hydrate 600 mg | Oseltamivir 75 mg (N=163) |
|---|---|---|---|
| Clinical response | | | |
| n | 163 | 162 | 163 |
| Yes, n (%) | 145 (89) | 143 (88) | 140 (86) |
| No, n (%) | 18 (11) | 19 (12) | 23 (14) |
| Clinical outcome, n (%): | | | |
| Clinical improvement | 145 (89) | 143 (88) | 140 (86) |
| Vital signs did not resolve | 8 (5) | 7 (4) | 13 (8) |
| Died on study | 10 (6) | 12 (7) | 10 (6) |

**Table 16. Primary endpoint: time to clinical response defined as resolution of 4 out of 5 symptom signs [Statistical Comparisons and Time to Clinical Response between the 600 mg IV Zanamivir hydrate Group and Each Other Group and 95%CI by the Bootstrap Method (IPP)]**

| | IV Zanamivir hydrate | IV Zanamivir hydrate | Oseltamivir 75 mg |
|---|---|---|---|
| Influenza Positive Population | (N=163) | (N=162) | (N=163) |
| Median time to clinical response, days | 5.87 | 5.14 | 5.63 |
| Median difference between treatments, days (95% CI) | -0.73 (-1.79, 0.75) | | -0.48 (-2.11, 0.97) |
| p-value from Wilcoxon rank-sum 2-sided test | 0.2496 | | 0.3912 |
| ICU/Mechanical ventilation subgroup | (N=68) | (N=54) | (N=68) |
| Median time to clinical response, days | 11.26 | 12.79 | 14.58 |
| Median difference between treatments, days (95% CI) | 1.53 (-4.29, 8.34) | | -1.79 (-11.1, 6.92) |
| p-value from Wilcoxon rank-sum 2-sided test | 0.8711 | | 0.5120 |
| Symptom onset ≤4 days subgroup | (N=127) | (N=131) | (N=121) |
| Median time to clinical response, days | 5.63 | 4.80 | 4.80 |
| Median difference between treatments, days (95% CI) | -0.83 (-1.98, 0.56) | | -0.00 (-1.05, 0.97) |
| p-value from Wilcoxon rank-sum 2-sided test | 0.0923 | | 0.8232 |
| Symptom onset >4 days subgroup[a] | (N=36) | (N=31) | (N=42) |
| Median time to clinical response, days | 6.48 | 9.81 | 19.32 |
| Median difference between treatments, days (95% CI) | 3.33 (-2.59, 7.81) | | -9.50 (-90.1, 2.64) |
| p-value from Wilcoxon rank-sum 2-sided test | 0.3164 | | 0.1781 |
| Female subgroup[a] | (N=65) | (N=70) | (N=90) |

| | | | |
|---|---|---|---|
| Median time to clinical response, days | 5.96 | 5.07 | 5.94 |
| Median difference between treatments, days (95% CI) | -0.89 (-2.75, 1.21) | | -0.87 (-3.72, 0.89) |
| p-value from Wilcoxon rank-sum 2-sided test | 0.4452 | | 0.2459 |
| Male subgroup[a] | (N=98) | (N=92) | (N=73) |
| Median time to clinical response, days | 5.86 | 5.31 | 4.75 |
| Median difference between treatments, days (95% CI) | -0.55 (-1.96, 1.11) | | 0.56 (-2.06, 1.88) |
| p-value from Wilcoxon rank-sum 2-sided test | 0.4308 | | 0.9644 |

The Wilcoxon rank sum test is adjusted for randomization strata for IPP and the gender subgroups
a. *Post-hoc* analysis

The median time to clinical response in days were not statistically different for IV Zanamivir 600 mg and oseltamivir 75 mg. That relates to the total influenza positive population and the subgroups: ICU/mechanical ventilation and symptom onset ≤ 4 days, which were part of the primary endpoint analysis. Thus, the study failed the primary goal of demonstrating superiority of Zanamivir 600 mg IV over oseltamivir 75 mg. Also, *post-hoc* analysis showed that for the subgroups: symptom onset > 4 days, female and male, there were no significant differences between treatments.

The median time to clinical response was 0.48 days shorter for IV Zanamivir 600 mg compared to oseltamivir 75 mg. There was a large non-significant difference in favour of IV zanamivir in the subgroup symptom onset > 4 days, time to clinical response was 9.8 days for zanamivir 600 mg IV and 19 days for oseltamivir 75 mg (p value 0.178).

**Secondary endpoints**

**Table 17. Results for secondary endpoints**

| Secondary endpoints | IV Zanamivir 600 mg BID N=162 | Oseltamivir 75 mg BID N=163 |
|---|---|---|
| TTCR and time to improvement in respiratory status | Statistical comparison between arms p-value= 0.4100 | |
| Mortality rate (numbers) at day 14 | 8 | 5 |
| day 28 | 9 | 9 |
| end | 12 | 10 |
| Change in Katz activities of daily living (ADL) score Mean (SD), post-treatment+28 days | 1.72 (2.3) | 1.98 (2.1) |
| Virological endpoints | See text on virology | |
| Incidence and duration of 12 influenza symptoms | The incidence and duration of symptoms were generally similar across treatment | |
| Incidence of complications and antibiotic use | | |
| AEs influenza related (%) | 20 | 25 |
| Antibiotic use (%) | 10 | 18 |
| Ventilation status Mechanical ventilation (%) | 23 | 31 |
| Length of ICU (median days) | 6.0 | 7.0 |
| hospital stay (median days) | 6.0 | 7.0 |
| Time (median days) | | |
| absence of fever, | 0.8 | 1.5 |
| improved respiratory status | 3.6 | 2.8 |
| oxygen saturation | 5.6 | 4.5 |
| hearth rate | 3.4* | 2.8* |
| systolic blood pressure | 3.7* | 4.6* |

* excluding patients with normal readings at day 1.

## Ancillary analyses

### Clinical response (cumulative incidence)

The cumulative incidence of clinical response was comparable until about Day 10, after which a higher cumulative incidence was observed for the IV zanamivir arms vs. oseltamivir. For 600 mg IV vs. oseltamivir, the p-value from the log-rank test adjusting for randomisation stratification was 0.1417.

**Figure 2** **Kaplan-Meier Plot: Time to Clinical Response by Treatment Group (IPP)**

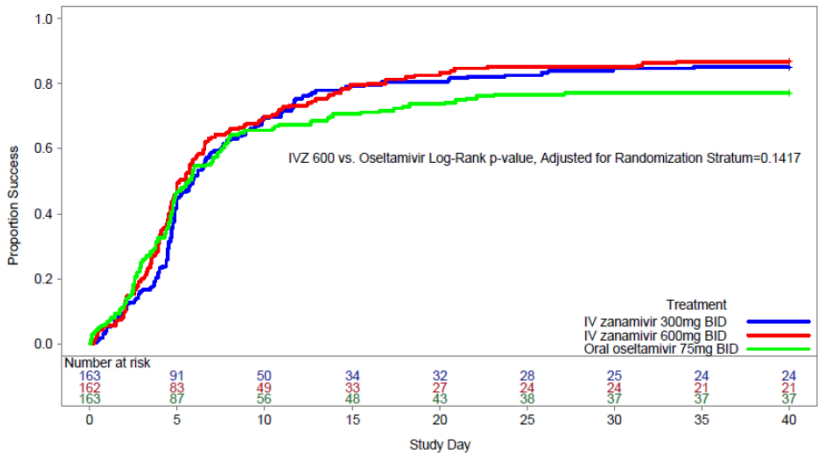



**Figure 3**

The ICU/mechanical ventilation subgroup responded more slowly and with more separation between treatment arms. The median treatment difference was 1.79 days in favour of 600 mg IV zanamivir vs. oseltamivir.

**Figure 3** **Kaplan-Meier Plot: Time to Clinical Response by Treatment Group and ICU/Mechanical Ventilation Subgroup (IPP)**

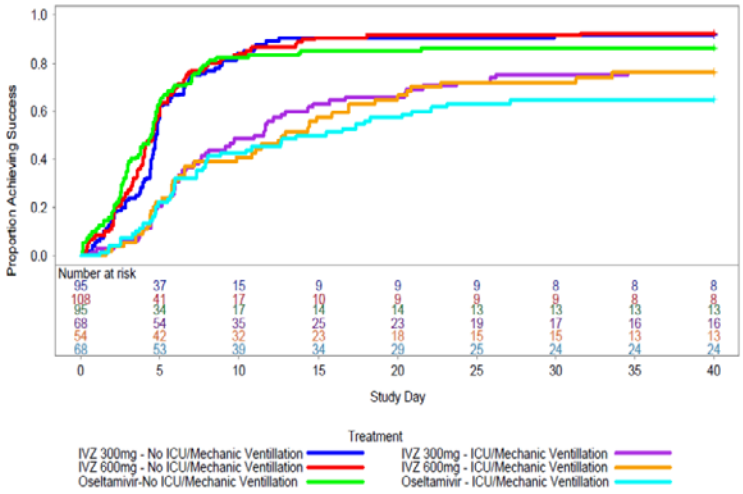



**Figure 4**

There was more separation observed in the *post-hoc* analysis of the late symptom onset subgroup (>4 days) with a slower response in the oseltamivir arm (median treatment difference of 9.50 days in favour of 600 mg IV zanamivir compared to oseltamivir).

An additional *post-hoc* analysis of gender effect on clinical response did not show a difference in cumulative incidence of clinical response by gender.

Based on Kaplan-Meier, 600 mg IV zanamivir demonstrated improved TTCR vs. oseltamivir in subjects receiving mechanical ventilation at baseline (p-value value from log-rank analysis is p=0.0696 and p=0.0617 by Wilcoxon-rank sum test). There was an imbalance in mortality across the treatment arms in

this analysis with 5/28 (18%) deaths in the 300 mg IV zanamivir arm, 6/25 (24%) deaths in the 600 mg IV zanamivir arm and 3/27 (11%) deaths in the oseltamivir arm.

The combined analysis of TTCR and time to improvement in respiratory status showed no significant difference between either treatment comparison in the overall IPP or the two subgroups.

**Clinical reponse rates by duration ≤5 Day Treatment Course vs >5 Day Treatment Course**

The duration of double-blind treatment detailed in the protocol was 5 days. However, the initial 5-day treatment course could have been extended for up to 5 additional days if clinical symptoms or patient characteristics as assessed by the investigator warranted further treatment. A summary of length of treatment (≤5 Day Treatment Course and >5 Day Treatment Course) for the Influenza Positive Population (IPP) is presented below. The majority of subjects (88%) received no more than a 5 day course of treatment and treatment was extended in approximately 12% of subjects.

**Table 18. Summary of Length of Treatment (IPP)**

| | Total Subjects N | ≤5 Day Treatment Course | >5 Day Treatment Course |
|---|---|---|---|
| IV zanamivir 300 mg BID | 163 | 143 (88) | 20 (12) |
| IV zanamivir 600 mg BID | 162 | 144 (89) | 18 (11) |
| Oral oseltamivir 75 mg BID | 163 | 141 (87) | 22 (13) |

Overall, the clinical response rate was higher in the subgroup of subjects who received ≤5 days of treatment, this would be expected compared with those subjects who required the treatment course to be extended.

**Table 19. Clinical Response Rates by Duration of Treatment (≤5 Day Treatment Course and >5 Day Treatment Course, IPP)**

| | IV zanamivir 300 mg | IV zanamivir 600 mg | Oseltamivir 75 mg |
|---|---|---|---|
| Subjects with ≤5 day treatment course, n | 143 | 144 | 141 |
| Clinical response, n (%) | 126 (88) | 127 (88) | 115 (82) |
| Reasons success criteria not met | | | |
| Vital signs did not resolve | 2 (1) | 2 (1) | 4 (3) |
| Discontinued study: Adverse event | 1 (<1) | 3 (2) | 1 (<1) |
| Discontinued study: Investigator discretion | 1 (<1) | 0 | 4 (3) |
| Discontinued study: Lost to follow-up | 1 (<1) | 0 | 1 (<1) |
| Discontinued study: Withdrew consent | 1 (<1) | 3 (2) | 5 (4) |
| Initiated switch/rescue therapy | 5 (3) | 1 (<1) | 7 (5) |
| Died on study | 6 (4) | 8 (6) | 4 (3) |
| Subjects with >5 day treatment course, n | 20 | 18 | 22 |
| Clinical response, n (%) | 13 (65) | 14 (78) | 11 (50) |
| Reasons success criteria not met | | | |
| Vital signs did not resolve | 4 (20) | 0 | 3 (14) |
| Discontinued study: Adverse event | 0 | 0 | 0 |
| Discontinued study: Investigator discretion | 1 (5) | 0 | 2 (9) |
| Discontinued study: Lost to follow-up | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Discontinued study: Withdrew consent | 0 | 0 | 0 |
| Initiated switch/rescue therapy | 0 | 2 (11) | 2 (9) |
| Died on study | 2 (10) | 2 (11) | 4 (18) |

**Outcomes by Influenza A and B**

Subtyping results from all available virology assays on all assessment days were taken into account in order to obtain comprehensive data on influenza types and subtypes. Using this approach, influenza type information was obtained for all 488 subjects in the Influenza Positive Population (IPP). The majority of subjects (84%) were infected with influenza A (410 subjects). A total of 70 subjects (14%) were infected with influenza B and there were 9 subjects (2%) with co-infections (8 with influenza A & influenza B co-infection and one with influenza A subtype coinfection). Influenza subtypes were similar across treatment groups.

Clinical response rates and time to clinical response (TTCR) for subjects in the IPP who were infected with influenza A or influenza B are summarised below. Subjects with co-infection were excluded from the analysis. In both subgroups, the proportion of subjects achieving a clinical response was higher in the IV zanamivir arms than the oseltamivir arm. Clinical response rates were similar across the subgroups.

**Table 20. Clinical Response Rates by Influenza A or Influenza B (IPP)**

| | IV zanamivir 300 mg | IV zanamivir 600 mg | Oseltamivir 75 mg |
|---|---|---|---|
| Subjects with Influenza A, n | 139 | 134 | 137 |
| Clinical response, n (%) | 120 (86) | 117 (87) | 105 (77) |
| Reasons success criteria not met | | | |
| Vital signs did not resolve | 5 (4) | 1 (<1) | 6 (4) |
| Discontinued study: Adverse event | 1 (<1) | 3 (2) | 1 (<1) |
| Discontinued study: Investigator discretion | 2 (1) | 0 | 5 (4) |
| Discontinued study: Lost to follow-up | 0 | 0 | 1 (<1) |
| Discontinued study: Withdrew consent | 1 (<1) | 2 (1) | 3 (2) |
| Initiated switch/rescue therapy | 5 (4) | 2 (1) | 9 (7) |
| Died on study | 5 (4) | 9 (7) | 7 (5) |
| Subjects with Influenza B, n | 23 | 24 | 23 |
| Clinical response, n (%) | 19 (83) | 21 (88) | 18 (78) |
| Reasons success criteria not met | | | |
| Vital signs did not resolve | 1 (4) | 1 (4) | 1 (4) |
| Discontinued study: Adverse event | 0 | 0 | 0 |
| Discontinued study: Investigator discretion | 0 | 0 | 1 (4) |
| Discontinued study: Lost to follow-up | 1 (4) | 0 | 0 |
| Discontinued study: Withdrew consent | 0 | 1 (4) | 2 (9) |
| Initiated switch/rescue therapy | 0 | 0 | 0 |
| Died on study | 2 (9) | 1 (4) | 1 (4) |

Note: Subjects co-infected with influenza A and influenza B are excluded from this summary

**Table 21. Time to Clinical Response with Comparison between the 600 mg IV Zanamivir Group and Each Other Group by the Bootstrap Method by Influenza A or Influenza B (IPP)**

| | IV Zanamivir 300 mg | IV Zanamivir 600 mg | Oseltamivir 75 mg |
|---|---|---|---|
| Subjects with Influenza A, n | 139 | 134 | 137 |
| Median time to clinical response, days | 5.63 | 5.14 | 5.82 |
| Median difference between treatments, days (95% CI) | -0.48 (-1.58, 0.96) | | -0.67 (-2.34, 0.85) |
| Subjects with Influenza B, n | 23 | 24 | 23 |
| Median time to clinical response, days | 6.94 | 4.66 | 4.77 |
| Median difference between treatments, days (95% CI) | -2.28 (-10.43, 0.94) | | -0.11 (-6.86, 2.75) |

In summary, there was a small improvement in clinical response rates and TTCR for 600 mg IV zanamivir compared with 300 mg IV zanamivir or oseltamivir for subjects infected with influenza A or influenza B.

**Outcomes by Time of Symptom Onset Relative to Initiation of Treatment (≤2 Days or >2 Days)**

Entry criteria allowed for subjects to be included within 6 days of symptom onset. Clinical response rates and TTCR for subjects in the IPP with time of symptom onset to initiation of treatment of ≤2 days or >2 days are summarised below.

The proportion of subjects who met the criteria for clinical response in the symptom onset ≤2 days subgroup were similar across treatment groups with a slightly higher number reaching a clinical response

in the IV zanamivir arms compared with the oseltamivir arm. Similar results were observed in the analysis for the symptom onset >2 days subgroup.

**Table 22. Clinical Response Rates by Time of Symptom Onset to Initiation of Treatment (≤2 Days or >2 Days, IPP)**

| | IV zanamivir 300 mg | IV zanamivir 600 mg | Oseltamivir 75 mg |
|---|---|---|---|
| Subjects with symptom onset ≤2 days, n | 49 | 53 | 57 |
| Clinical response, n (%) | 43 (88) | 49 (92) | 46 (81) |
| Reasons success criteria not met | | | |
| Vital signs did not resolve | 2 (4) | 1 (2) | 0 |
| Discontinued study: Adverse event | 1 (2) | 1 (2) | 0 |
| Discontinued study: Investigator discretion | 0 | 0 | 2 (4) |
| Discontinued study: Lost to follow-up | 0 | 0 | 1 (2) |
| Discontinued study: Withdrew consent | 0 | 1 (2) | 1 (2) |
| Initiated switch/rescue therapy | 1 (2) | 1 (2) | 3 (5) |
| Died on study | 2 (4) | 0 | 4 (7) |
| Subjects with symptom onset >2 days, n | 114 | 109 | 106 |
| Clinical response, n (%) | 96 (84) | 92 (84) | 80 (75) |
| Reasons success criteria not met | | | |
| Vital signs did not resolve | 4 (4) | 1 (<1) | 7 (7) |
| Discontinued study: Adverse event | 0 | 2 (2) | 1 (<1) |
| Discontinued study: Investigator discretion | 2 (2) | 0 | 4 (4) |
| Discontinued study: Lost to follow-up | 1 (<1) | 0 | 0 |
| Discontinued study: Withdrew consent | 1 (<1) | 2 (2) | 4 (4) |
| Initiated switch/rescue therapy | 4 (4) | 2 (2) | 6 (6) |
| Died on study | 6 (5) | 10 (9) | 4 (4) |

Overall, the TTCR was slightly longer in the symptom onset >2 days subgroup compared with the symptom onset ≤2 days subgroup and TTCR was longer in the oseltamivir arm compared with the 600 mg IV zanamivir arm in both subgroups.

**Table 23. Time to Clinical Response with Comparison between the 600 mg IV Zanamivir Group and Each Other Group by the Bootstrap Method by Time of Symptom Onset to Initiation of Treatment (<=2 Days or >2 Days, IPP)**

| | IV Zanamivir 300 mg | IV Zanamivir 600 mg | Oseltamivir 75 mg |
|---|---|---|---|
| Subjects with symptom onset ≤2 days, n | 49 | 53 | 57 |
| Median time to clinical response, days | 5.75 | 4.06 | 4.68 |
| Median difference between treatments, days (95% CI) | -1.69 (-3.58, 0.07) | | -0.62 (-1.94, 0.94) |
| Subjects with symptom onset >2 days, n | 114 | 109 | 106 |
| Median time to clinical response, days | 5.91 | 5.77 | 6.98 |
| Median difference between treatments, days (95% CI) | -0.13 (-1.63, 1.33) | | -1.21 (-2.65, 1.17) |

In summary, there was a small improvement in clinical response rates and TTCR for 600 mg IV zanamivir compared with oseltamivir in both the symptom onset ≤2 days and >2 days subgroups with the larger improvement in TTCR in the symptom onset >2 day group.

**Effect of prior oseltamivir therapy**

Up to 3 days (or 6 doses which could span 4 calendar days) of prior anti-influenza therapy was allowed including Day 1 (before the first dose of study drug). In the Influenza Positive Population (IPP), 255 subjects (52%) received prior oseltamivir and the median duration of treatment was 2 days in each treatment arm.

**Table 24 . Summary of Prior Exposure to Oseltamivir (IPP)**

| | IV Zanamivir 300 mg (N=163) | IV Zanamivir 600 mg (N=162) | Oseltamivir 75 mg (N=163) | Total (N=488) |
|---|---|---|---|---|
| Duration (Days)[a] | | | | |
| n | 90 | 80 | 85 | 255 |
| Mean [SD] | 1.8 [0.79] | 1.8 [0.74] | 1.6 [0.59] | 1.7 [0.72] |
| Median [Min, Max][a,b] | 2 [1, 4] | 2 [1, 4] | 2 [1, 3] | 2 [1, 4] |

Clinical response rates and time to clinical response (TTCR) for subjects in the IPP who did or did not receive prior oseltamivir are summarised below. In both subgroups, the proportion of subjects achieving a clinical response was higher in the IV zanamivir arms than the oseltamivir arm. Overall, there were slightly higher clinical response rates in the subgroup with no prior oseltamivir use.

**Table 25. Clinical Response Rates by Prior Oseltamivir Use (IPP)**

| | IV zanamivir 300 mg | IV zanamivir 600 mg | Oseltamivir 75 mg |
|---|---|---|---|
| Subjects with prior oseltamivir use, n | 90 | 80 | 85 |
| Clinical response, n (%) | 72 (80) | 64 (80) | 61 (72) |
| Reasons success criteria not met | | | |
| Vital signs did not resolve | 6 (7) | 2 (3) | 6 (7) |
| Discontinued study: Adverse event | 0 | 3 (4) | 1 (1) |
| Discontinued study: Investigator discretion | 2 (2) | 0 | 4 (5) |

| | | | |
|---|---|---|---|
| Discontinued study: Lost to follow-up | 1 (1) | 0 | 0 |
| Discontinued study: Withdrew consent | 1 (1) | 2 (3) | 3 (4) |
| Initiated switch/rescue therapy | 1 (1) | 2 (3) | 5 (6) |
| Died on study | 7 (8) | 7 (9) | 5 (6) |
| Subjects with no prior oseltamivir use, n | 73 | 82 | 78 |
| Clinical response, n (%) | 67 (92) | 77 (94) | 65 (83) |
| Reasons success criteria not met | | | |
| Vital signs did not resolve | 0 | 0 | 1 (1) |
| Discontinued study: Adverse event | 1 (1) | 0 | 0 |
| Discontinued study: Investigator discretion | 0 | 0 | 2 (3) |
| Discontinued study: Lost to follow-up | 0 | 0 | 1 (1) |
| Discontinued study: Withdrew consent | 0 | 1 (1) | 2 (3) |
| Initiated switch/rescue therapy | 4 (5) | 1 (1) | 4 (5) |
| Died on study | 1 (1) | 3 (4) | 3 (4) |

The median TTCR was longer in subjects who received prior oseltamivir compared with subjects who did not receive oseltamivir prior to inclusion into the study for all 3 treatment arms. In subjects who received prior oseltamivir, TTCR was longer in the oseltamivir arm compared with both IV zanamivir groups, however differences were small. In subjects who did not receive prior oseltamivir, TTCR was longer in the oseltamivir arm compared with 600 mg IV zanamivir but not 300 mg IV zanamivir, however differences were minimal.

**Table 26. Time to Clinical Response with Comparison between the 600 mg IV Zanamivir Group and Each Other Group by the Bootstrap Method by Prior Oseltamivir Use (IPP)**

| | IV Zanamivir 300 mg | IV Zanamivir 600 mg | Oseltamivir 75 mg |
|---|---|---|---|
| Subjects with prior oseltamivir use, n | 90 | 80 | 85 |
| Median time to clinical response, days | 6.54 | 6.92 | 7.30 |
| Median difference between treatments, days (95% CI) | 0.38 (-2.55, 6.10) | | -0.39 (-5.21, 5.44) |
| Subjects with no prior oseltamivir use, n | 73 | 82 | 78 |
| Median time to clinical response, days | 5.00 | 4.49 | 4.73 |
| Median difference between treatments, days (95% CI) | -0.51 (-2.05, 0.03) | | -0.24 (-1.08, 0.49) |

In summary, subjects with prior oseltamivir use had slightly lower clinical response rates and longer TTCR compared to subjects who had not received oseltamivir prior to study treatment.

**Analysis by age category**

The number of subjects enrolled in the pivotal Phase III study NAI114373 are summarised by age (<65, 65 to <75, 75 to <85 and ≥85) in table below. In the Intent-to-Treat Exposed (ITT-E) population, the majority of subjects (397, 65%) were in the <65 age group, 103 (17%) were in the 65 to <75 age group, 84 subjects (14%) were in the 75 to <85 age group and 31 (5%) were ≥85 years old. There were no notable differences across the treatment arms with respect to the distribution of the age for the ITT-E population and Influenza Positive Population (IPP). Numbers are small but generally similar across treatment arms for the subgroups.

**Table 27. Summary of Subject Accountability by Age (All Subjects)**

| | IV zanamivir 300 mg | IV zanamivir 600 mg | Oseltamivir 75 mg | Total |
|---|---|---|---|---|
| Overall ITT-E (All ages) | N=201 | N=209 | N=205 | N=615 |
| Age <65 years, n | 135 | 134 | 128 | 397 |
| ITT-E, n (%) | 135 (100) | 134 (100) | 128 (100) | 397 (100) |
| IPP, n (%) | 113 (84) | 103 (77) | 102 (80) | 318 (80) |
| Subgroups | | | | |
| ICU/mechanical ventilation, n (%) | 53 (39) | 37 (28) | 46 (36) | 136 (34) |
| Symptom onset ≤4 days, n (%) | 87 (64) | 85 (63) | 75 (59) | 247 (62) |
| Symptom onset >4 days, n (%) | 26 (19) | 18 (13) | 27 (21) | 71 (18) |
| Age 65 to <75 years, n | 29 | 36 | 38 | 103 |
| ITT-E, n (%) | 29 (100) | 36 (100) | 38 (100) | 103 (100) |
| IPP, n (%) | 25 (86) | 30 (83) | 28 (74) | 83 (81) |
| Subgroups | | | | |
| ICU/mechanical ventilation, n (%) | 10 (34) | 9 (25) | 12 (32) | 31 (30) |
| Symptom onset ≤4 days, n (%) | 20 (69) | 24 (67) | 20 (53) | 64 (62) |
| Symptom onset >4 days, n (%) | 5 (17) | 6 (17) | 8 (21) | 19 (18) |
| Age 75 to <85 years, n | 28 | 29 | 27 | 84 |
| ITT-E, n (%) | 28 (100) | 29 (100) | 27 (100) | 84 (100) |
| IPP, n (%) | 18 (64) | 20 (69) | 22 (81) | 60 (71) |
| Subgroups | | | | |
| ICU/mechanical ventilation, n (%) | 4 (14) | 6 (21) | 8 (30) | 18 (21) |
| Symptom onset ≤4 days, n (%) | 14 (50) | 15 (52) | 19 (70) | 48 (57) |
| Symptom onset >4 days, n (%) | 4 (14) | 5 (17) | 3 (11) | 12 (14) |
| Age ≥85 years, n | 9 | 10 | 12 | 31 |
| ITT-E, n (%) | 9 (100) | 10 (100) | 12 (100) | 31 (100) |
| IPP, n (%) | 7 (78) | 9 (90) | 11 (92) | 27 (87) |
| Subgroups | | | | |
| ICU/mechanical ventilation, n (%) | 1 (11) | 2 (20) | 2 (17) | 5 (16) |
| Symptom onset ≤4 days, n (%) | 6 (67) | 7 (70) | 7 (58) | 20 (65) |
| Symptom onset >4 days, n (%) | 1 (11) | 2 (20) | 4 (33) | 7 (23) |

Clinical response rates and time to clinical response (TTCR) for subjects in the IPP are summarised by age in tables below.

The proportion of subjects in the IPP who met the criteria for clinical response was similar across treatment groups for the 65 to <75, 75 to <85 and ≥85 years age groups. For the <65 years age group, the proportion of subjects who met the criteria for clinical response was 86% in the 300 mg IV zanamivir arm, 92% in the 600 mg IV zanamivir arm and 77% in the oseltamivir arm. Overall, the clinical response rate was higher in the younger age groups and decreased with increasing age, although numbers in the older age groups are small limiting interpretation of these results.

**Table 28. Clinical Response Rates by Age (IPP)**

| | IV zanamivir 300 mg | IV zanamivir 600 mg | Oseltamivir 75 mg |
|---|---|---|---|
| Age <65 years, n | 113 | 103 | 102 |
| Clinical response, n (%) | 97 (86) | 95 (92) | 79 (77) |
| Reasons success criteria not met | | | |
| Vital signs did not resolve | 5 (4) | 1 (<1) | 6 (6) |
| Discontinued study: Adverse event | 0 | 2 (2) | 1 (<1) |
| Discontinued study: Investigator discretion | 1 (<1) | 0 | 3 (3) |
| Discontinued study: Lost to follow-up | 1 (<1) | 0 | 1 (<1) |
| Discontinued study: Withdrew consent | 1 (<1) | 2 (2) | 4 (4) |
| Initiated switch/rescue therapy | 2 (2) | 1 (<1) | 4 (4) |
| Died on study | 6 (5) | 2 (2) | 4 (4) |
| Age 65 to <75 years, n | 25 | 30 | 28 |
| Clinical response, n (%) | 21 (84) | 25 (83) | 22 (79) |
| Reasons success criteria not met | | | |
| Vital signs did not resolve | 0 | 0 | 1 (4) |
| Discontinued study: Adverse event | 1 (4) | 0 | 0 |
| Discontinued study: Investigator discretion | 1 (4) | 0 | 1 (4) |
| Discontinued study: Lost to follow-up | 0 | 0 | 0 |
| Discontinued study: Withdrew consent | 0 | 1 (3) | 1 (4) |
| Initiated switch/rescue therapy | 1 (4) | 1 (3) | 1 (4) |
| Died on study | 1 (4) | 3 (10) | 2 (7) |
| Age 75 to <85 years, n | 18 | 20 | 22 |
| Clinical response, n (%) | 16 (89) | 16 (80) | 17 (77) |
| Reasons success criteria not met | | | |
| Vital signs did not resolve | 0 | 1 (5) | 0 |
| Discontinued study: Adverse event | 0 | 1 (5) | 0 |
| Discontinued study: Investigator discretion | 0 | 0 | 1 (5) |
| Discontinued study: Lost to follow-up | 0 | 0 | 0 |
| Discontinued study: Withdrew consent | 0 | 0 | 0 |
| Initiated switch/rescue therapy | 1 (6) | 0 | 2 (9) |
| Died on study | 1 (6) | 2 (10) | 2 (9) |
| Age ≥85 years, n | 7 | 9 | 11 |
| Clinical response, n (%) | 5 (71) | 5 (56) | 8 (73) |
| Reasons success criteria not met | | | |
| Vital signs did not resolve | 1 (14) | 0 | 0 |
| Discontinued study: Adverse event | 0 | 0 | 0 |
| Discontinued study: Investigator discretion | 0 | 0 | 1 (9) |
| Discontinued study: Lost to follow-up | 0 | 0 | 0 |
| Discontinued study: Withdrew consent | 0 | 0 | 0 |
| Initiated switch/rescue therapy | 1 (14) | 1 (11) | 2 (18) |
| Died on study | 0 | 3 (33) | 0 |

The median TTCR for each treatment arm and the median difference and associated 95% confidence interval between 600 mg IV zanamivir and the other two treatment arms were assessed by the bootstrap percentile method and are presented in table below for subjects in the <65, 65 to <75, 75 to <85 and ≥85 years age groups. It should be noted that for subjects not achieving a clinical response, 99.9 days was assigned for TTCR as defined in the analysis plan. The TTCR was similar across treatment arms for subjects in the <65 and 65 to <75 years age groups. The TTCR was shorter in the oseltamivir arm compared with the 600 mg IV zanamivir arm for the 75 to <85 and ≥85 years age groups where TTCR was

more protracted in these older age groups however numbers are small, limiting interpretation of these results. The numerical differences and wide confidence intervals (CI) seen in the ≥85 years age group is likely driven by the small sample size and the relatively higher number of subjects in the 600 mg IV zanamivir arm who did not achieve clinical response and were assigned a TTCR of 99.9 days.

**Table 29. Time to Clinical Response with Comparison between the 600 mg IV Zanamivir Group and Each Other Group by Age by the Bootstrap Method (IPP)**

| | IV zanamivir 300 mg | IV zanamivir 600 mg | Oseltamivir 75 mg |
|---|---|---|---|
| Overall IPP, n | 163 | 162 | 163 |
| Median time to clinical response, days | 5.87 | 5.14 | 5.63 |
| Median difference between treatments, days (95% CI) | -0.73 (-1.79, 0.75) | | -0.48 (-2.11, 0.97) |
| Age <65 years, n | 113 | 103 | 102 |
| Median time to clinical response, days | 5.87 | 4.61 | 4.76 |
| Median difference between treatments, days (95% CI) | -1.26 (-2.32, -0.16) | | -0.15 (-1.66, 0.71) |
| Age 65 to <75 years, n | 25 | 30 | 28 |
| Median time to clinical response, days | 4.85 | 6.54 | 6.43 |
| Median difference between treatments, days (95% CI) | 1.69 (-3.38, 5.30) | | 0.11 (-3.36, 4.46) |
| Age 75 to <85 years, n | 18 | 20 | 22 |
| Median time to clinical response, days | 6.27 | 9.26 | 7.19 |
| Median difference between treatments, days (95% CI) | 2.98 (-5.93, 9.79) | | 2.07 (-8.16, 8.47) |
| Age ≥85 years, n | 7 | 9 | 11 |
| Median time to clinical response, days | 10.94 | 20.00 | 8.54 |
| Median difference between treatments, days (95% CI) | 9.06 (-89.44, 95.11) | | 11.45 (-79.90, 94.00) |

In summary, there were no notable differences in outcomes by age across treatment groups. As would be expected, the clinical response rates decreased and TTCR increased with increasing age.

**Influence of nausea /vomiting at baseline**

The presence and severity of a predefined list of influenza symptoms which included nausea and vomiting were assessed at baseline. In the Intent-to-Treat Exposed (ITT-E) population, nausea was present in 24% of subjects and vomiting in 12% of subjects, overall the percentage of subjects with nausea and vomiting was the same for the 600 mg IV zanamivir arm and the oseltamivir arm.

**Table 30. Summary of Nausea and Vomiting at Baseline (ITT-E Population)**

| | IV zanamivir 300 mg (N=201) | IV zanamivir 600 mg (N=209) | Oseltamivir 75 mg (N=205) |
|---|---|---|---|
| Symptoms of influenza[a], n/N (%) | | | |
| Nausea | 48/201 (24) | 51/208 (24) | 49/203 (24) |
| Vomiting | 21/201 (10) | 27/208 (13) | 27/204 (13) |

The presence and severity of a predefined list of influenza symptoms which included nausea and vomiting were assessed at baseline. In the Intent-to-Treat Exposed (ITT-E) population, nausea was present in 24% of subjects and vomiting in 12% of subjects, overall the percentage of subjects with nausea and vomiting was the same for the 600 mg IV zanamivir arm and the oseltamivir arm.

**Table 31 . Summary of Nausea and Vomiting at Baseline (ITT-E Population)**

| | IV zanamivir 300 mg (N=201) | IV zanamivir 600 mg (N=209) | Oseltamivir 75 mg (N=205) |
|---|---|---|---|
| Symptoms of influenza[a], n/N (%) | | | |
| Nausea | 48/201 (24) | 51/208 (24) | 49/203 (24) |
| Vomiting | 21/201 (10) | 27/208 (13) | 27/204 (13) |

In order to present the time to clinical response (TTCR) and clinical response rates for subjects who did not have nausea and vomiting symptoms at baseline, the following rule was applied:

- Subjects who had either nausea *or* vomiting at any severity level were classified as a 'yes' and subjects with a reported absence of both symptoms were classified as a 'no', also:
- One symptom is experienced at any severity level and the other is 'unable to assess': classified as 'yes'
- One symptom is absent and the other is 'unable to assess': classified as 'missing'
- Both symptoms are 'unable to assess': classified as 'missing'

The proportion of subjects in the Influenza Positive Population (IPP) without nausea and/or vomiting at baseline who met the criteria for clinical response was 90% in the 600 mg IV zanamivir arm compared with 76% in the oseltamivir arm and 88% in the 300 mg IV zanamivir arm. The proportion of subjects with nausea and/or vomiting at baseline who met the criteria for clinical response was similar between the treatment arms: 89% in the 300 mg IV zanamivir arm, 92% in the 600 mg IV zanamivir arm and 88% in the oseltamivir arm.

The median TTCR for each treatment arm and the median difference and associated 95% confidence interval between 600 mg IV zanamivir and the other two treatment arms were assessed by the bootstrap percentile method and are presented below for subjects in the IPP with or without nausea and/or vomiting at baseline. It should be noted that for subjects not achieving a clinical response, 99.9 days was assigned for TTCR as defined in the analysis plan. The TTCR was similar across treatment arms for subjects with or without nausea and/or vomiting at baseline. Overall, TTCR was slightly longer in subjects without nausea and/or vomiting at baseline.

**Table 32 . Time to Clinical Response with Comparison between the 600 mg IV zanamivir Group and Each Other Group by the Bootstrap Method for Subjects with and without Nausea and/or Vomiting at Baseline (IPP)**

| | IV zanamivir 300 mg | IV zanamivir 600 mg | Oseltamivir 75 mg |
|---|---|---|---|
| Subjects without nausea/vomiting at baseline, n | 104 | 104 | 100 |
| Median time to clinical response, days | 5.70 | 5.32 | 5.02 |
| Median difference between treatments, days (95% CI) | -0.38 (-1.66, 0.94) | | 0.30 (-1.80, 1.22) |
| Subjects with nausea/vomiting at baseline, n | 38 | 37 | 41 |
| Median time to clinical response, days | 4.78 | 4.06 | 4.28 |
| Median difference between treatments, days (95% CI) | -0.72 (-1.48, 0.16) | | -0.22 (-1.30, 1.53) |

In summary, in the IPP only slightly more subjects in the oseltamivir arm had nausea and/or vomiting at baseline compared with the IV zanamivir arms. The presence or absence of these symptoms did not appear to significantly impact the clinical response rate or TTCR.

**Mortality**

There were 41 deaths in the ITT-E population [15 (7%), 15 (7%) and 11 (5%)] in respective arms.

Thirty-two subjects in the influenza positive population (IPP) [6%, 7% and 6% in the 300 mg IV zanamivir, 600 mg IV zanamivir and oseltamivir arms, respectively] died during the study. The number of deaths was similar across treatment groups.

In the IPP, 18 subjects died on or before day 14 and 26 died on or before day 28. Median time to death was 16 days (range 10 to 39), 10 days (range 2 to 37) and 17 days (range 2 to 32) in respective treatment groups.

Seventeen subjects in the IPP died due to complications of influenza (with complications determined as per investigator assessment), 3%, 4% and 4% in the 300 mg IV zanamivir, 600 mg IV zanamivir and oseltamivir arms, respectively. Of those subjects, 11 (2% in each treatment arm) died on or before day 14 and 15 (3% in each treatment arm) died on or before day 28. Median time to death was 14 days (range 10 to 19), 7 days (range 2 to 37) and 12.5 days (range 2 to 32), respectively.

The tables below shows both 90% and 95% confidence intervals as specified in the Reporting Analysis Plan for study NAI114373.

**Table 33. Summary of Overall Mortality (IPP)**

| | IV zanamivir 300 mg (N=163) | IV zanamivir 600 mg (N=162) | Oseltamivir 75 mg (N=163) |
|---|---|---|---|
| Total number of deaths<br>n (%) | 10 (6) | 12 (7) | 10 (6) |
| Days to death<br>n<br>Mean [SD]<br>Median [Min, Max] | 10<br>19.8 [11.13]<br>16 [10, 39] | 12<br>14.4 [11.68]<br>10 [2, 37] | 10<br>16.3 [9.59]<br>17 [2, 32] |
| Difference in deaths % (90% CI) | 1.3% (-3.3%, 5.9%) | | 1.3% (-3.3%, 5.9%) |
| Difference in deaths % (95% CI) | 1.3% (-4.2%, 6.7%) | | 1.3% (-4.2%, 6.7%) |

Non-inferiority assessed by overall mortality was not achieved for the comparison of 600 mg IV zanamivir against oseltamivir based on the predefined non-inferiority margin of 5%.

**Table 34. Summary of Mortality Attributable to Complications of Influenza (IPP)**

| | IV zanamivir 300 mg (N=163) | IV zanamivir 600 mg (N=162) | Oseltamivir 75 mg (N=163) |
|---|---|---|---|
| Deaths considered attributable to influenza<br>n (%) | 5 (3) | 6 (4) | 6 (4) |
| Days to death considered attributable to influenza<br>n<br>Mean [SD]<br>Median [Min, Max] | 5<br>14.2 [4.27]<br>14 [10, 19] | 6<br>12.7 [13.11]<br>7 [2, 37] | 6<br>14.7 [11.45]<br>12.5 [2, 32] |
| Difference in deaths % (90% CI) | 0.6% (-2.7%, 3.9%) | | 0% (-3.4%, 3.5%) |
| Difference in deaths % (95% CI) | 0.6% (-3.3%, 4.6%) | | 0% (-4.1%, 4.1%) |

Non-inferiority assessed by attributable mortality was achieved for the comparison of 600 mg IV zanamivir against oseltamivir based on a non-inferiority margin of 5%.

### Functional status

Based on the Katz ADL score 15% zanamivir and 20% oseltamivir IPP subjects did not return to pre-morbid functional status. The mean time to return to pre-morbid functional status was 5.7 days for 300 mg IV zanamivir, 4.6 days for 600 mg IV zanamivir and 6.4 days for oseltamivir.

**Figure 8** **Kaplan-Meier Plot: Time to Return to Pre-Morbid Functional Status by the Katz ADL Score (IPP)**

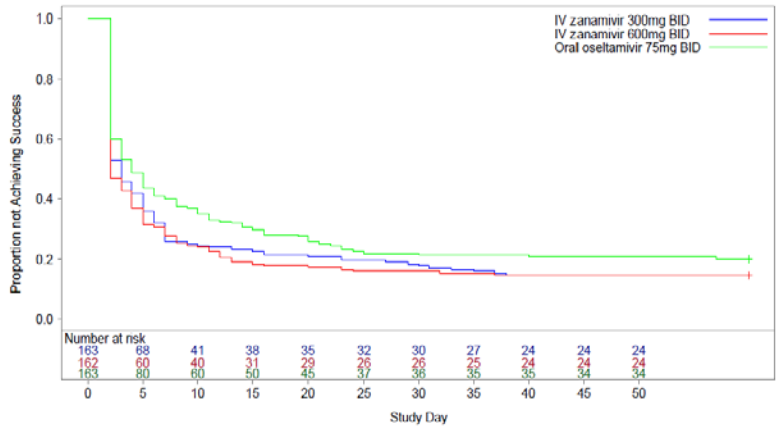



**Figure 5**

By the end of the study (PT+28), 26 subjects (6%) were still on bed rest while 49 (12%) reported limited ambulation and 344 (82%) were unrestricted. The level of activity was similar across treatment groups, with 86% and 83% subjects in the 300 mg and 600 mg IV zanamivir arms, respectively with unrestricted activity by end of study compared with 77% in the oseltamivir arm.

### Symptom duration /complications

Due to the conditional nature of the data collected, the following assumptions were made to calculate the duration of symptoms: “unable to assess” at Day 1 assumed the symptom was *not* present and would not contribute the “number of days” but if a subject had an “unable to access” after Day 1, then the previous result was carried forward. Additionally, if there was a missed assessment, the previous result was carried forward. Overall, the incidence of influenza symptoms was similar across treatment groups but there were more subjects with sore throat in the 600 mg IV zanamivir arm (71% vs. 58% and 60%) and more with nausea and vomiting in the oseltamivir arm (nausea: 47% vs. 35% and 31%; vomiting: 28% vs. 17% and 14%).

Influenza complications identified by the investigator from AEs were recorded for 108 (22%) IPP subjects. The most common complications included respiratory disorders (10%) and infectious disorders (6%). Pneumonia was the commonest individual complication.

### Ventilatory support

There were 80 (16%) subjects in the IPP on mechanical ventilation but none on ECMO at baseline. Most subjects in the IPP required ventilation or oxygenation support at some point during the study (21%

mechanical ventilation, 8% BiPAP, 4% CPAP and <1% ECMO). Ventilatory support and supplemental oxygen requirement was similar across treatment groups except that more subjects in the oseltamivir group received BiPAP compared with the IV zanamivir groups (14% vs. 5% and 6%). The median duration of mechanical ventilation (invasive and non-invasive combined) was 9.0, 5.2 and 8.2 days for the 300 mg IV zanamivir, 600 mg IV zanamivir and oseltamivir groups, respectively. The median duration of supplemental oxygen was 4.4, 4.2 and 3.7 days, respectively.

The duration of hospitalization and ICU stay was similar across treatment arms.

**Viral load/ virological improvement**

For the population of subjects who were PCR positive at Baseline from NP swabs (N=410), the median time to virologic improvement for influenza A and B from nasopharyngeal (NP) swabs was 3.0 days for all treatment arms. Virological improvement was defined as a 2 log drop in viral load and the rate of success for those positive at baseline were 90% for Zanamivir hydrate IV 600 mg and 92% for oseltamivir 75 mg.

**Table 35. Summary of Time to Virologic Improvement for Influenza A and B by pPCR (Nasopharyngeal, Positive at Baseline, IPP)**

| | IV Zanamivir hydrate 300 mg | IV Zanamivir hydrate 600 mg | Oseltamivir 75 mg (N=163) |
|---|---|---|---|
| **Virologic Improvement,** | 134 | 136 | 140 |
| Success, n (%) | 116 (87) | 122 (90) | 129 (92) |
| **Days to Success, n** | | | |
| n | 116 | 122 | 129 |
| Mean [SD] | 4.0 [3.46] | 4.8 [5.57] | 4.2 [3.88] |
| Median [Min, Max] | 3.0 [2, 34] | 3.0 [2, 35] | 3.0 [2, 34] |

Among 55 subjects who were PCR positive from ET aspirates at baseline (N=55), the median time to virologic improvement was 2.5 days for 600 mg IV zanamivir arm vs. 4 days for the other arms.

The median time to no detectable viral RNA as determined by qPCR for all subjects from NP swabs was 4 days across all treatment groups. For the population of subjects who were culture positive at baseline in NP swabs (N=264), the median time to no detectable virus was 3.0 days across all treatment groups.

The reductions in viral load were similar across treatment groups for influenza A and B combined (drops of 1.50, 1.83 and 1.75 $\log_{10}$ vp/mL by Day 3 for the 300 mg IV zanamivir, 600 mg IV zanamivir and oseltamivir arms, respectively). Similar reductions in viral load were seen across treatment groups for the influenza types/subtypes. For subjects who were positive at baseline by qVC from NP swabs, the median change from baseline on Day 3 was - 2.01 $\log_{10}$ $TCID_{50}$/mL for all treatment groups.

**Development of resistance**

In study **NAI114373** 238 Day 1 and 248 post Day 1 samples, a total of 502 cultured samples (nasopharyngeal) from 262 subjects (126 subjects with both Day 1 and post Day 1 samples) had sufficient viral titer for phenotypic analysis. Although many influenza A/H1N1pdm09, A/H3N2 and influenza B viruses showed shifts in susceptibility of >2 to Zanamivir, all were <10 and therefore within

the normal range of inhibition. Influenza A/H3N2 and influenza B viruses show normal levels of inhibition to oseltamivir (fold change <10). However, influenza A/H1N1pdm09 viruses demonstrate an elevated shift in susceptibility to oseltamivir as a result of the presence of the known resistance substitution, H275Y. From measurements of IC50 at baseline and during treatment, no strains were found to be resistant to zanamivir, while 5 samples were found to be resistant to oseltamivir.

The H275Y substitution which is the most common oseltamivir resistance substitution was detected during treatment in four subjects (four immunocompetent patients and one immunocompromised) in the oseltamivir arm and conferred high level resistance to oseltamivir but remained sensitive to Zanamivir. A fifth subject (immunocompetent) in the 600 mg IV zanamivir arm harboured a H275Y at Baseline and a H275H/Y at Day 3, but had reverted to wildtype by Day 5. Subject 2475 had had 1 day of prior treatment with oseltamivir, which may have contributed to the selection of the H275Y substitution by Day 1.

Two variants were identified in Day 2 samples from 2 subjects in the 300mg IV Zanamivir arm with potential resistance associated NA substitutions, N294N/S and T325I in H3N2 viruses. Both subjects with resistant genotypes were immunocompetent and had positive clinical responses. The viruses in this study could not be cultured so the effect on susceptibility could not be determined. To ascertain the effect of the NA substitutions N294S and T325I on susceptibility to zanamivir reverse genetics analysis was carried out. Recombinant H3N2 virus with the N294S substitution was shown not to have an affect on susceptibility to zanamivir. However, recombinant virus with the T325I substitution could not be cultured so its effect on susceptibility could not be determined. The T325I substitution appears to reduce fitness of the virus which is a property commonly linked to resistance. In conclusion the T325I substitution may confer zanamivir resistance, although conclusive data could not be obtained as the virus could not be cultured.

No known zanamivir-associated resistance mutations developed in the 600 mg IV Zanamivir arm, demonstrating the high barrier to resistance of zanamivir.

## Summary of main study

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

**Table 36. Summary of efficacy for trial NAI114373**

| | | | |
|---|---|---|---|
| **Title:** A Phase III international, randomized, double-blind, double-dummy study to evaluate the efficacy and safety of 300 mg or 600 mg of intravenous Zanamivir twice daily compared to 75 mg of oral oseltamivir twice daily in the treatment of hospitalised adults and adolescents with influenza | | | |
| Study identifier | NAI114373: | | |
| Design | Phase III, randomized, double-blind, double-dummy, 3-arm study to evaluate the efficacy, antiviral activity and safety of IV Zanamivir compared to oral oseltamivir. | | |
| | Duration of main phase: | | Approximately 33 days for subjects whose treatment duration was 5 days, up to approximately 38 days for subjects whose treatment duration was extended to a maximum of 10 days |
| Hypothesis | Superiority of IV Zanamivir 600 mg | | |
| Treatments groups | IV Zanamivir 600 mg | | IV Zanamivir 600 mg BID, 5-10 days, 209 |
| | IV Zanamivir 300 mg | | IV Zanamivir 600 mg BID, 5-10 days, 201 |
| | oseltamivir 75 mg | | Oral oseltamivir 75 mg BID, 5-10 days, 205 |
| Endpoints and definitions | Primary endpoint | TTCR | Time to clinical response in subjects with confirmed influenza. Clinical response defined as resolution of at least 4 of the 5 signs maintained for at least 24 hours, or hospital discharge. Fever and oxygen saturation plus respiratory status, hearth rate, systolic blood pressure (2 out of 3) |
| | Secondary endpoint | | TTCR and time to improvement in respiratory status |
| | Secondary endpoint | | Mortality rate at day 14, 28 and end |
| | Secondary endpoint | | Change in Katz activities of daily living (ADL) score and other parameters of functional status |
| | Secondary endpoint | | Virological endpoints |
| | Secondary endpoint | | Incidence and duration of influenza symptoms |
| | Secondary endpoint | | Incidence of complications and antibiotic use |
| | Secondary endpoint | | Ventilation status |
| | Secondary endpoint | | Length of ICU and hospital stay |
| | Secondary endpoint | | Time to absence of fever, improved respiratory status, oxygen saturation, hearth rate and systolic blood pressure |
| Database lock | 18.03.2015 | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis** | | |

| | | | | |
|---|---|---|---|---|
| Analysis population and time point description | IPP-influenza positive population (ITT exposed, all randomized who received at least one dose with proven influenza infection) | | | |
| Descriptive statistics and estimate variability | Treatment group | IV Zanamivir 300 mg | IV Zanamivir 600 mg | Oseltamivir 75 mg |
| | Number of subject | 163 | 162 | 163 |
| | Median TTCR (days), primary endpoint | 5.87 | 5.14 | 5.63 |
| | <variability statistic> | missing | missing | missing |
| | Mortality, number | 10 | 12 | 10 |
| | Length of hospital stay (days, median) | 10.0 | 8.0 | 9.0 |
| | Min, max | 1, 108 | 2, 64 | 1, 58 |
| | Duration of ventilator support (days, median) | 9.0 (n=46) | 5.2 (n=37) | 8.2 (n=50) |
| | Min, max | 0, 38 | 0, 36 | 0, 36 |
| | | | | |

| | | | |
|---|---|---|---|
| Effect estimate per comparison | Primary endpoint | Comparison groups | IV Zanamivir 600 mg vs. Oral oseltamivir 75 mg |
| | | Median difference | -0.48 |
| | | CI | -2.11, 0.97 |
| | | P-value-Wilkoxon rank-sum 2-sided test | 0.3912 |
| | | Comparison groups | IV Zanamivir 600 mg vs. IV Zanamivir 300 mg |
| | | Median difference | -0.73 |
| | | CI | -1.79, 0.75 |
| | | P-value-Wilkoxon rank-sum 2-sided test | 0.2496 |

Regarding the dose effect relationship the applicant claims that both 300 mg and 600 mg doses demonstrated a similar efficacy profile. The recommended dose of 600 mg was the maximum daily dose for use in clinical trials based on the nonclinical data. The obvious advantage of the higher dose is higher concentration of zanamivir in the target organs which means less chance of developing resistance and better effect against viral strains with reduced sensitivity towards zanamivir. Further justification for the selected dose has been presented by the applicant in response to question related to dose.

## *Supportive studies*

**NAI113678 : An Open-Label, Multi-Centre, Single Arm Study to Evaluate the Safety and Tolerability of Intravenous Zanamivir hydrate in the Treatment of Hospitalized Adult, Adolescent and Paediatric Subjects with Confirmed Influenza Infection.**

This was an uncontrolled study in which IV zanamivir was administered twice daily for 5 days to hospitalized subjects with laboratory confirmed influenza (based on a positive RDT, antigen test, virus culture or RT-PCR). Treatment could be extended to 10 days if viral shedding was ongoing or if clinical symptoms warranted further treatment with IV zanamivir.

Eligible subjects included adults, children, pregnant women, renally impaired and immunocompromised subjects. The permitted time from onset of symptoms to initiation of study medication was up to 7 days. The target enrolment was 200 subjects, to include ~150 adults/adolescents and ~50 paediatric subjects with an aim to enrol across the following age cohorts:

• Cohort 1: 6 months to <1 year

• Cohort 2: 1 year to <2 years

• Cohort 3: 2 years to <6 years

• Cohort 4: 6 years to <13 years

• Cohort 5: ≥13 years

The adult dose and adjustment schema were as reported in the Phase III study. The paediatric dose schema is shown below.

**Table 37: Initial dose amounts and twice daily maintenance dose regimens of IV Zanamivir hydrate for pediatric and adolescent subjects with normal and impaired renal function**

| Adolescents (13 to <18 years) | Initial Dose | Maintenance Dose (given q12 hours) | | | | |
|---|---|---|---|---|---|---|
| | | CLcr or $CL_{CRRT}$ (mL/min) | | | | |
| | | ≥ 80 | 50 to <80 | 30 to <50 | 15 to <30 | <15 |
| | | Begin twice-daily (q12h) maintenance dosing 12 hours after initial dose | | | Begin twice-daily (q12h) maintenance dosing 24 hours after initial dose | Begin twice-daily (q12h) maintenance dosing 48 hours after initial dose |
| ≥50 kg body weight | 600 mg | 600 mg | 400 mg | 250 mg | 150 mg | 60 mg |
| <50 kg body weight | 12 mg/kg | 12 mg/kg | 8 mg/kg | 5 mg/kg | 3 mg/kg | 1.2 mg/kg |
| Children (6 to <13 years) | Initial Dose | Maintenance Dose (given q12 hours) | | | | |
| | | CLcr or $CL_{CRRT}$ (mL/min/1.73m$^2$) | | | | |
| | | ≥ 80 | 50 to <80 | 30 to <50 | 15 to <30 | <15 |
| | | Begin twice-daily (q12h) maintenance dosing 12 hours after initial dose | | | Begin twice-daily (q12h) maintenance dosing 24 hours after initial dose | Begin twice-daily (q12h) maintenance dosing 48 hours after initial dose |
| ≥50 kg body weight | 600 mg | 600 mg | 400 mg | 250 mg | 150 mg | 60 mg |
| <50 kg body weight | 12 mg/kg | 12 mg/kg | 8 mg/kg | 5 mg/kg | 3 mg/kg | 1.2 mg/kg |
| Infants and Children (6 months to <6 years) | Initial Dose | Maintenance Dose (given q12 hours) | | | | |
| | | CLcr or $CL_{CRRT}$ (mL/min/1.73m$^2$) | | | | |
| | | ≥ 80 | 50 to <80 | 30 to <50 | 15 to <30 | <15 |
| | | Begin twice-daily (q12h) maintenance dosing 12 hours after initial dose | | | Begin twice-daily (q12h) maintenance dosing 24 hours after initial dose | Begin twice-daily (q12h) maintenance dosing 48 hours after initial dose |
| >42.8 kg body weight | 600 mg | 600 mg | 400 mg | 250 mg | 150 mg | 60 mg |
| ≤42.8 kg body weight | 14 mg/kg | 14 mg/kg | 9.3 mg/kg | 5.8 mg/kg | 3.5 mg/kg | 1.4 mg/kg |

The primary objective was safety, but a number of clinical and virology endpoints similar to study NAI114373 was reported.

Exploratory analyses were performed to investigate the relationship between serum zanamivir PK to selected clinical, safety and virology endpoints.

**Table 38. Clinical and Virology Endpoints for PK/PD Analyses**

| Clinical Endpoints | Virology Endpoints |
|---|---|
| Mortality at Day 14<br>Mortality at Day 28<br>Length of total ICU stay<br>Length of hospital stay<br>Time to afebrile status | Decrease from Baseline on Day 3 by qPCR<br>Decrease from Baseline on Day 3 by qVC<br>Decrease from Baseline on Day 5 by qPCR<br>Time to virological improvement (one occasion)<br>Time to virological improvement (two successive occasions)<br>Time to undetectable viral RNA<br>Time to absence of cultivable virus |

The initial analysis was conducted with Pearson's correlation analyses to examine the correlations between PK parameters (i.e. AUC and Cmax from initial dose and AUC, Cmax and Cmin from repeat dose) and selected clinical, safety, or virology endpoints for the initial and maintenance doses. If any of the endpoints showed a consistent association with PK parameters, additional logistic regression analysis was carried out for overall evaluation.

Also in this study a separate virology report was included with assessment of viral susceptibility to zanamivir and presence of resistance substitutions that emerged during treatment.

Results – Adults

There were 130 adults enrolled of which 87 received ≤5 days and 43 received >5 days zanamivir. Of 23 withdrawn from study, 20 were due to fatal AEs. Subjects were 57% male with median age 47.5 years (24% were ≥60 years). Three subjects were pregnant and one was immediately post-partum. Four were on CRRT, 2 were on intermittent haemodialysis and one was on intermittent peritoneal dialysis.

At baseline, 60 (46%) were on mechanical ventilation and 3 were receiving ECMO. Another 46 subjects (35%) were receiving supplementary oxygen without mechanical ventilation.

Most (104; 80%) had received prior oseltamivir/oseltamivir phosphate and 2 had prior inhaled zanamivir. The median duration of prior influenza antiviral treatment was 2 days (range 1 to 12 days).

Using data from all available virology assays on all assessment days influenza subtype information was obtained from 125/130 subjects (96%) with A/H1N1pdm2009 in 71%, A/H3N2 in 12%, influenza A (subtype unknown) in 11%, and influenza B in 2%. The type/subtype was unknown in 4% of subjects.

Median time to virologic improvement (2 log reduction in titres in nasopharyngeal swabs or sustained undetectable virus <2.7 $\log_{10}$ copies/ml on two or more occasions using qPCR) was 3 days regardless of the final duration of treatment and was also 3 days for those who were PCR positive at baseline.

**Table 19** **Time to Virologic Improvement (Two Log Drop in Viral Load or Sustained Undetectable in Quantitative PCR) in Subjects PCR Positive at Baseline**

| | Zanamivir ≤5 days (N=87) | Zanamivir >5 days (N=43) | Total N=130 |
|---|---|---|---|
| **Virologic improvement** | | | |
| n | 64 | 27 | 91 |
| Censored, n (%) | 10 (16) | 5 (19) | 15 (16) |
| Success, n (%) | 54 (84) | 22 (81) | 76 (84) |
| **Days to success** | | | |
| n | 54 | 22 | 76 |
| Mean [SD] | 4.1 [3.69] | 4.4 [2.44] | 4.2 [3.36] |
| Median [Min, Max] | 3 [1, 26] | 3.5 [2, 12] | 3 [1, 26] |

**Table 39**

The median influenza A and B viral load by qPCR at baseline was 4.67 $\log_{10}$ copies/ml, and the median change was -0.75 $\log_{10}$ copies/ml by Day 3. For those who were PCR positive at baseline (n=93), the median viral load was 5.34 $\log_{10}$ copies/ml, and the median change was -1.42 $\log_{10}$ copies/ml by Day 3. Although the sample size was small, median baseline qPCR viral load was higher for A/H3N2 vs. H1N1pdm09 (6.98 vs. 5.34 $\log_{10}$ copies/ml, respectively).

Subjects who started treatment <5 days after symptom onset had higher median virus titres at baseline compared with those who started treatment ≥5 days after symptom onset (5.11 vs. 3.89 $\log_{10}$ copies/ml, respectively) and the median decrease in viral load was greater if treatment was started within 5 days.

The median time to no detectable viral RNA as determined by qPCR was 3 days.

Using all the viral load data excluding any non-detectable samples there was no correlation between the qPCR and qVC assays for measuring viral load within nasopharyngeal swabs (Pearson's correlation coefficient ρ=-0.012, p=0.88) or in endotracheal samples (Pearson's correlation coefficient ρ=0.45, p=0.31).

There were 26 deaths (20%) of which 17 (13%) occurred on or before day 14 and 22 (17%) on or before day 28. Median time to death was 10.5 days (range 1 to 44 days). Another 4 subjects died after day 28. Of those subjects who died due to complications of influenza (determined as per investigator assessment), 13 (10%) died on or before day 14 and 14 (11%) died on or before day 28 with a median time to death of 5 days (range 1 to 44 days).

Overall, 81 subjects (62%) contributed to the time to clinical response composite endpoint, while 49 (38%) never reached success criteria. The median time to clinical response was 9 days (range 2 to 32 days). The median time to return to normal criteria for each individual vital sign contributing to the composite clinical response endpoint was between 2 and 8 days.

The median duration of hospitalisation was 15 days (range 1 to 133 days) and 108 (83%) had a stay in ICU with a median duration of 11.5 days (range 1 to 104 days; including possibly days in ICU before entry into the study). Excluding subjects who died the median duration of hospitalisation was 19 days (range 2 to 133 days).

There were 100 subjects (77%) with a discharge date recorded. The median time to discharge was 16 days (2 to 133 days).

Stepwise logistic regression showed that H3N2 subtype, Hispanic ethnicity and delayed time to treatment with zanamivir were significant risk factors associated with mortality (p<0.05) whereas age was marginally significant (p=0.078). Therefore, the adjusted OR of 4.516 indicates that the odds of death are 4.516 times higher for subjects with H3N2 subtype than those without. Each single day delay in start of treatment increased the odds of death by 40%, and every 10 years increase in age increased the odds of

death by 37%. Multivariate Cox regression with stepwise selection method on time to mortality also confirmed the findings of the logistic regression.

Results – Paediatrics (<18 years)
Of 73 paediatric subjects enrolled into age cohorts shown below, 71 received zanamivir.

**Table 40**

**Table 6 Summary of Subject Discontinuation from the Study[a] (ITT-E Population)**

| Cohort | 1 | 2 | 3 | 4 | 5 | Total |
|---|---|---|---|---|---|---|
| Age | 6m to <1y | 1 to <2y | 2 to <6y | 6 to <13y | 13 to <18y | 6m to <18y |
| Total | 7 | 11 | 12 | 27 | 14 | 71 |
| **Completion Status, n (%)** | | | | | | |
| Completed[b] | 7 (100) | 9 (82) | 12 (100) | 26 (96) | 11 (79) | 65 (92) |
| Prematurely Withdrawn | 0 | 2 (18) | 0 | 1 (4) | 3 (21) | 6 (8) |
| **Primary reason for Withdrawal, n (%)** | | | | | | |
| Adverse Event[c] | 0 | 1 (9) | 0 | 1 (4) | 3 (21) | 5 (7) |
| Lost to follow-up | 0 | 1 (9) | 0 | 0 | 0 | 1 (1) |

Source Data: Table 1.2

a. Two subjects withdrew consent prior to receiving study drug and are not included in this table.
b. A subject was considered to have completed the study if they had received study drug and attended the Follow-up Post-Treatment +23 Days Assessment.
c. Five subjects who withdrew from the study due to an AE had a fatal AE during the study that led to their withdrawal

All 5 subjects who withdrew due to an AE died. Overall 61% received at least 5 days of treatment and 25 were prematurely withdrawn from zanamivir at investigators' discretion. Most (66%) were male, the median age was 7 years and 40 had at least one chronic underlying medical condition, including 9 immunocompromised subjects. Most subjects were confirmed to be influenza positive by rapid test for Influenza A or B (48%) or PCR (41%). Also, 34/58 subjects (59%) who had a chest X-ray at Baseline had an infiltrate present, 24 (34%) were on mechanical ventilation at baseline and another 4 were receiving ECMO while 12 were receiving supplementary oxygen but were not ventilated.

Most (50; 70%) had received influenza specific therapies before study entry and 49 had received prior oseltamivir with a median duration of prior treatment of 2 days (range 1 to 11 days).

Using results from all available virology samples and assays on all assessment days virus subtype information was obtained from 70/71 treated subjects. A/H3N2 and influenza B were reported in 25 subjects each, A/ H1N1pdm2009 in 12 and influenza A (subtype unknown) in 7. One subject was co-infected with A/H3N2 and B and the type/subtype was unknown in another subject.

For the total population, the median time to virologic improvement was 3 days (range 1 to 25 days) with no appreciable difference among the age cohorts (range 3 to 4 days). For the population who were PCR positive at baseline the median time to virologic improvement was 4.0 days with no appreciable difference among the age cohorts.

**Table 21** **Time to Virologic Improvement (Two Log Drop in Viral Load or Sustained Undetectable in Quantitative PCR) in Subjects PCR Positive at Baseline: Any Virus, by Cohort (ITT-E Population)**

| Cohort | 1 | 2 | 3 | 4 | 5 | Total |
|---|---|---|---|---|---|---|
| Age | 6m to <1y (N=7) | 1 to <2y (N=11) | 2 to <6y (N=12) | 6 to <13y (N=27) | 13 to <18y (N=14) | 6m to <18y (N=71) |
| **Virologic improvement** | | | | | | |
| n | 5 | 10 | 10 | 21 | 9 | 55 |
| Censored, n (%) | 0 | 3 (30) | 1 (10) | 8 (38) | 2 (22) | 14 (25) |
| Success, n (%) | 5 (100) | 7 (70) | 9 (90) | 13 (62) | 7 (78) | 41 (75) |
| **Days to success** | | | | | | |
| n | 5 | 7 | 9 | 13 | 7 | 41 |
| Mean [SD] | 4.4 [2.70] | 9.3 [9.50] | 4.2 [1.64] | 4.5 [1.13] | 5.0 [3.70] | 5.3 [4.54] |
| Median [Min, Max] | 4.0 [2, 9] | 4.0 [3, 25] | 3.0 [3, 7] | 5.0 [3, 6] | 4.0 [2, 13] | 4.0 [2, 25] |

**Table 41**

Virologic improvement occurred sooner for subjects infected with influenza A/H3N2 than with A/H1N1pdm09 or B.

Among 55/71 (77%) subjects with NP samples that were positive at baseline by qPCR, the median viral load at baseline was 6.66 $\log_{10}$ copies/mL and the median change viral load from baseline was -1.81 $\log_{10}$ copies/mL by day 3 and -2.94 $\log_{10}$ copies/mL at day 5. In this subset, the median baseline qPCR viral load was highest in subjects with influenza B followed by A/H1N1pdm09 and then A/H3N2 (7.17, 6.76, and 5.90 $\log_{10}$ copies/mL, respectively). The change in viral load at Day 3 was greatest for H3N2.

Subjects who started treatment <5 days after symptom onset had higher median virus titres at baseline compared with those who started treatment ≥5 days after symptom onset (6.25 vs. 5.665 $\log_{10}$ copies/ml, respectively). The median decrease in viral load was greater if treatment was started <5 days from symptom onset.

For the population who were virus culture positive, the median viral load at baseline by qVC was 3.0 $\log_{10}$ $TCID_{50}$/ml and the median change in viral load from baseline was -1.76 $\log_{10}$ $TCID_{50}$/ml by day 3.

Overall, the median time to no detectable viral RNA as determined by qPCR was 4 days and the median time to no detectable virus as determined by qVC was 3 days.

For the 9 subjects classified as immunocompromised the median time to virologic improvement was 5 days and 44% achieved undetectable viral RNA compared to 62% in the ITT-E population although the median time to no detectable viral RNA was slightly shorter

Three of the 5 subjects who died did so on or before day - 14. Median time to death was 12 days (range 6 to 25 days).

Among 24 subjects on mechanical ventilation there were 13 still receiving this treatment by day 5 and 3 by the end of the study (post treatment +23 days).

Clinical response was achieved in 65 subjects (92%) with a median time of 6 days (range 1 to 42 days). The median duration of hospitalisation was 6 days (range 1 to 45 days) and the median duration ICU stay was 7.5 days (range 2 to 50 days). For 65 subjects (92 %) with a discharge date recorded the median time to discharge was 6.0 days (1 to 45 days).

The median time to return to pre-morbid functional status was 5.0 days for the overall population, but ranged from 3.0 days for cohort 2 to 8.0 days for cohort 1.

Resistance

In study **NAI113678 adults** a low number of 50 throat samples out of 612 were phenotyped. The mean IC50s for the influenza A/H1N1pdm09, A/H3N2 and influenza B viruses were 0.20 ± 0.06 nM, 0.26 ± 0.07 nM and 1.61 ± 0.35 nM respectively, were within the ranges previously observed. The role of the HA mutations observed in this study in susceptibility to Zanamivir is not clear. Two resistance associated HA mutations, S162N and Q223R in influenza A/H1N1pdm09 viruses from two subjects emerged during treatment with Zanamivir. There is no clear evidence of treatment emergent NA resistance mutations.

In study **NAI113678 children** relatively few viruses were subjected to phenotypic analysis. Out of approximately 90 Day 1, and 200 post Day 1 samples, a total of 48 cultured samples from 35 subjects had sufficient viral titer for phenotypic analysis. Neither mean IC50 nor IC90 values increased during treatment. One immunocompetent subject (a 9 month old infant) had a treatment emergent substitution E119G in the NA gene on day 5 of treatment. This substitution is known to confer resistance to NAIs, however no phenotypic data were available for this subject. The subject had received oseltamivir for 3 days prior to enrolling in the study. One subject harboured the H275Y NA substitution at baseline, which may have been selected during 2 days of prior oseltamivir treatment. One subject harboured a treatment emergent HA resistance substitution but the effect on susceptibility could not be determined.

**NAI115215**

This was a small uncontrolled Japanese study that enrolled 21 adults (≥16 years of age; 20 confirmed influenza) hospitalised with influenza who were treated with 600 mg IV BID.

The primary objective was safety, but a number of clinical and virology endpoints, similar to study NAI114373 were reported.

The following efficacy endpoints were evaluated as secondary endpoint:

> Time to absence of fever, time to improved respiratory status, oxygen saturation, heart rate and systolic blood pressure, time to clinical response (TTCR same as NAI114373), time to return to pre-morbid level of activity, incidence and duration of clinical symptoms of influenza, incidence of complications of influenza and associated antibiotic use, ventilation status, length of ICU and hospital stays.

The median time to absence of fever was 24.9 hours (range 9.5 to 82.3) and the median time to clinical response was 85 hours (range 12.7 to 530 hours; n=20). The median time to return to pre-morbid level of activity as measured by the 3-point scale was 87.6 hours (range 21 to 714 hours; n=16). No subject had a stay in ICU at any point during the study.

The median time to virologic improvement was 3.0 days (range 2 to 5 days, n=19), the median time to no detectable viral RNA by quantitative RT-PCR from nasopharyngeal samples was 5.5 days (range 4 to 7 days; n=10) and the value based on quantitative viral culture was 3.0 days (range 2 to 4 days; n=17). For those with A/H3N2, the median viral load by qPCR at baseline was 8.92 $\log_{10}$ copies/ml with median changes on days 3 and 5 that were -2.74 and -3.73 $\log_{10}$ copies/mL.

**CUP REL113375**

As of 31 January 2017, the CUP for zanamivir aqueous solution supplied treatment to 3063 seriously ill hospitalised patients with influenza for which suitable approved alternative anti-viral treatment was unavailable, inappropriate or ineffective. Among the 783 patients with a CRF, most (76%) had underlying

medical conditions and 73% required mechanical ventilation, with 21% receiving ECMO. In this group of 783 patients the physicians considered the clinical outcome for 30% to be recovered or resolved, 37% not recovered or resolved and 26% fatal. Emerging signs of impairment of function or significant toxicities were noted most frequently for the renal (11%), hepatic (10%) and cardiovascular systems (10%).

**NAI115008 – CUP retrospective chart review**

With >1000 patients treated globally in the CUP up to 31 January 2011, this global retrospective chart review was used to obtain details on a subset. Tier 1 consisted of paediatric and pregnant/postpartum patients (1-14 days post-delivery) and Tier 2 cohort consisted of non-pregnant adults treated at Tier 1 centres. The review included 113 patients from 34 sites in 12 countries of which 8 were pregnant at hospital admission (4 second and 4 third trimester) and 3 were postpartum.

The physician was responsible for reviewing the patient's medical record and completing the CRF. The following data were collected:

Length of hospital stay, length of intensive care unit stay, underlying medical conditions, influenza history, oxygenation/ventilation, zanamivir treatment course, selected concomitant medications, clinical course/outcome, complications of influenza, all deaths.

Exploratory statistical analyses were performed to assess the relationship of the outcome (survival/death) and various factors including: gender, race, age, time from illness onset to initiation of antiviral therapy, and time from illness onset to hospital admission.

All patients had a diagnostic test for influenza and influenza A H1N1 2009 was the most common influenza sub-type identified. Among 12 paediatric patients with data, resistance was detected in 4 (H275Ysubstitution). Among 18 adult patients with data, resistance was detected in 4 (2 with an influenza H275Y variant and 2 with an E274 variant).

More than 80% of paediatric and adult patients received oseltamivir therapy during the hospitalisation period in which they received zanamivir aqueous solution. The route of zanamivir aqueous solution administration for the majority of paediatric (92%) and adult (76%) patients was IV and the median number of IV doses was 10 (range 1 to 37). The median time from hospitalisation to initiation of IV zanamivir was 4 days.

Overall, 34 paediatric patients (68%) were considered recovered or recovering at the time of their hospital discharge while 16 (32%) died (15 in the hospital and 1 after discharge). Also, 32 adult patients (51%) were considered recovered or recovering at the time of hospital discharge while 27 (43%) died (24 in the hospital and 3 after discharge).

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

Key clinical data on 600 mg IV Zanamivir across studies is presented below.

**Table 42. Key clinical data on 600 mg IV Zanamivir across studies (I)**

**(The numbers have been collected from CSRs or Summary report. IPP= influenza positive population, ITT-E intent to treat exposed population)**

| Study | % in IPP relative to ITT-E | Influenza type | % with underlying disease | % mechanical ventilation baseline | % with prior oseltamivir |
|---|---|---|---|---|---|
| **NAI114373** | 78 | 45% H3N2<br>36% H1N1pdm09<br>14% influenza B | 73 | - | 52 |
| **NAI113678 Adult** | 96 | 71% H1N1pdm09<br>12% H3N2<br>2% influenza B | 77 | 46 | 80 |
| **NAI113678 Children**<br>**6 m to < 18 y** | 99 | 35% H3N2<br>35% influenza B<br>17% H1N1pdm09<br>10% influenza A (unspecified) | 56 | 34 | 69 |
| **NAI115215** | 86 | 71% H3N2<br>14% influenza B | 76 | - | 29 |
| **NAI115008 Adults Compassionate use** | 100 | 67% H1N1pdm09<br>5% H1N1 seasonal<br>17% not known | 73 | 81* | 76 |
| **NAI115008 Children <6 m to < 18 y Compassionate use** | 100 | 68% H1N1pdm09<br>80% influenza A<br>4% influenza B<br>16% not known | 74 | 88* | 86 |

* no baseline.

**Table 43. Key clinical data on 600 mg IV Zanamivir across studies (II)**

| Study | Time from symptom start to treatment (days) Median (min-max) | Duration of treatment (days) Median (min-max) | Duration of hospitalization (days) Mean (min-max) |
|---|---|---|---|
| **NAI114373** | 3 (1 – 7) | 6 (1 – 11) | 11.9 (2 – 64) |
| **NAI113678 Adult** | 4.5 (1 -7) | 6.7 (1 – 11) | 21.6 (1 – 133) |
| **NAI113678 Children 6 m to < 18 y** | 4 (1 – 7) | 6 (1 – 11) | 11.8 (1 – 45) |
| **NAI115215** | (76% < 2 days) | 6 (1 – 6) | 7.1 (2.7 – 22) |
| **NAI115008 Adults Compassionate use** | Time from hospitalisation to treatment 4 (0 – 55) | 5 ( 1 – 23) | 32.8 (2 – 158) |
| **NAI115008 Children <6 m to < 18 y Compassionate use** | Time from hospitalisation to treatment 4 (0 – 296) | 5 (1 – 37) | 45.8 (4 – 301) |

**Table 44. Key clinical data on 600 mg IV Zanamivir across studies (III)**

| Study | TTCR Days Median (min-max) | Mortality (%) | % clinical response | Time to No Detectable Virus Median (min – max) |
|---|---|---|---|---|
| **NAI114373** | 5.1* | 7 | 87 | 4 (2 – 57) |
| **NAI113678 Adult** | 9 (2 – 32) | 20 | 62 | 3 (1 – 31) |
| **NAI113678 Children 6 m to < 18 y** | 6 (1 – 42) | 7 | 92 | 4 (1 – 28) |
| **NAI115215** | 3.5 (0.5 – 22) | 5 | 95 | 3 (2 – 4) |
| **NAI115008 Adults Compassionate use** | - | 38 | 51** | - |
| **NAI115008 Children <6 m to < 18 y Compassionate use** | - | 30 | 68** | - |

* min, max and confidence interval of primary endpoint missing?

** recovered or recovering

**Virology**

Several correlations of virological and clinical responses were investigated in the Phase II and Phase III zanamivir studies NAI113678 and NAI114373. Correlations between Pharmacokinetic (PK)/ Pharmacodynamic (PD) parameters and virology and clinical responses were explored.

A statistically significant correlation between time to clinical response (TTCR) and the reduction in viral load as determined by quantitative polymerase chain reaction (PCR) on day 3 was identified in NAI114373: Pearson's correlation coefficient = 0.1380, p-value = 0.0123. Other correlations could not be identified. Patients hospitalised with influenza often have an immunological features of disease progression and although they respond to antiviral treatment do not necessarily respond clinically.

**Table 45. Summary of Correlations between viral load and clinical response**

| **Study** | Correlation | Pearson's Correlation Coefficient | P-value |
|---|---|---|---|
| NAI114373 | Day 2, change in viral load from Baseline[1] vs. TTCR | 0.0914 | 0.0984 |
| NAI114373 | Day 3, change in viral load from Baseline[1] vs. TTCR | 0.1380 | 0.0123 |
| NAI113678 paediatric cohort | Day 3, change in viral load from Baseline[1] vs TTCR | 0.2909 | 0.0650 |
| 1. Viral load determined by quantitative PCR. Source data: NAI114373 Figure 2.32 and Figure 2.33, NAI113678 Figure 2.34. | | | |

Of the 28 outliers that had time to No Quantitative PCR and time to Sustained Virological Improvement of greater than 20 days, none had any resistance associated substitutions and only one subject in NAI114373 showed a fold shift in susceptibility of 6.16 (influenza A/H3N2) relative to a reference strain, which is within the normal range of inhibition categorised by the World Health Organisation. The clinical status of these outliers reflects the overall study populations, 71% of which had underlying medical conditions and 7% were immunocompromised. Although these 28 outliers had longer time to virological response, the majority (86%) responded clinically.

In conclusion, the 28 outliers did not have any single virological or clinical parameter there may account for lack of a virological response.

## Clinical studies in special populations

Zanamivir IV has been tested in clinical studies in age groups from 6 months to elderly and in patients with underlying diseases including immunosuppressed subjects.

**Table 46. The number of subjects in the age intervals 56-74, 75-84 and 85+.**

| | **Age 65-74** | **Age 75-84** | **Age 85+** |
|---|---|---|---|

| | (Older subjects number / total number) | (Older subjects number / total number) | (Older subjects number / total number) |
|---|---|---|---|
| Controlled Trials | 65 | 57 | 19 |
| Non Controlled trials | 20 | 14 | 6 |

## 2.5.2. Discussion on clinical efficacy

### *Design and conduct of clinical studies*

Based on the design of the above studies, it is only the main study **NAI114373** with an active control arm that has the potential to appropriately evaluate efficacy. The use of oseltamivir, considered a standard treatment, as a control was according to scientific advice. Indeed, the comparator was 75 mg oral oseltamivir, which is being used extensively for treatment of uncomplicated influenza as well as in patients hospitalised for severe, complicated influenza. Although there are no efficacy data from randomised, placebo-controlled trials in hospitalised influenza patients, oseltamivir has been recommended and used for many years. Use of placebo control is considered unethical for this patient group, therefore the use of oseltamivir as an active comparator is supported. The limitation by using this comparator is that no claim of efficacy can be made unless superiority is demonstrated. The extensive use of oseltamivir is based on efficacy shown for uncomplicated influenza in outpatients, the effect on viral load and case reports and retrospective studies in hospitalised influenza patients.

The patient population enrolled met criteria that would be widely regarded as defining a population considered to have complicated influenza. There was stratification at randomisation based on time from onset of symptoms to initiation of treatment (≤4 days and 5 to 6 days; 6 days was the maximum allowed). The SmPC has been revised and it is now stated that treatment with Dectova should commence as soon as possible and usually within 6 days of the onset of symptoms of influenza.

With a mean and median duration of treatment ~6 days in each group, some subjects had their treatment extended according to protocol. Only 12% of patients (11-13% across treatment groups) received more than 5 days treatment.

For NAI114373, the primary endpoint was the time to clinical response (TTCR) in subjects with confirmed influenza. Clinical response was defined as resolution of at least 4 of the 5 signs within the respective resolution criteria, maintained for at least 24 hours, or hospital discharge, whichever occurred first. The 5 responses were: fever AND oxygen saturation AND 2 out of 3, including respiratory status, hearth rate and systolic blood pressure. The same endpoints have been used for hospitalised influenza patients for other anti-influenza drugs.

A large number of secondary efficacy endpoints were assessed:

The combined analysis of TTCR and time to improvement in Respiratory Status, mortality rate, functional status (change from baseline, time and proportion that return to baseline), incidence and duration of clinical symptoms of influenza, complications and antibiotic use, ventilation status, length of ICU and hospital stays, time to absence of fever, time to improved respiratory status, oxygen saturation, heart rate and systolic blood pressure.

Virology endpoints are also relevant for efficacy and both viral load and the presence of resistant strains were thoroughly measured and reported. A separate virology report was included with assessment of viral susceptibility to zanamivir at baseline and throughout treatment by NA and HA sequence analysis

and NA enzyme inhibition assay, frequency of resistance substitutions that emerged during treatment and the presence and frequency of minority species with resistance substitutions.

- Time to virologic improvement, defined as a 2 log drop in viral load or sustained undetectable viral RNA as measured by qPCR from nasopharyngeal samples, time to no detectable viral RNA by qPCR and viral culture, change from Baseline in viral load as measured on Day 3 and Day 5, and Day 8, Day 10 and/or last day of randomized treatment.
- Proportion of subjects with undetectable viral RNA by qPCR and absence of cultivable virus samples on Day 3 and 5, and Day 8, Day 10 and/or last day of randomized treatment.
- Viral susceptibility to zanamivir and oral oseltamivir at Baseline and throughout treatment by NA and HA sequence analysis and NA enzyme inhibition assay.

PK was also part of the study. However, due to sparse PK sampling (one end-of-infusion sample on Day 1 and a pre-dose, end-of-infusion and post-dose sample on Day 4) calculation of AUC was not planned for PK analysis.

Only study NAI114373 had efficacy as primary endpoint. The main controlled study **NAI114373** and the two supportive studies **NAI 113678** and **NAI115215** were all adequate regarding methods, conducting, analysis and reporting. The large number of secondary endpoints related to clinical outcome and virology data for all three studies gave detailed and valuable information. The large variability in the patient populations regarding age, underlying disease, time to treatment, progress and severity of influenza disease influence the precision of the endpoints. On the other hand, the variability may gain insight into what factors that have the largest impact on disease progression. Statistical analysis of factors affecting endpoints was conducted and reported for studies **NAI113678** and **NAI115008** Compassionate use.

### *Efficacy data and additional analyses*

In the pivotal trial **NAI114373,** the median time-to-clinical-response in days was not statistically different for IV zanamivir 600 mg and oseltamivir 75 mg. That relates to the total influenza positive population and the subgroups: ICU/mechanical ventilation and symptom onset ≤ 4 days, which were part of the primary endpoint analysis. Thus, the study failed the primary goal of demonstrating superiority of zanamivir 600 mg IV over oseltamivir 75 mg. Also, *post-hoc* analysis showed that for the subgroups: symptom onset > 4 days, female and male, there were no significant differences between treatments.

The median time to clinical response was 0.48 days shorter for IV zanamivir 600 mg compared to oseltamivir 75 mg. There was a large non-significant difference in favour of IV zanamivir in the subgroup symptom onset > 4 days, time to clinical response was 9.8 days for zanamivir 600 mg IV and 19 days for oseltamivir 75 mg (p value 0.178).

A comparison of outcomes for subgroups with up to or more than 5 days treatment is limited by the smaller numbers in the latter subset. Nevertheless, as expected, the clinical response rates were lower and median TTCRs longer in the latter subset. This finding applied across the three treatment groups and there was no disadvantage for zanamivir.

The indication applied for has a patient population limited by: 1) when circulation strains are resistant to approved anti-influenza medications and/or 2) cannot take medicines by other route than IV. The indication represents a patient population where zanamivir IV has a potential to be superior to other influenza therapies. However, none of the potential advantages of IV zanamivir was demonstrated in the comparative study or in other studies. Firstly, the inclusion criteria in study NAI114373 included the ability of patients to take oral capsules (randomised to oral oseltamivir) and secondly the circulation of oseltamivir-resistant virus was very low in the study period. Thus, the potential superiority of IV zanamivir over oral oseltamivir for the limited patient population according to the proposed indication

could not be demonstrated. The one thing that was demonstrated was that IV zanamivir and oral oseltamivir had similar clinical and virology outcomes for the selected patient population.

When the superiority analysis against oral oseltamivir failed, and there are no randomised studies to compare oseltamivir with placebo for hospitalised patients with complicated influenza, there is no direct proof of efficacy of zanamivir in this population of hospitalised influenza patients.

A positive side of the clinical data, however, pertains to the fact that the patients represent a wide spectrum of severity of disease, age groups, underlying diseases and influenza strains. Both the pandemic H1N1pdm09 and seasonal H3N2 strains are well represented in the data, with a smaller fraction of influenza B. In some of the studies high mortality due to influenza was reported. The large and detailed patient data material was analysed for risk factors of importance for clinical outcome. Clearly, the time from symptom onset to treatment was one of the important factors. The applicant has performed an analysis of the effect of delayed start of treatment with zanamivir controlling for the prior use of oseltamivir. The data show that there is a large positive effect of early start of treatment (≤4 days) compared to delayed treatment (> 4 days), regardless of prior treatment with oseltamivir. The patients receiving prior treatment with oseltamivir had slower response rate compared to those who did not receive oseltamivir prior to treatment, which could be due to differences in disease severity. In the pivotal study about half of all subjects had received oseltamivir for a median of 2 days before study entry but they still met the entry criteria. Clinical response rates were higher in those with no prior oseltamivir use, but this observation applied across the three treatments, with preservation of numerical superiority for zanamivir, suggesting that it was not oseltamivir use *per se* that was impacting the treatment effect but likely an issue related to duration of illness at the time of enrolment. Median TTCR results overall are in keeping with clinical responses since those who had received pre-study oseltamivir took longer to respond in each treatment group. When comparing the proposed zanamivir dose (600 mg BID) with oseltamivir, TTCR values were slightly longer for oseltamivir regardless of prior treatment. However, in those without prior oseltamivir usage the TTCR was slightly longer for 300 mg BID IV vs. the oseltamivir group. The results suggest that the proposed dose performs at least as well as oseltamivir regardless of prior oseltamivir treatment. Furthermore, the revised indication would direct usage towards those who likely already received and failed oseltamivir.

The breakdown of clinical response rates and TTCR in subsets with and without nausea and/or vomiting at baseline, do not indicate that having one or both symptoms had a negative impact on the responses to oseltamivir. Therefore, the concern that the presence of these symptoms might have favoured IV zanamivir over oral oseltamivir has been addressed.

The following subgroup analyses for the primary endpoint TTCR were performed:

1) Influenza A versus influenza B
2) start with treatment ≤ 48 hours after onset of disease versus start with treatment > 48 hours after onset of disease.

Clinical response rates were similar cross subgroups influenza A and B. The TTCR was slightly longer in the symptom onset > 2 days subgroup compared with the symptom onset ≤ 2 days subgroup.

The applicant has provided the breakdown of clinical response rates and TTCR values by age sub-group. It is agreed that the results within subgroups should be interpreted with some caution. For the most part there is no disadvantage for zanamivir (both or at least one dose group) compared to oseltamivir. It does appear that the fewer subjects aged ≥85 years were least likely to do well, but this observation applies across treatments. Overall, considering the limitations of the numbers in the oldest categories, there are no specific concerns raised by the findings by age sub-group.

Regarding the dose effect relationship the applicant claims that both 300 mg and 600 mg doses demonstrated a similar efficacy profile. The recommended dose of 600 mg was the maximum daily dose

for use in clinical trials based on the nonclinical data. The obvious advantage of the higher dose is higher concentration of zanamivir in the target organs, which means less chance of developing resistance and better effect against viral strains with reduced sensitivity towards Zanamivir. The applicant has adequately justified the dose of 600 mg.

In study **NAI113678** the results from stepwise logistic regression identified four important risk factors for mortality. H3N2 subtype, Hispanic ethnicity, and delayed time to treatment with Zanamivir were significant risk factors associated with mortality ($p<0.05$); whereas age was marginally significant ($p=0.078$). Each single day delay in start of treatment increased the odds of death by 40%, and every 10 years increase in age increased the odds of death by 37%. The small numbers in the Hispanic ethnic group precludes any reliable conclusions on the effect on increased risk of mortality. It was not unexpected that more older subjects were infected with H3N2 than H1N1pdm09 strains and had a higher risk of adverse influenza outcomes. There were insufficient numbers to assess the interaction term in the model between A/H3N2 and age. However, the median age of influenza A/H3N2 infected subjects was higher than the median age of all other subjects, Factors found not to be strongly associated ($p > 0.1$) with mortality in this exploratory analysis included: duration of treatment, gender, pre-study antiviral use, immunomodulator use, BMI, and Baseline qPCR viral load. No consistent statistically significant correlations were identified between PK parameters and virology endpoints.

The number of paediatric patients in study NAI113678 in each age interval is small: n=7 (6m to< 1y), n=11 (1 to<2y), n=12 (2 <6y), n=27 (6 to<13y), n=14 (13 to<18y). A comparison with the adult population in the same study is difficult because the adults were exposed to the pandemic H1N1pdm09 strain when it was introduced and experienced high mortality and more severe disease compared to the children. The higher frequency of clinical response among the children is probably due to different study period resulting in exposure to different influenza strains with variable virulence. There is no indication of large differences in clinical outcome comparing data from children and adults.

In the Compassionate use programme study **NAI15008** exploratory statistical analyses were performed to assess the relationship of the outcome and various factors such as gender, race, age time from illness onset to initiation of therapy. The analyses were limited by small sample size. The only significant factor was time from symptom onset to first zanamivir administration, which may potentially have had impact on survival in adult and pregnant patients.

**Viral load**

Study **NAI114373** is discussed, but the results from study **NAI113678 Adults and children** are comparable. The majority of patients experienced a clearance of virus within 3 days after start of treatment with no detectable viral RNA and no virus detected by culture. The range in time to no detectable virus is large (1-36 days) and many patient lack post treatment measurements.

At baseline the number of virology samples are n=156, while the numbers measured post treatment are less than half (n=73 and 58 at days post treatment +28 and +5, respectively). One out of 73 patients is positive at post treatment + 28 days. The median time to success of 3.0 days is satisfactory. However, the mean days to success being 6.7, the standard deviation 8.86 and the maximum number of days being 35, indicate that a large proportion of patients used a long time to clear the virus.

No single factor could characterise the patients that had more than 20 days to sustained virological improvement and no quantitative PCR detection, but a majority (86%) of them achieved clinical success.

**Resistance**

Across studies, 10 subjects in studies NAI113678 and NIA114373 had oseltamivir NA resistance substitutions. Seven patients fully recovered, two failed to respond and one died on the study. Six

subjects showed a reduction in viral load and four did not show a virological response. None of the viruses isolated from these subjects showed a >5-fold change in susceptibility to zanamivir. The presence of oseltamivir resistant virus did not seem to affect the clinical outcome of the subjects treated with IV zanamivir.

There have been nine case reports in the scientific literature of treatment emergent resistant viruses with known resistance substitutions isolated from immunocompromised patients who received IV Zanamivir via the CUP and one from an immunocompromised adult from study NAI113678 (E119D), who died on the study. Influenza infections in immunocompromised patients have been shown to have prolonged viral replication despite antiviral therapy, and therefore an increased risk of antiviral resistance emergence and persistent illness.

Treatment-emergent resistance to zanamivir is rare and is more commonly reported in immunocompromised patients (see detailed in “Pharmacology” section). There are 10 recorded cases of treatment-emergent zanamivir resistance in immunocompromised subjects, one from the IV zanamivir study NAI113678, one following treatment with nebulised zanamivir and two from inhaled zanamivir, reported in the literature, and six from the IV zanamivir Compassionate Use Programme. The clinical outcome was 9 deaths and one survived. The SPC, section 4.4, has been updated with a warning regarding a higher possibility of development of resistance in immunocompromised and the importance to monitoring resistance.

## *Additional expert consultation*

A Scientific Advisory group (SAG) meeting was organised to address the following concerns:

1. ***The strength of available evidence to support the efficacy of NAIs in complicated influenza, and the extent to which data generated with other NAI’s can be extrapolated to i.v. zanamivir***

It was acknowledged by the SAG that reviews of the available data on the clinical efficacy of NAIs in the treatment of complicated influenza by public health agencies, independent scientific review panels, and professional bodies have resulted in widespread recommendations to use NAIs in this patient group.

The SAG discussed the available evidence in support of the efficacy of NAIs in complicated and potentially life-threatening influenza and concluded that although the body of evidence is weak, relying on observational studies and meta-analyses, it is nevertheless consistent with a clinical benefit.

However, the group noted that the available evidence on the efficacy of NAIs in complicated and potentially life-threatening influenza is particularly weak in the paediatric population and identified this as a research priority. The group also raised the issue that the lack of definitions for ‘complicated’ and ‘life threatening’ influenza further complicates interpretation of data and implementation of guidelines.

The SAG considered whether it was reasonable to extrapolate data generated with other NAIs to IV zanamivir. The SAG were in agreement that, given what is known about the mechanism of action, comparable data from *in vitro* and *in vivo* studies, and studies in uncomplicated influenza, relevant data generated with other NAI’s could be reasonably extrapolated to IV zanamivir.

***2. The expectation of clinical benefit for i.v. zanamivir when used in complicated influenza given available in-vitro and in-vivo data for inhaled and i.v. zanamivir***

In the pivotal Phase III study, IV zanamivir failed to meet the primary endpoint of superiority in time to clinical response, showing similar clinical and virologic outcomes compared to oseltamivir.

Whilst evidence of efficacy has not been demonstrated in prospective randomised controlled trials in the treatment of complicated influenza, the SAG concluded that an expectation of clinical benefit can be derived based on the totality of the available evidence on NAIs and the development programmes for inhaled and IV zanamivir.

The SAG agreed that *in vitro/ in vivo* data obtained for inhaled and IV zanamivir provide a reasonable expectation of clinical benefit when used in complicated influenza.

***3. The safety profile of i.v. zanamivir***

The safety profile of IV zanamivir has been determined in influenza patients with a range of comorbidities and co-medications, which would be reflective of the real-world population of complicated influenza.

Considering the data seen by the experts and notwithstanding possible limitations in the size of the study population, the Group expressed the view that the safety profile of IV zanamivir is likely to be acceptable.

***4. Zanamivir's place in therapy if it was approved.***

The SAG considered the medical need for IV zanamivir and the proposed indication in the application to EMA.

The SAG members were in agreement that there is an unmet medical need for IV zanamivir. Primarily, IV zanamivir would offer a parenteral option to critically ill patients and others with complicated and potentially life-threatening influenza in whom NAI treatment is recommended but who are unable to receive oral or inhaled NAIs. In addition, zanamivir has a different resistance profile to other NAIs and IV zanamivir would be of value in patients infected with oseltamivir/peramivir resistant influenza strains who are unable to receive treatment with inhaled zanamivir.

The proposed indication would limit the use of IV zanamivir to second-line or "last-resort" treatment in most circumstances.

The experts were in agreement with the indication as proposed, which clearly covers the group of patients who may benefit from the therapeutic intervention. No extra restrictions, neither further widening of the indication was recommended

5. ***Whether and which other meaningful data could be collected to further support efficacy of zanamivir i.v. in complicated influenza***.

The applicant had proposed the following measures:

- Post-authorisation effectiveness study (PAES)

- Post-authorisation European Pregnancy Registry
- Neonatal study (0-6 months of age) as part of Paediatric Investigation Plan (PIP)

The SAG extensively discussed the proposed measures and expressed the need for more robust data collection in order to further substantiate the effectiveness of IV Zanamivir. The retrospective chart review effectiveness study was not considered fully satisfactory since there are uncertainties regarding data completeness and quality when making use of medical records alone. This could potentially challenge reliable adjustment for confounding factors. The SAG were also unclear about the comparator group, and highlighted the importance of concurrent controls given that influenza severity and resistance profiles change over time.

Also, the SAG expressed a concern that the available information may not be adequate to inform the correct use of IV zanamivir in some select sub-group of patients, such as patients on renal replacement therapy or ECMO. It was acknowledged that it may be difficult to obtain adequate comparative clinical data in these subgroups but the SAG felt it would be desirable to supplement the clinical data with PK/PD data in these subgroups to properly inform the clinical use of IV zanamivir.

The SAG supported the proposed Post-authorisation European Pregnancy Registry and the neonatal study.

Following the SAG, the indication was further narrowed following comments raised by the CHMP, and the Applicant submitted a revised SmPC addressing these concerns.

### *Additional efficacy data needed in the context of a MA under exceptional circumstances*

The following measures have been agreed with the CHMP:

The applicant commits to a retrospective observational chart review study to evaluate the clinical effectiveness of treatment with zanamivir 10 mg/ml solution for infusion in a cohort of ICU-treated patients with complicated influenza. A detailed protocol has been submitted and the study is to be initiated soon after obtaining the MA.

In addition, a prospective observational study to evaluate the clinical effectiveness of treatment with zanamivir 10 mg/ml solution for infusion in patients with complicated influenza infection if and when specific conditions are met which may lead to an increase usage of IV zanamivir, is agreed. Examples of such conditions being when European Public Health Clinical Practice Guidelines for the treatment of influenza recommend the early or first line use of IV zanamivir, such as during a severe influenza pandemic or when there is influenza known to be resistant to other antivirals than zanamivir widely circulating in the European Union as reported by the European Reference Laboratory Network for Human Influenza (ERLI-Net). The applicant envisages Scientific Advice regarding the design and criteria for initiation of the prospective study.

## 2.5.3. Conclusions on the clinical efficacy

The comparative study in hospitalised influenza patients showed that 600 mg IV zanamivir and 75 mg oral oseltamivir have similar results regarding clinical and virology endpoints. As there is no data on oseltamivir compared to placebo in hospitalised influenza patients from randomised clinical trials there is no definite demonstration of efficacy.

The indication is limited to patients infected with influenza virus strains that are resistant to approved therapies or who are unable to receive therapy through other routes than IV administration. The potential

benefit of zanamivir IV to the limited patient population was not demonstrated in the studies due to lack of circulating strains resistant to oseltamivir. Nevertheless, zanamivir has *in vitro* activity against viruses with the most common mechanisms of resistance to oseltamivir and peramivir. In a human challenge study (though preventative setting), the proposed dose clearly showed virological and clinical effects. Oseltamivir is widely used to treat complicated influenza even though data are lacking to unequivocally demonstrate its benefit. If oseltamivir-resistant virus emerges to a considerable extent having an IV preparation of zanamivir available for use would be expected efficacious. In cases of resistance to oseltamivir or peramivir, there would be a lack of alternative therapies and considering the severity of the potential life-threatening disease, the rationale of a medical need for IV zanamivir can be agreed. This is supported by the fact that approximately 3000 patients have been treated in the Compassionate use programme (CUP).

Compared to CUP, the use of IV zanamivir based on a Marketing Authorisation (under exceptional circumstances) is favourable in that more systematic collection of data from use will be generated through Risk Management Plan and Periodic Safety Updates. Furthermore, two specific obligations related to collect further data on effectiveness are agreed.

The applicant has presented a review of the current public health recommendations for use of NAIs in complicated influenza and the clinical data that support the recommendations. Recent review of the public health recommendations included studies by Cochrane, studies from the 2009 H1N1 pandemic and others.

The public health guidelines from Europe and globally, as well as recent reviews on clinical data, support current recommendations. Guidelines from USA, England WHO, ECDC, Japan and Australia have been presented. NAIs are generally recommended for use against severe influenza. According to ECDC there are 21 countries in EU/EEA that have national recommendations regarding influenza antiviral use for patients with severe or progressive influenza requiring hospitalisation. Antiviral agents are also recommended for outpatients who are at risk of influenza complications.

The recent confirmation of the public health recommendations [ECDC, 2017] about the use of NAIs together with the fact that 3000 patients have received IV zanamivir in compassionate use programme, demonstrates the medical need involved. It is unfortunate that the absolute efficacy of NAIs in the treatment of complicated influenza has not been determined in RCTs against placebo, and probably never will due to the inherent difficulties involved. However, in spite of that, it is a fact that NAIs have for a long time been used as a standard of care in hospitals and there are data from different sources to support the recommendation and use.

Regarding justification for the dose regimen, the selection of 600 mg IV BID for 5-10 days can be accepted.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a MA under exceptional circumstances:

*1. A retrospective observational chart review study to evaluate the clinical effectiveness of treatment with zanamivir 10mg/ml solution for infusion in a cohort of intensive care unit-treated (ICU) patients with complicated influenza infection*

*2. A prospective, observational effectiveness study of IV zanamivir in patients with complicated influenza*

## 2.6. Clinical safety

### Patient exposure

The clinical safety is based on 201 subjects exposed in phase I studies, 643 patients treated in clinical trials phase II and III and 3176 patients treated in the Compassionate Use Programme (3063 from CUP + 113 from a chart review within the CUP programme). One of the supportive studies (phase II NAI113678, incl. both children and adults) was performed during the influenza A/H1N1 pandemic 2009/2010. Both studies in the Compassionate Use Programme included patients treated during the influenza A/H1N1 pandemic 2009/2010.

In the pivotal study (NAI114373) the safety of zanamivir IV could be compared to safety of oseltamivir treatment.

Safety is evaluated in both children and adults:

**Table 47**

Table SIII.2: Age group and gender (IV zanamivir)

| Age group | Subjects | | Person time (days) | |
|---|---|---|---|---|
| | M | F | M | F |
| **Infants and toddlers** | | | | |
| 6 months to less than 1 year | 6 | 1 | 39 | 6 |
| 1 year to less than 2 years | 7 | 4 | 31 | 27 |
| **Children** | | | | |
| 2 years to 5 years | 8 | 4 | 43 | 24 |
| 6 years to 12 years | 18 | 9 | 82 | 71 |
| Adolescents | | | | |
| 13 years to 17 years | 13 | 6 | 69 | 30 |
| **Adults** | | | | |
| 18 years to 64 years | 357 | 214 | 1794 | 1216 |
| **Elderly people** | | | | |
| 65-74 years | 58 | 36 | 334 | 184 |
| 75-84 years | 48 | 28 | 276 | 139 |
| 85 + years | 10 | 17 | 51 | 102 |
| **Total** | 525 | 319 | 2719 | 1799 |

Studies included in this analysis are C92-083, NAIB1003, NAIB1008, NAIB1009, NAIA1010, NAI108127, NAI114346, NAI115070, NAI106784, NAI117104, NAI113678, NAI114373 and NAI115215.

In the clinical trials phase II and III zanamivir IV were administered 300mg BID or 600mg BID.

In the compassionate use programme patients were either administered IV zanamivir 600 mg or nebulized zanamivir 25 mg x 4, mentioned as administration of zanamivir aqueous solution, but most patients (98%) were administered IV zanamivir.

### *Adverse events*

In the pivotal phase III study NAI114373, in the open-label phase II study NAI113678 with adult and paediatric cohorts and in the open-label study in Japanese patients NAI115215, the safety assessments included AE recording, haematology and clinical chemistry, ECGs, and vital signs.

In the Compassionate use programme (study REL113375) physicians are asked to provide safety and clinical outcome data to GSK via a brief CRF. However, only SAE reporting is mandatory in accordance with local regulations. As the programme is not a GSK-sponsored clinical study, the quality and completeness of the data cannot be assured, and it is possible that not all SAEs have been reported. Completion of the CRF to collect safety and clinical follow-up information for patients in the CUP was optional and the CRF was only returned for 783/3063 patients (26%). Furthermore, as the CUP was not a clinical study, there was no monitoring and no mechanism to resolve inconsistencies or obtain missing data. Abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsened from Baseline and judged by the treating physician to be clinically significant, were to be recorded as AEs or SAEs. As a condition of receiving zanamivir aqueous solution for compassionate use, treating physicians were asked to report all SAEs from the time of first dose through 14 days after completion of treatment to GSK. For analysis of safety, data was collected from a Master Summary Tracking Sheet including data on the patient and dosage, from the CRF filled in by the physician and from GSK Global Clinical and Pharmacovigilance database ARGUS, where adverse events where recorded.

The retrospective chart review (NAI115008) was specifically designed to collect safety and clinical outcome data from any paediatric or pregnant patients (collectively referred to as the “Tier 1” cohort). In addition, as a secondary objective, data were collected from other adult patients (referred to as the “Tier 2” cohort).

In the clinical trials drug-related AEs were seen in 7-22% of adult patients and in 7% of children. Most common AEs in adults were diarrhoea (7%), constipation (6%), increase in liver transaminases (5%) and cytolytic hepatitis (4%). In the CUP, drug-related AEs were seen in 2% of patients, most common were pyrexia (<1%). In the CUP mostly treatment-related AEs were reported, but no pattern of drug-related AEs could be seen.

In the following a more detailed overview of the AEs seen in the individual studies is given. The reactions seen in the clinical trials and in the CUP studies are reflected in the proposed SmPC section 4.8. All reactions should, however, be referred to in the table format with frequencies.

An overall summary of AEs for IV zanamivir-treated subjects in the Phase II (NAI113678) and Phase III (NAI114373 – pivotal and NAI115215 – Japanese) studies is presented in Table below.

**Table 48**

**Table 8 Overall Summary of AEs for Subjects in Phase II/III Studies (Safety Population; Studies NAI114373, NAI113678, and NAI115215)**

| | NAI114373 | | | NAI113678 (Adult Cohort) | NAI113678 (Paediatric Cohort) | NAI115215 |
|---|---|---|---|---|---|---|
| | IV zanamivir 300 mg (N=201) | IV zanamivir 600 mg (N=209) | Oseltamivir 75 mg (N= 205) | IV zanamivir 600 mg (N=130) | IV zanamivir 600 mg (N=71) | IV zanamivir 600 mg (N=21) |
| Any AE, n (%) | 111 (55) | 128 (61) | 134 (65) | 110 (85) | 51 (72) | 13 (62) |
| Any drug-related AE, n (%) | 25 (12) | 22 (11) | 35 (17) | 28 (22) | 5 (7) | 3 (14) |
| Any Grade 3 or 4 events, n (%) | 39 (19) | 45 (22) | 44 (21) | 57 (44) | 23 (32) | 2 (10) |
| Any Death | 15 (7) | 15 (7) | 11 (5) | 26 (20) | 5 (7) | 1 (5) |
| Any SAE [a] | 38 (19) | 33 (16) | 38 (19) | 44 (34) | 15 (21) | 4 (19) |
| Any AE leading to discontinuation from study [a], n (%) | 14 (7) | 16 (8) | 13 (6) | 20 (15) | 5 (7) | 1 (5) |
| Any AE leading to discontinuation of study drug, n (%) | 8 (4) | 10 (5) | 11 (5) | 17 (13) | 2 (3) | 0 |
| Any protocol-defined liver event, n (%) [b] | 4 (2) | 3 (1) | 7 (3) | 17 (13) | 2 (3) | - |

Source Data: m5.3.5.1 NAI114373 CSR Section 7.1 and Section 7.2; m5.3.5.2 NAI113678 Adult CSR Section 7.1 and Section 7.2; m5.3.5.2 NAI113678 Paediatric CSR Section 7.1 and Section 7.2; m5.3.5.2 NAI115215 CSR Section 7.1 and Section 7.2

a. Including fatal events.

b. Subject 1458 (600 mg IV zanamivir arm) experienced a liver event (ALT≥5xULN) and should have been included in Source Data Table 3.13 but was not included because there were no data related to this event in the liver event form of the eCRF/dataset. Subject 872 (oseltamivir arm) entered the study as a protocol violator and met liver event criteria before receiving IP (i.e., was not a protocol-defined liver event and should not have been included in the analysis, and was not reported as AE). Subject 247 (oseltamivir arm) experienced the liver event at the end of S/R 600 mg IV zanamivir treatment

Note: In NAI113678, paediatric (6 months to <13 years) and adolescent (13 to <18 years) subjects received an age-adjusted, weight-based dose intended to provide comparable systemic exposures to 600 mg in adults. In NAI114373, the standard doses were adjusted in subjects with respect to age, weight, and renal function.

In general, the incidences of AEs across all categories in the adult cohort of Phase II Study NAI113678 were higher compared with the Phase III study. This is not surprising given that the adult cohort of the Phase II study enrolled patients primarily during the H1N1 pandemic and immediate post-pandemic period. In addition, the adult cohort Phase II entry criteria favoured sicker patients compared with the Phase III study (e.g., Phase III patients had to be able to take oral medication for enrolment and fewer were in an ICU setting or receiving ECMO).

***Pivotal study NAI114373 (phase III)***

In the pivotal study NAI114373, the most common events were diarrhoea (6%) and constipation (5%). These AEs were also the most common events in the 600 mg IV zanamivir and 75 mg oseltamivir groups; diarrhoea and hypertension were the most common AEs in the 300 mg IV zanamivir group. In general, the nature and incidence of AEs were similar across treatment groups.

Eighty-two subjects (13%) reported AEs considered by the investigator to have a possible causal relationship to the study drug, with slightly more considered attributable to study drug in the oseltamivir arm (17%) compared with the 300 mg and 600 mg IV zanamivir arms (12% and 11%, respectively).

Overall, the most common drug-related AEs were diarrhoea, increased ALT, and increased aspartate aminotransferase (AST), each occurring in a similar percentage of subjects in the 2 IV zanamivir groups as well as the oseltamivir group.

**Table 49**

**Table 14 Drug-Related Adverse Events Reported in ≥ 1% of Subjects in any Treatment Group (Safety Population, Study NAI114373)**

| Preferred Term | IV zanamivir 300 mg (N=201) | IV zanamivir 600 mg (N=209) | Oseltamivir 75 mg (N=205) |
|---|---|---|---|
| Any Event, n (%) | 25 (12) | 22 (11) | 35 (17) |
| Diarrhoea | 2 (<1) | 4 (2) | 4 (2) |
| ALT increased | 3 (1) | 2 (<1) | 4 (2) |
| AST increased | 3 (1) | 2 (<1) | 2 (<1) |
| Blood creatine phosphokinase increased | 1 (<1) | 0 | 3 (1) |

Source Data: m5.3.5.1 NAI114373 CSR Table 3.5

No safety signals or clinically significant trends in clinical laboratory values, vital signs or ECG values were identified that were considered attributable to IV zanamivir.

Exclusion criteria were: Patients with creatinine clearance ≤10 mL/min who were not being treated with continuous renal replacement therapy (CRRT), who required routine/intermittent haemodialysis or continuous peritoneal dialysis, who met liver chemistry toxicity criteria or with underlying chronic liver disease with evidence of severe liver impairment, who had a history of severe cardiac disease or clinically significant arrhythmia and female subjects who were pregnant or were breastfeeding were not included in the pivotal study.

***Supportive study NAI113678 (phase II)***

***Adult cohort:***

Twenty-eight subjects (22%) reported AEs considered by the investigator to have a possible causal relationship to the study drug. The most common drug-related AEs were increased ALT (5%) and cytolytic hepatitis (4%).

**Table 50**

**Table 15 Drug-related Adverse Events in >1 Subject (Safety Population, Study NAI113678, Adult Cohort)**

| Preferred Term | Total N=130 n (%) |
|---|---|
| **Any Drug-related Event** | **28 (22)** |
| Alanine aminotransferase increased [a] | 6 (5) |
| Cytolytic hepatitis [a] | 5 (4) |
| Aspartate aminotransferase increased | 2 (2) |
| Hepatic enzyme increased [a] | 2 (2) |
| Hypertension | 2 (2) |
| Phlebitis | 2 (2) |
| Thrombophlebitis | 2 (2) |
| Encephalopathy | 2 (2) |

Source Data: m5.3.5.1 NAI113678 Adult CSR Table 7.7

a. In total, 13 subjects reported liver-related AEs (i.e., ALT increased, cytolytic hepatitis, and hepatic enzyme increased)

There were no specific patient groups excluded from the study. Adjustment of dose were done to patients with impaired renal function.

***Paediatric cohort:***

Five subjects (7%) reported AEs considered by the investigator as possibly related to study drug (Table 16). The most common drug-related AE was neutropenia, which was reported in 2 subjects (3%). Both incidences of treatment-related neutropenia were also indicated by the investigator to be related to influenza

**Table 51**

**Table 16 Drug-related Adverse Events (Safety Population, Study NAI113678, Paediatric Cohort)**

| Cohort | 1 | 2 | 3 | 4 | 5 | Total |
|---|---|---|---|---|---|---|
| Age | 6m to <1y (N=7) n (%) | 1 to <2y (N=11) n (%) | 2 to <6y (N=12) n (%) | 6 to <13y (N=27) n (%) | 13 to <18y (N=14) n (%) | 6m to <18y (N=71) n (%) |
| **Any Drug-related Event** | 0 | 2 (18) | 0 | 2 (7) | 1 (7) | 5 (7) |
| Neutropenia | 0 | 2 (18) | 0 | 0 | 0 | 2 (3) |
| Aspartate aminotransferase increased | 0 | 0 | 0 | 1 (4) | 0 | 1 (1) |
| Delirium | 0 | 0 | 0 | 1 (4) | 0 | 1 (1) |
| Eosinophilia | 0 | 0 | 0 | 0 | 1 (7) | 1 (1) |
| Insomnia | 0 | 0 | 0 | 1 (4) | 0 | 1 (1) |
| Left ventricular hypertrophy | 0 | 0 | 0 | 0 | 1 (7) | 1 (1) |
| Troponin I increased | 0 | 0 | 0 | 0 | 1 (7) | 1 (1) |
| Vomiting | 0 | 0 | 0 | 0 | 1 (7) | 1 (1) |

Source Data: m5.3.5.2 NAI113678 Paediatric CSR Table 3.8

Exclusion criteria: There were no specific patient groups excluded from the study.

***Supportive study NAI115215 (Japanese cohort)***

Drug-related AEs during the On-treatment Period and Follow-up Period were reported in 3 subjects (14%). Reported drug-related AEs were injection site joint redness, pyrexia, diarrhoea, and haemoglobin decreased (1 subject each; 5%).

There were no specific patient groups excluded from the study. Adjustments of dose were done to patients with impaired renal function.

***Compassionate use programme (study REL113375 and NAI115008)***

In ***study REL113375*** treating physicians reported non-serious AEs for 4% of patients with a CRF. Renal and urinary disorders were most frequent (2%), followed by infections and infestations (1%), and investigations (1%). When summarised by AE preferred term, all non-serious AEs occurred in <1% of patients. The most frequently reported were: renal impairment (7 patients), renal failure (5 patients), and thrombocytopenia (5 patients).

Treating physicians were asked on the CRF if there was a reasonable possibility that an AE may have been caused by zanamivir. A small percentage of patients (2%) had at least one non-serious AE that was considered possibly related to IV zanamivir treatment by the treating physician. The most frequent of these was pyrexia (4 patients [<1%]).

**Table 52**

**Table 17 Summary of Related Non-Serious AEs by System Organ Class (CRF, REL113375)**

| Preferred Term | IV Zanamivir N=783 |
|---|---|
| **Any event** | **14 (2)** |
| Pyrexia | 4 (<1) |
| Transaminases increased | 2 (<1) |
| Rash | 2 (<1) |
| Rhabdomyolysis | 2 (<1) |
| Renal failure | 2 (<1) |
| Anaemia | 1 (<1) |
| Eosinophilia | 1 (<1) |
| Thrombocytopenia | 1 (<1) |
| Thrombocytocis | 1 (<1) |
| Blood creatinine increased | 1 (<1) |
| Rash macular | 1 (<1) |
| Hepatic function abnormal | 1 (<1) |
| Hyperbilirubinaemia | 1 (<1) |
| Clostridium colitis | 1 (<1) |
| Hypertriglyceridaemia | 1 (<1) |
| Seizure | 1 (<1) |

Data source: m5.3.5.4 REL113375 CSR Table 9.4

In ***study NAI115008***, the chart review, only AEs considered by the treating physician to be drug-related were reported. Treating physicians were asked to provide details on any treatment-emergent events they considered related to administration of zanamivir aqueous solution within the following body systems: cardiovascular, hepatic, gastrointestinal, haematology, or renal organ systems, or other. No distinction was made between possibly or probably related. Of note, the individual who completed CRFs was not necessarily the treating physician.

Among paediatric patients, treatment-emergent events were reported for 13 (26%) patients, most frequently in the renal organ system (7 [14%] patients). Few treatment-emergent events were documented in more than one patient; these included: renal failure in 6 patients (12%), hypotension in 3 patients (6%), and renal impairment in 2 patients (4%).

Among adult patients, treatment-emergent events were reported for 11 (17%) patients. Only one treatment-emergent event was recorded for a pregnant patient (circulatory disturbance). In adults, the greatest numbers of treatment-emergent AEs were reported for the cardiovascular organ system (14%). Overall, fewer patients in the Tier 1 pregnancy group (9%) had treatment-emergent events documented than in the Tier 2 adult group (19%). Treatment-emergent events reported for more than one adult patient included: 8 patients (13%) with hypotension, 3 patients (5%) with paralytic ileus, 3 patients (5%) with renal failure, 2 patients (3%) with acute neuro-psychologic disorder, and 2 patients (3%) with encephalopathy.

The severity of AEs was not analysed in the CUP or in Study NAI115008.

Both studies included patients treated during the influenza A/H1N1 pandemic 2009/2010. The chart review included both children and pregnant women.

### *Serious adverse event / deaths / other significant events*

#### *Pivotal study NAI114373*

Grade 3 and 4 AEs: In total, 128 subjects (21%) reported any Grade 3 or 4 AEs, the incidence of which was similar across all 3 treatment groups (Table 18). Overall, the most common Grade 3 or 4 AEs were respiratory failure (1%, 3% and 1% of subjects in the 300 mg IV zanamivir, 600 mg IV zanamivir and oseltamivir arms, respectively) and acute respiratory distress syndrome (1%, 3% and <1% of subjects in the 300 mg IV zanamivir, 600 mg IV zanamivir and oseltamivir arms, respectively).

Fifteen subjects (2%) reported Grade 3 or 4 AEs considered by the investigator to have a possible causal relationship with study drug.

Serious Adverse Events (SAEs): A total of 109 subjects (18%) reported SAEs during the study. The 2 most common SAEs were respiratory failure and pneumonia. Three SAEs were hepatic reactions. The nature and frequency of SAEs were similar across treatment groups.

**Table 53**

**Table 28 Summary of Treatment-Related Serious Adverse Events (Safety Population, Study NAI114373)**

| Preferred Term | IV zanamivir 300 mg (N=201) | IV zanamivir 600 mg (N=209) | Oseltamivir 75 mg (N=205) |
|---|---|---|---|
| Any Event, n (%) | 2 (<1) | 1 (<1) | 3 (1) |
| Cardiac arrest | 1 (<1) | 0 | 0 |
| Drug-induced liver injury | 0 | 0 | 1 (<1) |
| Influenza | 1 (<1) | 0 | 0 |
| ECG signs of ventricular hypertrophy | 0 | 0 | 1 (<1) |
| Respiratory failure | 0 | 1 (<1) | 0 |
| Dermatitis allergic | 0 | 0 | 1 (<1) |

Source Data: m5.3.5.1 NAI114373 CSR Table 3.6

Fatal AEs: A total of 41 subjects (7%) died during the study, 15 subjects (7%) in each of the IV zanamivir arms and 11 subjects (5%) in the oseltamivir arm. The 3 most common causes of death were respiratory failure, acute respiratory distress syndrome and septic shock. Overall, there were no notable difference in nature and frequency of deaths across treatment groups. Two of the deaths (respiratory failure and worsening of influenza A) were considered by the investigator to have a possible causal relationship to zanamivir.

**Table 54**

**Fatal Adverse Events Reported in ≥2 Subjects in Any Treatment Group (Safety Population)**

| Preferred Term | IV zanamivir 300 mg (N=201) | IV zanamivir 600 mg (N=209) | Oseltamivir 75 mg (N=205) |
|---|---|---|---|
| **Any Event, n (%)** | 15 (7) | 15 (7) | 11 (5) |
| Respiratory failure | 3 (1) | 3 (1) | 2 (<1) |
| Acute respiratory distress syndrome | 4 (2) | 3 (1) | 0 |
| Septic shock | 4 (2) | 1 (<1) | 2 (<1) |
| Multi-organ failure | 2 (<1) | 1 (<1) | 2 (<1) |
| Pneumonia | 3 (1) | 0 | 1 (<1) |
| Renal failure acute | 2 (<1) | 0 | 0 |

***Supportive study NAI113678***

***Adult cohort***

Grade 3 or 4 AEs: Fifty-seven subjects (44%) reported a Grade 3 or 4 AEs and 16 subjects (12%) reported Grade 3 or 4 AEs considered by the investigator to have a possible causal relationship with study drug, the most common of which were cytolytic hepatitis (2%), ALT increased (2%), hepatic enzyme increased (2%) and encephalopathy (2%).

Serious adverse events (AEs): Forty-four subjects (34%) reported SAEs during the study. The most common SAEs were pneumonia, respiratory failure, septic shock and cardiac arrest. Twenty-two subjects (17%) had SAEs while on study treatment. Seven subjects (5%) reported SAEs considered by the investigator to have a possible causal relationship with study drug. There were two cases each of cytolytic hepatitis and encephalopathy and one each of Torsade de Pointes, ventricular arrhythmia, ventricular tachycardia and renal failure.

Deaths: Twenty-six subjects (20%) died during the study. The most common causes of death were respiratory failure (4%), sepsis (2%), pneumonia (2%), multi-organ failure (2%) and bronchopulmonary aspergillosis (2%). None of the deaths was considered by the investigator to have a possible causal relationship to zanamivir. Fourteen subjects (11%) died during the treatment period.

***Paediatric cohort:***

Grade 3 or 4 AEs: Twenty-three subjects (32%) reported Grade 3 or 4 AEs. The most common Grade 3 or 4 AEs were hypotension (4%), neutropenia (4%), and respiratory failure (4%). Two subjects (3%) reported Grade 3 or 4 AEs considered by the investigator as possibly related to study drug (NAI113678 Paediatric CSR Table 3.12). Both AEs were neutropenia reported for subjects in Cohort 2 and were also indicated to be related to influenza.

Serious Adverse Events (SAEs): Fifteen subjects (21%) reported SAEs during the study. The most common SAEs were tachycardia and respiratory failure. Six subjects (8%) reported SAEs during the treatment period.

Drug-related SAEs: No subjects reported SAEs considered by the investigator as possibly related to study drug.

Deaths: Five subjects (7%) died during the study. Multi-organ failure, encephalitis, brain herniation, lactic acidosis and respiratory failure were reported in one subject each. None of the deaths was considered by the investigator as possibly related to Zanamivir. Three subjects (4%) died during the treatment period.

***Supportive study NAI115215 (Japanese)***

Grade 3 and 4 AEs: Grade 3 or 4 or severe AEs during the On-treatment Period plus Follow-up Period were reported in 2 subjects (10%). Reported Grade 3 or 4 or severe AEs during the On-treatment Period plus Follow-up Period were pneumonia bacterial, haemoglobin decreased, and hypokalaemia (1 subject each; 5%). Pneumonia bacterial and hypokalaemia were reported in the same subject. Among Grade 3 or 4 or severe AEs, one case with haemoglobin decrease (level not provided) was considered to be drug related by the investigator.

Serious adverse events (SAEs): SAEs including fatal SAE were reported in 4 subjects (19%) in the study. The reported non-fatal SAEs were respiratory tract infection, hyperthyroidism and haemoglobin decreased (1 subject each). Among non-fatal SAEs, haemoglobin decreased was considered to be drug-related by the investigator.

Deaths: One subject (5%) died due to pneumonia bacterial during the study. This event was not considered to be drug-related by the investigator.

***Compassionate use programme (study REL113375 and chart review NAI115008)***

***REL113375 - Serious adverse events (SAEs):***

In study REL113375, as a condition of receiving zanamivir aqueous solution for compassionate use, treating physicians were asked to report all SAEs from the time of first dose through 14 days after completion of treatment to GSK. As of the 31 January 2017 data cut-off date, 411 patients had at least one SAE in the ARGUS database.

Among the 411 patients with at least 1 SAE, the most frequently reported SAEs were death (18%), respiratory failure (14%), and multiple organ dysfunction syndrome (11%).

Among patients with at least one SAE, 73 had an SAE considered possibly related (or with an unknown relationship) to zanamivir aqueous solution treatment. Related SAEs were most frequently in the Blood and Lymphatic Systems or Renal and Urinary Disorders SOC.

**Table 55**

**Table 14 Summary of Drug-related SAEs by SOC (ARGUS Data)**

| System Organ Class | Zanamivir N = 411 |
|---|---|
| | n (%) |
| Any event | 73 (18) |
| Blood and lymphatic system disorders | 13 (3) |
| Renal and urinary disorders | 12 (3) |
| Investigations | 10 (2) |
| Respiratory, thoracic and mediastinal disorders | 10 (2) |
| Hepatobiliary disorders | 9 (2) |
| Cardiac disorders | 8 (2) |
| Gastrointestinal disorders | 6 (1) |
| Nervous system disorders | 6 (1) |
| General disorders and administration site conditions | 5 (1) |
| Skin and subcutaneous tissue disorders | 5 (1) |
| Infections and infestations | 2 (<1) |
| Psychiatric disorders | 2 (<1) |
| Injury, poisoning and procedural complications | 1 (<1) |
| Metabolism and nutrition disorders | 1 (<1) |
| Vascular disorders | 1 (<1) |

Data source: Table 9.10

By preferred term, the most frequent SAE considered possibly related (or with an unknown relationship) to treatment with zanamivir aqueous solution was acute kidney injury (8 patients [2%]), followed by alanine aminotransferase increased (5 patients [1%]) and hepatic failure (5 patients [1%]).

***REL 113375 - Deaths***:

Of the 411 patients with at least one SAE, 332 patients (81%) were known to have died, i.e., either had an SAE with an outcome of death, or had an SAE outcome other than death, but were otherwise known to have died. The estimated mortality rate for the CUP is therefore 332/3063 or 11%. Among the 411 patients with at least 1 SAE, the most frequently reported SAEs for patient who were known to have died were death (18%), respiratory failure (13%), and multiple organ dysfunction syndrome (11%).

In summary, data from the CUP have significant limitations regarding the interpretation and extrapolation of results. Patients who were eligible for compassionate use treatment represented the most severely ill patient population and were treated with zanamivir aqueous solution as salvage therapy very late in their course of illness. As a result, patients were at high risk of severe/fatal outcomes and the lack of a control cohort makes safety data difficult to interpret.

Completion of the CRF to collect safety and clinical follow-up information for patients in the CUP was optional and the CRF was only returned for 783/3063 patients (26%). Furthermore, as the CUP was not a clinical study, there was no monitoring and no mechanism to resolve inconsistencies or obtain missing data.

***NAI115008 (chart review) - Serious adverse events (SAEs) and deaths:***

GSK's safety reporting system (ARGUS) contains serious adverse event (SAE) reports for 23 patients who were included in the retrospective chart review, including 5 pregnant/postpartum patients. All SAEs were fatal except for events of hypernatremia, colitis, transient psychosis, pyrexia, and one SAE of cardiac arrest.

**Table 56**

| SAE Preferred Term | Number of Patients |
|---|---|
| Multiorgan failure | 3 |
| Respiratory failure | 3 |
| Cardiac arrest | 2 |
| Cerebral haemorrhage | 2 |
| Death | 2 |
| Acute respiratory distress syndrome | 1 |
| Colitis | 1 |
| Haemorrhage intracranial | 1 |
| Histiocytosis haematophagic | 1 |
| Hypernatraemia | 1 |
| Influenza | 1 |
| Pneumonia | 1 |
| Pulmonary haemorrhage | 1 |
| Pyrexia | 1 |
| Respiratory disorder | 1 |
| Transient psychosis | 1 |

Patients included in the retrospective chart review were a sample of severely ill hospitalised patients from around the world at the time of the 2009 influenza pandemic, most of whom (76%) had underlying medical conditions. Most patients (97%) were admitted to the ICU with all but 1 requiring ventilator support or supplemental oxygen, 27% receiving ECMO and the majority (79%) receiving inotropic medication, indicating multi-system organ failure.

The mortality rate in the retrospective chart review, including non-pregnant adults, was higher than that reported in the overall CUP and Phase II Study NAI113678 and may indicate possible physician bias toward entering patients with fatal outcomes in the retrospective chart review. In addition, the degree of critical illness of these patients was possibly even more severe than in other described populations.

The question of effectiveness of zanamivir IV treatment is not discussed in this context of fatal cases by the applicant, but "lack of efficacy" could have been considered a SAE in some of these cases. However, given the limitations of the CUP data and confounding factors, it is not possible to interpret the effect (or lack of effect) of zanamivir, when typically used as a last resort in patients with advanced disease.

## *Adverse events of special interest (AESIs)*

**Hepatic reactions**

Several liver-related adverse events were reported early in the open-label, single arm Phase II Study NAI113678. As a result, liver-related events were monitored closely during the remainder of the clinical programme. Adverse event and laboratory data from the blinded Phase III study of IV zanamivir (NAI114373) compared with oseltamivir show a low number of protocol-defined liver events (2%), and a similar incidence between treatment arms.

***Pivotal study (NAI114373):***

The incidence of protocol defined liver events was low (14 subjects, 2%) and similar across treatment groups. Three events were SAEs and 11 were AEs, of which two were consistent with Hy's Law criteria (ALT ≥3 upper limit of normal (ULN) and bilirubin ≥2 ULN). One was seen in the oseltamivir group (possibly related), the other in the zanamivir 300 mg group (not related). Four cases with an ALT≥5xULN, but bilirubin ≤2xULN, were considered study drug related. The applicant concludes that zanamivir IV did not appear to be associated with the development of drug-induced liver injury.

***Supportive study (NAI113678):***

***Adult cohort***

Seventeen subjects (13%) experienced protocol-defined liver events during the study; three were SAEs and 14 were AEs. Two of the 3 liver events which met the SAE criteria (i.e. Hy's law criteria: ALT ≥ 3 times the upper limit of the normal range [ULN] and bilirubin ≥2xULN [>35% direct bilirubin]) were considered by the investigator to have a possible relationship to Zanamivir. However, one subject was in acute cardiac shock at Baseline and died shortly thereafter. In the other subject meeting Hy's Law criteria, for whom the investigator assigned possible causality to zanamivir, ALT and bilirubin levels returned to Baseline by approximately 2 weeks following the end of IV zanamivir treatment. In the third subject with a liver SAE, the event was not attributed to study drug or participation, but to shock and underlying Hepatitis C.

Of the 14 liver AEs in which an elevation of ALT of at least 5 times the upper limit of the normal range was observed but Hy's law criteria were not met, 11 cases were considered by the investigator to be possibly study drug related. All 14 cases were reported to be 'resolved' 'or 'resolving' by the end of the study. The subjects' underlying influenza illness, other medical conditions and concomitant medications make evaluation of causality of hepatic related events difficult to assess. In the overall study population, there were no clinically significant trends in median ALT, AST and total bilirubin levels during or post-treatment.

Of those with treatment-emergent ALT elevations in the IV zanamivir ≤5 days group, the majority were shifts from 'normal' to Grade 1 (n=10). Two subjects shifted from 'normal' to Grade 2 and two to Grade 3. Of the 18 subjects who were Grade 1 at Baseline, 3 subjects each shifted to Grade 2, Grade 3, and Grade 4. One subject improved from Grade 2 to Grade 1. For those subjects who were normal at Baseline in the >5 day treatment group, 6 subjects shifted to Grade 1, two to Grade 2, and two to Grade 4.

Of the 75 subjects who were normal for total bilirubin at Baseline in the ≤5-day treatment group, the majority remained in the normal category. Three subjects shifted from normal to Grade 1, 2 subjects each to Grade 2 and Grade 3, and 1 subject to Grade 4. Two subjects shifted from Grade 3 to 4. Two subjects improved and shifted from Grade 1 or 2 to normal. In the >5 day treatment group, the majority of subjects were normal at Baseline and remained normal.

***Paediatric cohort:***

Two subjects (3%) experienced protocol-defined liver events during the study; 1 met SAE criteria (ALT ≥3 times the upper limit of the normal range [ULN] and bilirubin ≥2×ULN [>35% direct bilirubin]) and 1 was an AE (ALT ≥5x ULN). Neither was considered by the investigator as possibly related to zanamivir. In the overall adolescent and paediatric study population there were no clinically significant trends in median alanine aminotransferase (ALT), AST and total bilirubin levels during or posttreatment.

Most subjects had ALT levels within the normal range at Baseline and remained 'normal' throughout the study. Five subjects with **elevated ALT** at Baseline improved during the study. Fourteen subjects had

shifts to a higher grade. The majority of the shifts were from 'normal' to Grade 1 (n=9), and 2 subjects shifted from 'normal' to Grade 2. Two subjects shifted from Grade 1 to Grade 2 and 1 subject shifted from Grade 2 at Baseline to Grade 3.

Most subjects had **bilirubin** levels within the normal range at Baseline and remained 'normal'. Six subjects with elevated bilirubin at Baseline improved during the study. Six subjects had bilirubin shifts to a higher grade, all in cohorts 4 (6 to <13 years) and 5 (13 to <18 years).

***Supportive study NAI115215 (Japanese cohort)****:*

No hepatic events reported.

***Compassionate use programme***

***Study REL113375***:

Since a number of liver-related AEs were reported early in the Phase II study (NAI113678), all hepatic events reported in the CUP are closely reviewed. Of the 411 patients who were reported to have at least one SAE, 39 patients had an event in the broad Standardized MedDRA Query (SMQ) "Drug-Related Hepatic Disorders - Comprehensive Search". Of these 39 patients, 24 had a fatal outcome. All, with the exception of 2 cases with insufficient information, had multiple confounding factors including severity of the influenza-related disease, critical illness, underlying concurrent medical conditions, or concurrent medications. Overall, the majority of patients with reported hepatic findings were confounded and a causal association with zanamivir aqueous solution could not be established.

***Study NAI115008***:

In NAI115008, liver-related safety findings were reported as part of the clinical laboratory evaluations, but are discussed in this section to facilitate comparison across studies.

Of the 84 patients for whom both abnormal ALT and AST values were reported at any time during the influenza hospitalisation, 46 patients had ALT or AST values >3xULN, while 15 patients had ALT or AST >20xULN.

For the 16 patients with ALT >3xULN on treatment, ALT was ≥3xULN (or missing) at Baseline. Of the 26 patients with abnormal on-treatment ALT, alkaline phosphatase (ALP), and bilirubin values reported, 7 patients had elevated values that met the "possible Hy's Law" screening threshold for drug-induced liver injury (ALT >3xULN combined with bilirubin ≥2xULN and [ALP <3xULN or ALP missing]). Additional details are provided for each of these 7 patients in the NAI115008 CSR. For 3 cases the elevations occurred before the start of treatment with zanamivir aqueous solution (administered IV), which makes a causal relationship to zanamivir not possible. For the remaining 4 patients, elevated liver values were much more likely to have been caused by other factors than zanamivir aqueous solution.

**Cardiac reactions**

Serious treatment-related events in the cardiac disorders SOC were reported for one patient in the IV zanamivir 300 mg arm (one event of cardiac arrest, possibly related as considered by the investigator in NAI114373. Two patients in the adult cohort of NAI113678 (3 events; Torsades de Pointes, ventricular arrhythmia and ventricular tachycardia). In the first case, the investigator considered that there was no reasonable possibility that the cardiac arrest was caused by zanamivir but that there was a reasonable

possibility that the ventricular arrhythmia and Torsades de Pointes may have been caused by zanamivir. However, the investigator also considered that the events were also possibly due to the concomitant medication, and the Torsades de Pointes to be complications of influenza. In the second case the investigator considered that there was a reasonable possibility that the ventricular tachycardia may have been caused by zanamivir as no other cause was identified.

In order to conduct a comprehensive review of the events of arrhythmias, a search of the GSK global safety database (ARGUS) using the Standardised MedDRA Query (SMQ) Broad for cardiac arrhythmias was conducted. Fifty-five cases were retrieved which described use of the IV formulation of zanamivir, most of which were from the CUP. Six cases were from the pivotal Phase III study, 10 cases were from the Phase II study and one came from retrospective chart review. All of the cases occurred in patients who were seriously unwell. Many described patients on mechanical ventilation and in 35 cases the outcome was fatal.

Detailed review of individual cases does not support a causal relationship between IV zanamivir and cardiac arrhythmias in general, or between IV zanamivir and any particular type of cardiac arrhythmia. The reported cases are heavily confounded by the severely-ill status of patients receiving compassionate use treatment. Although “cardiac arrhythmias” is an adverse drug reaction (ADR) stated in the summary of product characteristics (SmPC) for oseltamivir, the scientific evidence for this is not apparent in the published literature, and there is no evidence to suggest a class effect.

It is proposed that cardiac arrhythmia should be monitored through routine post-marketing pharmacovigilance activity.

**Hypersensitivity reactions (anaphylaxis and skin reaction)**

In the Phase II/III studies, there was one, serious, related adverse event that may be suggestive of a hypersensitivity reaction. This was a case of respiratory failure in a 53-year-old in the IV zanamivir 600 mg arm of NAI114373. However, on review of the case by the Applicant, the symptoms in this case did not suggest an allergic origin. In the CUP, serious, treatment-related events that may be indicative of hypersensitivity were reported in the Skin and Subcutaneous Tissue Disorders SOC (3 rashes and one event of Stevens Johnson Syndrome). A review of clinical trials data and the cases of hypersensitivity and IV zanamivir in the GSK global safety database supports the addition of ‘rash’ and “urticaria” to the SmPC as ADRs in Section 4.8 with the frequencies of common and uncommon, respectively.

The current evidence does not support the addition of specific hypersensitivity terms, such as anaphylaxis or serious cutaneous adverse reactions with IV zanamivir. However, in view of the fact that hypersensitivity reactions are stated in the SmPC for zanamivir for inhalation it will also be added to Section 4.8 of the SmPC for IV zanamivir and a warning in SmPC 4.4 in line with SmPC for zanamivir for inhalation. Allergic-type reactions, including oropharyngeal oedema, facial oedema, anaphylactic/anaphylactoid reactions and severe skin reactions including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis to be listed with frequency “not known”.

## *Laboratory findings*

No abnormalities in laboratory tests were identified in any of the studies submitted.

Abnormal hepatic tests are not commented in this part; see discussion above.

ECG data have not reported clinically relevant changes, however, arrhythmias were reported as SAEs for a few patients; see above.

## *Safety in special populations*

### Age related aspects

**Table 57**

| | Intravenous Zanamivir 600 mg BID n=209 | | | | Intravenous Zanamivir 300 mg BID n=201 | | | | Oral Oseltamivir 75 mg BID n=205 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **MedDRA Terms** | **Age <65 N=134 (64%)** | **Age 65-74 N=36 (17%)** | **Age 75-84 N=29 (14%)** | **Age 85+ N=10 (5%)** | **Age <65 N=135 (67%)** | **Age 65-74 N=29 (14%)** | **Age 75-84 N=28 (14%)** | **Age 85+ N=9 (4%)** | **Age <65 N=128 (62%)** | **Age 65-74 N=38 (19%)** | **Age 75-84 N=27 (13%)** | **Age 85+ N=12 (6%)** |
| Total Adverse Events | 76 (57%) | 26 (72%) | 19 (66%) | 7 (70%) | 74 (55%) | 16 (55%) | 17 (61%) | 4 (44%) | 84 (66%) | 22 (58%) | 19 (70%) | 9 (75%) |
| SAEs – Total | 12 (9%) | 8 (22%) | 10 (34%) | 3 (30%) | 21 (16%) | 9 (31%) | 6 (21%) | 2 (22%) | 22 (17%) | 9 (24%) | 5 (19%) | 2 (17%) |
| - Fatal | 5 (4%) | 4 (11%) | 3 (10%) | 3 (30%) | 8 (6%) | 3 (10%) | 3 (11%) | 1 (11%) | 6 (5%) | 2 (5%) | 3 (11%) | 0 |
| - Life-threatening | 1 (0.7%) | 0 | 0 | 0 | 1 (0.7%) | 1 (3%) | 0 | 0 | 2 | 0 | 0 | 0 |
| - Hospitalization/prolong existing hospitalization | 7 (5%) | 5 (14%) | 7 (24%) | 0 | 11 (8%) | 4 (14%) | 3 (11%) | 1 (11%) | 13 (10%) | 7 (18%) | 1 (4%) | 2 (17%) |
| - Disability/incapacity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| - Other (medically significant) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.8%) | 0 | 1 (4%) | 0 |
| AE leading to drop-out | 6 (4%) | 3 (8%) | 4 (14%) | 3 (30%) | 6 (4%) | 4 (14%) | 3 (11%) | 1 (11%) | 8 (6%) | 2 (5%) | 3 (11%) | 0 |
| Psychiatric disorders | 9 (7%) | 2 (6%) | 2 (7%) | 1 (10%) | 5 (4%) | 3 (10%) | 3 (11%) | 0 | 13 (10%) | 5 (13%) | 3 (11%) | 2 (17%) |
| Nervous system disorders | 10 (7%) | 5 (14%) | 2 (7%) | 2 (20%) | 9 (7%) | 4 (14%) | 1 (4%) | 0 | 12 (9%) | 4 (11%) | 0 | 0 |
| Accidents and injuries | 1 (<1%) | 3 (8%) | 1 (3%) | 0 | 1 (<1%) | 1 (3%) | 0 | 0 | 4 (3%) | 0 | 1 (4%) | 0 |
| Cardiac disorders | 3 (2%) | 4 (11%) | 4 (14%) | 4 | 10 (7%) | 3 (10%) | 4 (14%) | 2 (22%) | 8 (6%) | 6 (16%) | 7 (26%) | 0 |

| | Intravenous Zanamivir 600 mg BID n=209 | | | | Intravenous Zanamivir 300 mg BID n=201 | | | | Oral Oseltamivir 75 mg BID n=205 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **MedDRA Terms** | **Age <65 N=134 (64%)** | **Age 65-74 N=36 (17%)** | **Age 75-84 N=29 (14%)** | **Age 85+ N=10 (5%)** | **Age <65 N=135 (67%)** | **Age 65-74 N=29 (14%)** | **Age 75-84 N=28 (14%)** | **Age 85+ N=9 (4%)** | **Age <65 N=128 (62%)** | **Age 65-74 N=38 (19%)** | **Age 75-84 N=27 (13%)** | **Age 85+ N=12 (6%)** |
| | | | | (40%) | | | | | | | | |
| Vascular disorders | 5 (4%) | 4 (11%) | 2 (7%) | 1 (10%) | 12 (9%) | 1 (3%) | 3 (11%) | 1 (11%) | 12 (9%) | 2 (5%) | 1 (4%) | 1 (8%) |
| Cerebrovascular disorders | 0 | 0 | 0 | 1 (10%) | 1 (<1%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Infections and infestations | 24 (18%) | 8 (22%) | 5 (17%) | 1 (10%) | 29 (21%) | 7 (24%) | 4 (14%) | 3 (33%) | 28 (22%) | 6 (16%) | 3 (11%) | 2 (17%) |
| Anticholinergic syndrome | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Quality of life decreased | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures | 2 (1%) | 3 (8%) | 1 (3%) | 0 | 3 (2%) | 2 (7%) | 1 (4%) | 0 | 3 (2%) | 1 (3%) | 0 | 0 |

Adverse reaction data has not identified any special safety concerns for a paediatric population.

In the supportive Study NAI113678, SAEs were reported less frequently in younger children (<6 years of age, 10%) relative to older children (6 to <13 years, 30%), adolescents (13 to <18 years, 29%), and adults (34%).

Among the paediatric and adolescent subjects, 2 of 71 (3%) experienced protocol-defined liver events. In contrast, 13% of adult subjects experienced liver events during the study. The difference may have been related to the higher overall morbidity of the adult subjects or to the high prevalence of influenza A/H1N1pdm2009 circulating when adults were enrolled into the study. Liver-related events are known to be associated with severe influenza, and multisystem organ failure was a key feature of influenza A H1N1pdm2009 in hospitalised critically ill subjects [Jain, 2009; Writing Committee of the WHO, 2010].

In the pivotal Study NAI114373, while the median age of the study population was nearly 10 years older than the study population in the adult cohort of NAI113678 (57 years versus 47.5 years) and there were 20% more subjects enrolled who were ≥60 years of age (44% versus 24%), no new or additional safety findings were observed in Study NAI114373 compared with the adult cohort of Study NAI113678.

In the zanamivir 600 mg arm of the Phase III study NAI114373, 134 patients were <65 years of age, 36 were between 65 and <75, 29 were between 75 and <85 and 10 were 85 years or older. In the zanamivir 600 mg arm, treatment-related AEs were reported for 12%, 14%, 3% and 0% for these age groups, respectively. The nature of the related AEs was similar across the age groups and the data did not indicate special safety concerns for the older adults.

**Ethnicity**

In the pivotal Phase III study (NAI114373), the Study NAI113678 adult cohort, and the Study NAI113678 paediatric cohort, the majority of subjects were Caucasian (76%, 75%, and 68%, respectively). In Study NAI115215, which was conducted in Japan, all subjects were Asian.

There were no notable differences in the nature or frequency of treatment-emergent AEs reported for subjects from Japan in Study NAI115215 compared with the subjects in Study NAI114373 or Study NAI113678.

In the adult cohort of NAI113678 75% were Caucasian, 8% African-American and 8% South-East Asian. In the paediatric cohort 68% were Caucasian, 18% African American/African, and 4% Japanese, 4% mixed race. In NAI114373 76% of subjects were Caucasian, 7% East Asian, 6% Central Asian and 4% African American/African. Furthermore, there are no pharmacokinetic or pharmacodynamic reasons to suspect that the safety profile will be significantly different in Asian populations.

**Use in patients with renal impairment (study NAI108127)**

Sixteen subjects with renal impairment were enrolled and all received a 100 mg single dose of IV zanamivir. Very few AEs were reported during the study. Only 2 AEs were reported in more than 1 subject: diarrhoea (3 subjects) and headache (3 subjects). Four subjects had AEs considered by the investigator to be drug-related, including abdominal pain, headache, and diarrhoea (1 subject each) and 1 subject with weakness, light headedness, intermittent pounding sensation, and rash on the arms and face. All these AEs resolved within 5 minutes to 4 days. No clinically significant changes in clinical laboratory data, vital signs, or ECGs were observed.

**Use in pregnancy**

The supportive Phase II Study NAI113678 allowed inclusion of pregnant women. Three subjects were pregnant (one in the second trimester, two in the third trimester), and 1 subject was 1 day postpartum. All 3 pregnant subjects survived and gave birth to healthy infants. No SAEs were reported in the pregnant or postpartum subjects.

Up to the data-lock point of 31 January 2017 in the CUP, 59 patients received zanamivir either during pregnancy or shortly postpartum/post-foetal death. Limited information has been received in the global safety database for 16 pregnant/postpartum patients. Of these, 12 were pregnant and four were

postpartum. The outcome for the pregnant mothers was fatal in 5 patients, positive in 6 patients and unknown in 1 patient. Serious AEs were reported in 9 pregnant patients.

The CUP retrospective chart review (NAI115008), Tier 1 included 8 pregnant patients and 3 postpartum patients (1 to 14 days post-delivery). Of the 8 patients who were pregnant at hospital admission, 4 were in the second trimester and 4 were in third trimester of pregnancy; all of these patients received zanamivir aqueous solution via the IV route of administration. Only 1 treatment-emergent event was recorded for a pregnant patient (circulatory disturbance). Overall, fewer patients in the Tier 1 pregnancy group (9%) had treatment-emergent events documented than in the Tier 2 adult group (19%). Four of the 11 pregnant/postpartum patients (36%) died.

No specific trend in difference in the safety profile was seen between different age groups in children. Most differences seen between studies in adults may be related to morbidity status of patients at baseline and influenza seasoning.

Based on the data provided, it is difficult to conclude on safety in pregnancy. Animal models have shown that placental transfer of zanamivir occurs. However, it is not known if this can occur in humans. Non-clinical data did not indicate a risk of teratogenicity or maternal or foetal toxicity at exposures approximately 3 times the human exposure at the clinical intravenous dose (600 mg BID).

Exposure in pregnant women with IV zanamivir is limited and the effect of IV zanamivir administered in pregnancy is unknown.

### *Safety related to drug-drug interactions and other interactions*

From Relenza (zanamivir for inhalation) it is known that zanamivir is not bound to proteins, and is not metabolized, nor modified in the liver. Clinically relevant interactions are therefore not expected. A drug interaction study (NAI112977) was performed in collaboration with the Influenza Clinical Research Network in Thailand [Pukrittayakamee, 2011]. The results indicated there was no evidence for significant PK interaction between IV zanamivir with oral oseltamivir 150 mg BID that could result in a change in the safety profile of IV zanamivir.

### *Discontinuation due to adverse events*

There were 7-15% of the reported AEs that were leading to premature discontinuation from the study. Most of these were related to different kind of respiratory impairment and can be disease related.

In the studies, 3 - 13% reported AEs were leading to premature discontinuation of investigational product. A wide spectrum of AEs leading to discontinuity were reported, including respiratory and hepatic reactions, and no specific pattern can be seen. Many of these may be disease related as well.

## 2.6.1. Discussion on clinical safety

The safety profile has been assessed based on 844 patients in clinical trials and 3149 patients in the Compassionate Use Programme.

**Safety profile**

The safety profile is rather similar in both 300 mg BID and 600 mg BID zanamivir drug-related AEs observed in 11-22%. The safety profile for zanamivir IV is similar to the safety profile of oral oseltamivir (drug-related AEs observed in 17%). Drug-related AEs were observed less commonly in children (7%). However, in the chart review study, about 26% of children were reported with treatment-emergent reactions.

In adults, the most common drug-related AEs in the clinical trials are gastrointestinal (diarrhoea) and hepatic reactions (transaminase increased, cytolytic hepatitis). In the compassionate use programmes, the most common drug-related AEs was pyrexia (REL113375 study) and in the chart review most frequent reported treatment-emergent events in adult patients was hypotension, paralytic ileus, renal failure, acute neuro-psychologic disorder and encephalopathy.

In children, neutropenia was most commonly observed in the clinical trial. In the compassionate use programmes, renal reactions were reported in 10%. Few treatment-emergent events were documented in more than one patient; renal failure, hypotension and renal impairment.

Causality assessment is in most patients confounded by co-mortality of the patients. Given the small number of clinical trials and the duration of follow-up on patients who participated in the studies, the clinical development programme for IV zanamivir is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. This is reflected in the SmPC section 4.8.

**Serious adverse events**

SAEs were seen in 18% in the pivotal study (7% died), 34% (20% died) in adults and 21% (7% died) in children the supportive study. In the CUP data, SAEs occurred in 13% of cases, of which 81% died. A majority of the SAEs were death, respiratory failure, multiple organ dysfunction and acute respiratory distress syndrome. Given the limitations of the CUP data and confounding factors, it is not possible to interpret the effect (or lack of effect) of zanamivir, when typically used as a last resort in patients with advanced disease.

**Cardiac reactions**

A few cases of treatment-related cardiac reactions (cardiac arrest, Torsade de Pointes, ventricular arrhythmias and ventricular tachycardia) were reported in the clinical trials which may have been caused by zanamivir and fifty-five cases of arrhythmias were identified the CUP studies. Cardiac reactions (cardiac arrhythmias) are listed as important potential risk in the RMP and to be further monitored through routine pharmacovigilance.

**Hepatic reactions**

The assessment of causality of hepatic reactions during zanamivir treatment can be difficult in patient groups included in the studies. In particular because of high degree of co-morbidity in patients hospitalised because of influenza and because abnormal liver function tests (increased transaminases) are reported in about 20% of patients with influenza (Polakos NK et al., Am J Path 2006;168: no 4; Jain S et al., N Engl J Med 2009;361;1-10).

Furthermore, majority of the cases were firstly treated with oseltamivir, then with zanamivir. Hepatic reactions like increase in transaminases and a few cases of hepatic failure, cholestasis and hepatocellular injury have been considered related to zanamivir treatment. Hepatotoxicity is not discussed in the non-clinical assessment.

The safety profile has been found similar for zanamivir and oseltamivir in the pivotal study. Hepatic reactions like increased transaminases, fulminant hepatitis, hepatic failure and hepatitis is listed in SmPC 4.8 for oseltamivir. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations, alkaline phosphatase increased and hepatocellular injury are proposed to be listed for Dectova in SmPC 4.8. To collect more knowledge on risk of hepatic reactions during treatment with zanamivir IV it is added as potential important risks in the RMP.

**Hypersensitivity reactions (anaphylaxis and skin reaction)**

In the CUP, there was one event of Stevens Johnson Syndrome was reported (not confirmed on review). A review of clinical trials data and the cases of hypersensitivity and IV zanamivir in the GSK global safety database supports the addition of 'rash' and "urticaria" to the SmPC as ADRs in Section 4.8 with the frequencies of common and uncommon, respectively and severe skin reactions including erythema multiforme, Stevens-Johnson syndrome and toxic with frequency "not known".

The current evidence does not support the addition of specific hypersensitivity terms, such as anaphylaxis or serious cutaneous adverse reactions with IV zanamivir. However, in view of the fact that these hypersensitivity reactions are stated in the SmPC for zanamivir for inhalation it will also be added to Section 4.8 of the SmPC for IV zanamivir and a warning in SmPC 4.4 in line with SmPC for zanamivir for inhalation. Allergic-type reactions including oropharyngeal oedema, facial oedema, anaphylactic/anaphylactoid reactions to be listed with frequency "not known".

**Pregnancy**

Safety in pregnancy is still considered as missing information. Limited serious adverse event data in pregnant/post-partum women from the ARGUS global safety database (n=59, with outcomes for 16 patients) did not identify any special safety concerns for this population. The proposal of a PASS (pregnancy registry) is endorsed. The study will be initiated when there is wide-spread resistance to oseltamivir and circulating influenza virus is susceptible to zanamivir. This might be far in the future, while pregnant women may be exposed from the time of marketing. It is proposed the Pregnancy registry should be established from the time of marketing and patients included consecutively as they are exposed independently of the pattern of resistance.

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

### *Additional expert consultations*

None.

## 2.6.2. Conclusions on the clinical safety

The safety profile of zanamivir IV is similar to oseltamivir as found in the pivotal study. The true safety profile is difficult to assess as the patients included were highly ill with influenza and had a high degree of co-morbidity. Mortality is rather high, but is considered associated to the seriousness of the influenza to

be treated and often related to respiratory related problems. Most drug-related AEs observed were diarrhoea and constipation in addition to increase in transaminases. A few serious hepatic reactions were seen. The causality in this severely ill population is difficult to assess, but cases have been considered drug-related by the investigator and the association to use of zanamivir cannot be fully excluded. The same is for some of the cases reported on cardiac arrhythmias and skin reactions. As appropriate, reactions are reflected in the proposed SmPC section 4.4 (warnings on hypersensitivity reactions) and in SmPC section 4.8 (hepatic and hypersensitivity reactions).

The safety specifications in the RMP include hepatic failure and cardiac arrhythmias as important potential risks.

The proposal of a PASS to collect more knowledge on safety during pregnancy is endorsed.

## *2.7. Risk Management Plan*

### *Safety concerns*

| **Risk Category** | **IV zanamivir** |
|---|---|
| **Important Identified Risks** | None |
| **Important Potential Risks** | Cardiac reactions (cardiac arrhythmias)<br>Severe cutaneous reactions<br>Hepatic failure<br>Neuropsychiatric events<br>Antiviral resistance/lack of efficacy |
| **Missing Information** | Use in Pregnancy<br>Lactation |

### *Pharmacovigilance plan*

| **Study Status** | **Summary of Objectives** | **Safety concerns addressed** | **Milestones** | **Due Dates** |
|---|---|---|---|---|
| Category 3 - Required additional pharmacovigilance activities | | | | |
| IV zanamivir pregnancy registry<br><br>(Protocol ID: 208140) | To evaluate pregnancy outcomes among women with complicated influenza exposed to IV zanamivir at any time during pregnancy | Missing information category:<br>Use in Pregnancy | Study Start | The study will be initiated before the start of the first northern hemisphere influenza season (~week 40) following marketing authorisation. |
| | | | Annual Report | An update report will be filed with the EMA each year, providing details of the number of treated patients enrolled and guidance on the likely study end date. |
| | | | Final Study Report | The date of final study report is dependent on study start date and |

| | | | | |
|---|---|---|---|---|
| | | | | completion of enrolment.<br><br>The final study report will be available within 6 months after eCRF completion for last subject |

### *Risk minimisation measures*

| **Safety concern** | **Routine risk minimisation activities** |
|---|---|
| Cardiac reactions (cardiac arrhythmias)<br>IV zanamivir | None |
| Severe cutaneous reactions<br>IV zanamivir | SmPC section 4.4 and 4.8; PIL section 2 and 4 |
| Hepatic failure<br>IV zanamivir | Routine risk communication:<br>SmPC section 4.8, PIL section 4 |
| Neuropsychiatric Events<br>Inhaled and IV zanamivir | Routine risk communication:<br>Inhaled zanamivir<br>SmPC section 4.4<br>PIL section 4, which contains a recommendation that parents should be especially careful to watch out for neuropsychiatric symptoms if their child or teenager has influenza.<br>IV zanamivir<br>SmPC section 4.4 and 4.8; PIL section 2 and 4 |
| Antiviral resistance/lack of efficacy<br>Inhaled and IV zanamivir | Routine risk communication<br>SmPC section 4.4 and 5.1 |
| Use in Pregnancy<br>Inhaled and IV zanamivir | Routine risk communication:<br>SmPC section 4.6<br>PIL section 2 |
| Lactation<br>Inhaled and IV zanamivir | Routine risk communication:<br>SmPC section 4.6<br>PIL section 2 |

### *Conclusion*

The CHMP and PRAC considered that the risk management plan version 07 is acceptable.

## *2.8. Pharmacovigilance*

### *Pharmacovigilance system*

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

### *Periodic Safety Update Reports submission requirements*

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant requested the harmonisation of the PSUR cycle with the Data Lock Point (DLP) of zanamivir, inhalation powder. Therefore, 31 January will be used to determine the forthcoming Data Lock Points.

## *2.9. Product information*

### 2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Relenza (zanamivir inhaled). The bridging report submitted by the applicant has been found acceptable.

### 2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Dectova (zanamivir) is included in the additional monitoring list as it is approved under exceptional circumstances under Article 14 (8) of Regulation (EC) No 726/2004.

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

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

The final proposed indication for Dectova is:

"Dectova is indicated for the treatment of complicated and potentially life-threatening influenza A or B virus infection in adult and paediatric patients (aged ≥6 months) when:

- The patient's influenza virus is known or suspected to be resistant to anti-influenza medicinal products other than zanamivir, and/or
- Other anti-viral medicinal products for treatment of influenza, including inhaled zanamivir, are not suitable for the individual patient.

Dectova should be used in accordance with official guidance."

There are no successful development programs with randomized, placebo controlled studies to provide robust evidence of efficacy in patients hospitalized due to influenza.

The main clinical endpoints in clinical trials to support registration of products in the treatment of influenza have generally included time to clinical response, with clinical response defined by a reduction of influenza symptoms, including fever and impact on respiratory status. Other endpoints that have been evaluated include mortality, complications following the influenza disease and functionality status.

Virological endpoints such as reduction of viral load in nasopharyngeal swabs, are not considered surrogate for clinical benefit. Still, the characterization of antiviral activity, as well as the pattern of resistance, including cross-resistance with other agents, forms an important part of a development program.

### 3.1.2. Available therapies and unmet medical need

All EU Member States recommend neuraminidase inhibitors (NAIs), in combination with clinical supportive care, for treatment of severe, complicated or progressive illness, and for patients at high risk of complications, irrespective of vaccination status. Oseltamivir oral (Tamiflu), zanamivir inhalation (Relenza) and peramivir IV (Alpivab) have received a Marketing Authorisation in Europe for treatment of influenza. For peramivir IV, the indication is limited to uncomplicated influenza. The reason for this limitation was lack of conclusive evidence of efficacy in hospitalised patients. In the case of oseltamivir oral and zanamivir inhalation, which are older products, the indication has no such limitation, even though these products have no efficacy data in hospitalised influenza patients based on randomized placebo-controlled studies. Nevertheless, oseltamivir is the recommended standard treatment in this patient population. The extensive use of oseltamivir is based on efficacy shown for uncomplicated influenza in outpatients, impact on viral load, case reports and retrospective studies in hospitalised influenza patients.

In a situation where the H275Y mutation in H1N1, a strain resistant to both oseltamivir and peramivir, is circulating, or other mutations with similar resistance pattern is circulating, there is a medical need for agents to which such variants are susceptible.

### 3.1.3. Main clinical studies

**NAI114373.** The main study NAI114373 was randomized, double-blind, with three arms, comparing 600 mg IV Zanamivir with comparator 75 mg oral oseltamivir and 300 mg IV Zanamivir. A total number 615 (ITT) patients aged ≥16 years were recruited which included 205 randomised to the control arm.

The primary endpoint was time to clinical response (TTCR). The patient population was hospitalised adults and adolescents (> 16 years) with influenza. A superiority analysis for the primary endpoint was performed. Further, the use of placebo control was considered inappropriate given the above mentioned guideline recommendations.

**Main inclusion Criteria**

Presence of influenza symptoms (fever, oxygen saturation, respiration rate, hearth rate, blood pressure) and laboratory confirmed or suspected influenza virus infection. Onset of influenza within 6 days prior to study enrollment.

**Exclusion Criteria**

Subjects who had taken more than a total of 3 days of approved anti-influenza therapy in the period from onset of symptoms and prior to enrolment; subjects who, in the opinion of the investigator, were not likely to survive beyond 48 hours from Baseline; subjects with creatinine clearance ≤ 10 mL/min.

Subjects who required (ECMO) at Baseline; subjects with underlying chronic liver disease or history of severe cardiac disease.

**Endpoints NAI114373**

The primary endpoint was the time to clinical response (TTCR) in subjects with confirmed influenza. Clinical response was defined as resolution of at least 4 of the 5 signs within the respective resolution criteria, maintained for at least 24 hours, or hospital discharge, whichever occurred first. The 5 responses were: fever AND oxygen saturation AND 2 out of 3, including respiratory status, heart rate and systolic blood pressure. Similar endpoint has been used for hospitalised influenza patients for other anti-influenza drugs.

**NAI113678.** This supportive study was an open-label, single arm study. Patients ≥6 months old, 130 in adult cohort and 71 in paediatric cohort.

The primary objective was to assess the safety and tolerability of intravenous (IV) Zanamivir in the treatment of hospitalized adult, adolescent and paediatric subjects with influenza infection. Children age categories: 6 months<1 year, 1 to <2 years, 2 to <6 years, 6 to <18 years. This was mainly a safety study, but virology and clinical endpoints as well as pharmacokinetics were included. The study was initiated in 2009 during the H1N1 pandemic and for the adult population H1N1pdm2009 was the dominating strain.

**NAI115215.** This supportive study was open-label, single arm study. in 21 patients aged ≥16 years.

The primary objective was to assess the safety and tolerability of 600 mg of IV Zanamivir twice daily in the treatment of hospitalized subjects with influenza infection.

**NAI115008.** This was an observational, retrospective, multi-center, cohort data collection study from the Compassionate Use program. This contains reports from 63 adults including pregnant and 50 paediatric patients. The treating physician reviewed recorded data including demographics, medical data, safety variables and treatment outcomes on a paper CRF.

## *3.2. Favourable effects*

Data from the single pivotal Phase III study NAI114373 demonstrated clinical benefit, antiviral effect and safety that was at least comparable to oseltamivir, the global standard of care. The median times to clinical response in days were not statistically different for IV zanamivir 600 mg and oseltamivir 75 mg. This was consistent in both the total influenza positive population and the subgroups: ICU/mechanical ventilation and symptom onset ≤ 4 days, which were part of the primary endpoint analysis. The median time to clinical response was 0.48 days shorter for IV zanamivir 600 mg compared to oseltamivir 75 mg.

For the population of subjects who were PCR positive at Baseline from nasopharyngeal swabs (N=410), the median time to virologic improvement for influenza A and B from nasopharyngeal swabs was 3.0 days for all treatment arms. Virological improvement was defined as a 2 log drop in viral load and the rate of success for those positive at baseline were 90% for zanamivir IV 600 mg and 92% for oseltamivir 75 mg.

There was minimal circulating influenza oseltamivir resistance during 2011-2015, the period of study conduct for NAI114373. Antiviral activity was very similar across treatment arms. Six subjects on oseltamivir developed treatment-emergent resistance (4 subjects developed H275Y in H1N1 strains, 1 subject developed D198D/G and another R292R/K both in H3N2 strains) and 1 subjects on the 300 mg IV

zanamivir arm developed potential treatment-emergent resistance (T325I in H3N2 strain). No treatment emergent resistance was observed in subjects on the 600 mg IV zanamivir.

The results of the supportive studies were generally consistent with the results of the pivotal study. Data from the clinical studies conducted as part of the IV zanamivir programme as well as data from the global CUP contribute to an assessment of the clinical benefit of the product. Clinical data are available from study NAI113678 and the CUP, and these patients are more closely matched to the proposed target population than the pivotal study. In the global CUP, over 3,000 patients have been treated with zanamivir (99% IV). Clinical data from NAI113678 is limited by its single arm, open-label design; however, subjects were observed to have a rapid antiviral response to 600 mg IV zanamivir treatment despite most patients having been treated with oseltamivir prior to study enrolment. Most adult subjects in this study were critically ill, with the majority in ICU and many on MV or ECMO. Treatment emergent resistance to zanamivir was not observed in the adult subjects with the exception of one adult subject where treatment-emergent resistance was noted in one sample (E119D) but not on subsequent samples.

## *3.3. Uncertainties and limitations about favourable effects*

Since superiority over oral oseltamivir was not demonstrated, and as there are no randomised studies comparing oseltamivir with placebo in hospitalised patients with complicated influenza, the available data do not provide comprehensive evidence of the clinical efficacy of Zanamivir in the population of hospitalized influenza patients.

Further on, in the study programme, the number of paediatric patients in each age interval is small: n=7 (6m to< 1y), n=11 (1 to<2y), n=12 (2 <6y), n=27 (6 to<13y), n=14 (13 to<18y). A comparison with the adult population in the same study (NAI113678) is difficult because the adults were exposed to the pandemic H1N1pdm09 strain and experienced high mortality and more severe disease compared to the children.

## *3.4. Unfavourable effects*

Exposure to IV zanamivir (irrespective of dose) is limited to 844 subjects within clinical trials, of which 643 received IV zanamivir as treatment for complicated influenza. The database includes a direct comparison with oral oseltamivir for 410 subjects with complicated influenza who were treated with 300 mg or 600 mg IV BID regimens. In the CUP, there were 3063 patients exposed as of 31 January 2017, of which 98% received IV administration, but there was no prospective and systematic collection of AEs in this total CUP. In addition, AEs have been assessed in a chart review study including 113 patients from the CUP.

Safety in adults

In adults, the most commonly reported drug-related AEs in the clinical trials are gastrointestinal (diarrhoea) and hepatic reactions (variably ALT and/or AST increases)); while in the CUP data pyrexia was the most commonly reported event. In this seriously ill population, a few cases of cardiovascular AEs including hypotension as well as renal failure, paralytic ileus and neuropsychiatric reactions were reported.

In the pivotal study, AEs deemed to be drug-related were observed in 11% of patients in the 600mg IV treatment group as compared to 17% in the oral Oseltamivir group. In the pivotal study, Grade 3 and 4 laboratory abnormalities (whether considered drug-related or unrelated) occurred at similar rates in

zanamivir and oseltamivir groups. There was no excess of ALT ≥5xULN in the zanamivir groups. In elderly, treatment-related AEs were reported for 12%, 14%, 3% and 0% for the age groups <65, 65 to <75, 75 to <85 and ≥85, respectively. The nature of the related AEs was similar across the age groups and the data did not indicate special safety concerns for the older adults.

Overall the safety profile of zanamivir and oseltamivir were similar.

Safety in children

Neutropenia was the most commonly reported adverse effect in the clinical trial NAI113678. In the CUP data, renal adverse effects were reported in 10%. There were no specific trends that were noticed in the rate or severity of different adverse events reported in children. In the chart review subgroup of the CUP, the reported incidence of adverse events in children was 26%, and the most frequently involved organ system was the renal organ system (7 [14%] patients). Few treatment-emergent events were documented in more than one patient; these included: renal failure in 6 patients (12%), hypotension in 3 patients (6%), and renal impairment in 2 patients (4%). For this dataset, there is no comparator arm.

Serious adverse events

In the pivotal study, a total of 109 subjects (18%) reported SAEs and a total of 41 (7%) subjects died. The most common SAEs were respiratory failure and pneumonia. The nature and frequency of SAEs were similar across treatment groups. SAEs deemed drug-related by the investigator were less than 1% in zanamivir arms and was 1% in the oseltamivir arm. In the CUP data, SAEs were reported in 13% of cases and 81% of the reported SAEs was death.

SAEs that were deemed drug related by the investigator were few. Six cases (<1%) in the pivotal study: One case of cardiac arrest and one case of influenza in the group administered 300mg zanamivir BID and one case with respiratory failure in the 600 mg BID group). In the oseltamivir group, there were three SAEs (1%) that were deemed drug related, which included one case with drug-induced liver injury, one case with ECG signs of ventricular hypertrophy and one case of allergic dermatitis.

SAEs deemed related by the investigator in the supportive study were seven cases (5%) in the adult cohort: Two cases of cytolytic hepatitis, two cases of encephalopathy, one case each of Torsade de pointes, ventricular arrhythmia, ventricular tachycardia and renal failure. None SAEs was considered related to zanamivir treatment in the paediatric cohort.

In the CUP data 18% (73/411) had SAEs related to zanamivir treatment, most frequently reported was reactions to Blood and Lymphatic System Disorder (3%) and to Renal and Urinary Disorders (3%) – most common term were acute kidney injury (eight patients - 2%), ALT increase (1%) and hepatic failure (1%).

*Cardiac reactions*

Few cases of Zanamivir treatment-related cardiac reactions (one case each of cardiac arrest, Torsade de Pointes, ventricular arrhythmias and ventricular tachycardia) were reported in all the clinical trials combined and fifty-five cases of arrhythmias were identified in the CUP Cardiac arrhythmias is characterized as an important potential risk.

*Hypersensitivity reactions (anaphylaxis and skin reaction)*

In the Phase II/III studies, there was no serious drug-related hypersensitivity reaction such as anaphylaxis, but one event of Stevens Johnson Syndrome was reported in the CUP. Cases of 'rash' and "urticaria" were identified in the GSK global safety database.

Renal toxicity

Zanamivir is eliminated by renal clearance; therefore, the dose of zanamivir when administered intravenously must be reduced in patients with renal impairment. Renal impairment is common in hospitalised patients with influenza or other chronic underlying conditions, however it is routine practice to monitor renal function in hospitalised patients and therefore this risk should be adequately mitigated.

## *3.5. Uncertainties and limitations about unfavourable effects*

The causality assessment of adverse events is in most patients confounded by co-morbidity of the patients.

It is not possible to evaluate with certainty, the causality of these events to zanamivir treatment. Notably, in the pivotal study, the safety profile of zanamivir did not markedly differ from that of oseltamivir. The majority of cases were associated with disease progression or comorbidity and symptoms of severe influenza disease. A review of all deaths reported in the two CUP studies including all pertinent information (including information on co-morbidity, antiviral treatment before zanamivir IV treatment started and time period from influenza debut till zanamivir treatment was started) did not raise any significant concerns. Further, the data from CUP is considered to be less robust than from clinical studies due to the severity of the underlying illness as well as the lack of a comparator arm.

Notably, abnormal liver function tests (increased transaminases) are reported in about 20% of patients with influenza (Polakos NK et al Am J Path 2006;168: no 4, Jain S et al N Eng j Med 2009;361;1-10). Furthermore, majority of the cases were firstly treated with oseltamivir, then with zanamivir. However, in several cases the study drug was discontinued due to hepatic reactions according to the criteria in the study protocol. Hence, it is considered that a possible causality to zanamivir or a contribution of zanamivir cannot be excluded.

Although the available data in children shows the safety profile to be consistent with that in adults, the number of children included and the spread in adverse events reported are limited and so there are some residual uncertainties.

Since the risk of DDIs appears to be low, no safety issue is expected due to PK interactions, however direct clinical experience demonstrating lack of DDI is limited.

*Pregnancy/lactation*

Pregnant women are recognised as a high-risk group as they suffer disproportionately from severe/complicated influenza requiring hospitalisation. There are insufficient data on the use of IV zanamivir in pregnant women to inform drug-associated risk. Data from several clinical studies have not shown an increased risk of adverse pregnancy outcomes following *in utero* exposure to inhaled zanamivir, but due to limited sample sizes and significant differences in exposure between 10 mg inhaled and 600 mg administered intravenously, no definitive conclusions can be drawn regarding the safety of zanamivir in pregnancy. Reproductive studies performed in rats and rabbits indicated that placental transfer of zanamivir occurs but there was no evidence of teratogenicity. Results from a rat peri and post-natal study

showed no clinically meaningful impairment of offspring development. A limited number of pregnant women participated in the clinical program (Phase II study NAI113678 and CUP), and while no adverse effects on the mother or fetus have been reported, the numbers are too small to draw robust conclusions on the safety in this population.

Safety in pregnancy and during lactation is still considered as missing information. The proposal of a PASS (pregnancy) is endorsed.

## *3.6. Effects Table*

**Table 58. Effects Table for Dectova 10 mg/ml solution for infusion in proposed indication**: for the treatment of complicated and potentially life-threatening influenza A or B virus infection in adult and paediatric patients (aged ≥6 months) when: The patient's influenza virus is known or suspected to be resistant to anti-influenza medicinal products other than zanamivir, and/or other anti-viral medicinal products for treatment of influenza, including inhaled zanamivir, are not suitable for the individual patient.

| Effect | Short Description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| TTCR | Time to clinical response, median | days | 5.15 | 5.63 | Median difference -0.48, p value comparison with oseltamivir 0.3912 | |
| Mortality | Overall mortality, end of study, number | % | 7 | 6 | Mortality considered attributable to influenza 3.7% in both groups. | |
| Hospital stay | Length of stay, median | days | 6 | 7 | | |
| ICU | Length of stay, median | days | 6 | 7 | | |
| ADL score | Change in Katz activities of daily living | mean | 1.72 | 1.98 | | |
| Ventilation status | Mechanical ventilation | % | 23 | 31 | | |
| Incidence of complications | AEs influenza related | % | 20 | 25 | | |
| | Antibiotic use | % | 10 | 18 | | |
| No detectable virus | No RNA or cultivation, end of study | % | 76 | 71 | | |
| Time to no virus | No RNA or cultivation, median | days | 4 | 4 | | |
| Time to virology improvement | Time to 2 log drop in viral load, median | days | 3 | 3 | | |

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

Treatment with oseltamivir is the recommended standard of care for patients with complicated influenza, even if no placebo-controlled studies have been performed demonstrating efficacy in such patients. The recommendation for such use is based on the ability of the oseltamivir to reduce viral load, the reduction of clinical symptoms in uncomplicated influenza demonstrated in placebo-controlled randomised studies, case reports and observational studies in hospitalised patients and a large number of nonclinical and *in vitro* studies.

The data from the controlled randomised study included in this dossier indicate that treatment with zanamivir 600 mg IV and oseltamivir 75 mg treatment result in comparable results related to both clinical endpoints and viral load in a hospitalised influenza population. The impact of treatment on outcome, however, is definitely confirmed, since there is no effect estimate for the comparator, oseltamivir, and there was no placebo arm.

Seasonal influenza strains as well as highly pathogenic avian influenza strains are susceptible to the antiviral effects of neuramindase inhibitors. The resistance profile of zanamivir differs from oseltamivir and peramivir in the case of the H275Y mutation in H1N1. While the strain is resistant to oseltamivir and peramivir, it remains sensitive to zanamivir. The H275Y may appear during treatment with oseltamivir and was also seen circulating in a large proportion of isolated influenza viruses ten years ago. In a situation where the H275Y mutation in H1N1 is circulating, or other mutation with similar resistance pattern is circulating, a medical need for an agent presumed to be active is identified. Further, it is asserted that highly pathogenic avian influenza strains are also sensitive to the neuraminidases and zanamivir IV could theoretically prove useful as treatment during any emerging pandemic (with or without avian strains), when the condition of the patient warrants IV administration.

In response to the need for further justification for use of zanamivir in complicated influenza the applicant has presented an extensive overview of public health guidelines from Europe and globally, as well as recent reviews on clinical data to support current recommendations. Guidelines from USA, England WHO, ECDC, Japan and Australia have been presented. NAIs are generally recommended for use against severe influenza. The recent confirmation of the public health recommendations about the use of NAIs together with the fact that 3000 patients have received IV zanamivir in compassionate use program, demonstrates the medical need involved. It is unfortunate that the absolute efficacy of NAIs in the treatment of complicated influenza has not been determined in RCTs against placebo, and probably never will due to the inherent difficulties involved. However, in spite of the deficiencies in the evidence, it is a fact that NAIs have for a long time been used as a standard of care in hospitalised influenza patients and there are data from different sources (observational studies, systematic reviews and meta-analyses) to support the recommendations and clinical use.

The safety profile of zanamivir IV is similar to oseltamivir as found in the pivotal study. Mortality is rather high, but is considered associated to the seriousness of the influenza to be treated and often due to problems related to respiration. Most AEs deemed drug related by the investigator, that were observed were diarrhoea and constipation in addition to increase in transaminases. A few serious hepatic reactions were seen. The causality of adverse drug reactions in this severely ill population is difficult to assess. The same is true, for some of the cases reported on cardiac arrhythmias and neutropenia. Hypersensitivity reactions, including anaphylaxis and serious skin reactions have been reported with NAIs and might be a risk for zanamivir IV as well. Overall, the available data shows that the adverse effect profile of zanamivir is comparable to that of oseltamivir.

In addition, the larger experience with use of zanamivir inhalation has not identified any serious safety concerns, which is reassuring. However, the systemic exposure when zanamivir is administered by the inhaled route is considerably lower. Therefore, the reassurance that can be drawn from the clinical experience with inhaled zanamivir is subject to limitations.

Safety in pregnant and lactating women is considered missing information.

### 3.7.2. Balance of benefits and risks

Oseltamivir is currently the standard treatment used in hospitals for influenza. That is so even if efficacy data from placebo-controlled randomised clinical trials in hospitalised patients with complicated influenza is lacking. Data from the comparative study NAI114373 show similar outcomes for oseltamivir and zanamivir IV on clinical and virological endpoints; however the clinical efficacy of zanamivir cannot be demonstrated by this study, since the efficacy of oseltamivir in complicated influenza has not been established by placebo-controlled randomized control studies. Rather, the indication of efficacy is inferred based on *in vitro* virology, animal studies, a challenge study in healthy volunteers, the efficacy

seen for inhaled zanamivir as well as oseltamivir, another neuraminidase inhibitor in uncomplicated influenza, and the plasma and BAL exposure reached at the selected dose.

The benefit of IV zanamivir can be inferred based on:

- evidence of adequate exposure at the infection target tissue (upper and lower respiratory tract), as compared to inhaled zanamivir, which has proven efficacy against uncomplicated influenza;
- demonstrated *in vitro* susceptibility and *in vivo* efficacy in preclinical models of infection;
- comparable effects of zanamivir iv and oseltamivir iv in study NAI114373;
- extrapolation of the efficacy from the Phase III randomised placebo-controlled studies of other NAIs conducted in patients with uncomplicated influenza, to that of the complicated setting; particularly with Relenza (inhaled zanamivir) against which comparable plasma and BAL fluid exposure levels are available;
- extrapolation of the available evidence supporting the public health guidance on use of neuraminidase inhibitors in the treatment of, hospitalized patients with influenza illness, and
- a generally favourable safety profile of NAIs including zanamavir i.v.

The Applicant has discussed and argued for the justification for submitting under exceptional circumstances based on the unmet need in the niche indication and the difficulty to generate conclusive evidence in the current circumstances, to which the CHMP agreed (see 3.7.3). This is in the context of the accepted effectiveness of NAIs in treatment of complicated influenza as reflected by the public health guidelines and the data used in support of public health guidelines. IV zanamivir was initiated as a response to the need of an IV formulation to be used in hospitals when resistant strains to oseltamivir circulate. Importantly, the different resistance pattern of zanamivir and oseltamivir could make zanamivir an important medicinal product to be used in situations where strains resistant to oseltamivir are circulating or emerge during treatment.

Given the lack of conclusive efficacy data from randomised placebo-controlled clinical trials for any neuraminidase inhibitor (NAI) in complicated influenza, the CHMP sought the inputs of experts (Scientific Advisory Group- SAG) on the available efficacy data for IV zanamivir to support a favourable benefit-risk conclusion in the context of a MAA under exceptional circumstances. The SAG acknowledged the deficiencies in the current evidence base for the efficacy of NAIs in the treatment of hospitalised influenza patients but were unanimous in their view that the available evidence from observational studies and meta-analyses was adequate to recommend the use of NAIs in the treatment of hospitalised influenza patients. In addition, the SAG agreed that based on the comparability of IV zanamivir and other NAIs in *in vitro*, *in vivo*, human challenge studies and the results of the pivotal study NAI114373, it was reasonable to expect that zanamivir IV would have a similar efficacy to oseltamivir in hospitalised influenza patients.

Based on the above, it is accepted that there is a reasonable expectation of benefit for the use of zanamivir IV in hospitalized influenza patients particularly those who do not have other appropriate anti-viral agents either due to the resistant pattern of the influenza virus or due to other practical/safety reasons.

The safety profile has been reasonably characterized and the available data do not raise any major concerns. Therefore, the benefit-risk analysis for the use of zanamivir IV (Dectova) in the treatment of hospitalised influenza patients for whom patient's influenza virus is known or suspected to be resistant to anti-influenza medicinal products other than zanamivir, and/or other anti-viral medicinal products for treatment of influenza, including inhaled zanamivir, are not suitable for the individual patient, is considered to be positive.

### 3.7.3. Additional considerations on the benefit-risk balance

As argued above, oseltamivir, the comparator used in the pivotal study has recognised efficacy in uncomplicated influenza and is the standard of care in complicated influenza, although the evidence in complicated influenza is from observational studies/meta-analyses rather than from randomized, placebo-controlled studies. Based on the results of the pivotal study, comparable efficacy of Zanamivir IV can be inferred.

Based on the *in-vitro* viral susceptibility profile, Zanamivir IV is expected to have efficacy in patients with complicated and life-threatening influenza who are infected with influenza virus resistant to other neuraminidase inhibitors including oseltamivir

In addition, given that zanamivir IV is expected to have the same exposure in patients who are unable to take other NAIs, efficacy can be anticipated in this patient population.

In order to get a better insight, the applicant commits to conduct post-approval studies to evaluate the effectiveness (and safety) of zanamivir in the post-authorisation setting.

The applicant describes plans for two post-authorisation effectiveness studies, as a specific obligation:

1. A retrospective observational chart review study to evaluate the clinical effectiveness of treatment with zanamivir 10 mg/ml solution for infusion in a cohort of intensive care unit-treated (ICU) patients with influenza infection. The primary objective is to compare all-cause in-hospital mortality in a group of ICU admitted patients with influenza who receive treatment with zanamivir IV as part of their clinical care with all-cause mortality in-hospital mortality in a propensity score-matched group of ICU patients who did not receive this therapy during the same influenza seasons and/or pandemic(s).

It is the opinion of the CHMP that it is challenging to obtain unbiased effectiveness data from such a patient population, but it is acknowledged that a prospective study may be difficult under current circumstances and therefore the design and plans for data analysis are considered relevant and supported.

2. A prospective study will be initiated when certain criteria related to increased use of zanamavir IV are met. Examples of such conditions being when European Public Health Clinical Practice Guidelines for the treatment of influenza recommend the early or first line use of IV zanamivir, such as during a severe influenza pandemic or when there is influenza known to be resistant to other antivirals than zanamivir widely circulating in the European Union as reported by the European Reference Laboratory Network for Human Influenza (ERLI-Net).

The applicant will seek Scientific Advice soon following receipt of the Marketing authorisation, regarding design and criteria for initiation of this prospective, observational study.

Additional data on safety will be provided by routine pharmacovigilance. However, a pregnancy registry is proposed to systematically collect more information on safety in pregnant women. This registry should be established from the time of marketing authorisation.

There is no important safety concern requiring additional risk minimisation measures for the moment.

### *Marketing authorisation under exceptional circumstances*

As comprehensive data on the product are not available and is not considered feasible to generate such data, a marketing authorisation under exceptional circumstances was requested by the applicant in the initial submission.

The CHMP considers that the applicant has sufficiently demonstrated that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use based on all three grounds: the proposed indication is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence; there is an inability to provide comprehensive information due to the present state of scientific knowledge; and it would be contrary to generally accepted principles of medical ethics to collect required information

The following arguments were carefully considered and supported by CHMP:

- Influenza virus that is resistant to other approved anti-influenza medications occurs so rarely that it is not feasible to conduct clinical studies in this patient population.
- Currently, there is a significant gap in the scientific knowledge:
    - Lack of data from placebo-controlled studies to quantify the benefit of current standard of care and consequent inability to derive conclusive evidence from a non-inferiority study
    - Lack of correlation of virologic and clinical responses which prevent use of biomarkers or surrogate endpoints to measure efficacy
- It is not feasible to conduct controlled clinical studies in a patient population who can only be administered anti-influenza medication via the IV route as there are no anti-influenza IV medications approved for hospitalised patients in the European Union. It would be unethical to conduct a placebo-controlled study in this extremely sick patient population who have complicated and potentially life threatening influenza

*1. Rarity*

Since the emergence of influenza A(H1N1)pdm2009, the global incidence of oseltamivir resistant virus has remained low, ranging from 0.8%-1.6%% in 2011-2014 based on data from the WHO [Lackenby, 2011; Takashita, 2015]. Based on an analysis of 10,641 influenza viruses circulating globally in 2013-2014, the proportion of A(H1N1)pdm09, A(H3N2), B/Victoria or B/Yamagata-lineage viruses with reduced or highly reduced susceptibility was low, on the order of 1.6%, 0.1%, 0.1% and 0.1% respectively to one or more of the NAIs tested (including oseltamivir, zanamivir, peramivir and laninamivir) [Takashita, 2015].

In the Phase III study, 1potential resistant virus from 1 subject in the 300 mg IV zanamivir arm with NA substitutions T325I emerged during treatment. There was no resistance detected in subjects in the 600 mg IV zanamivir arm in the Phase III study. Six subjects in the oseltamivir arm of the Phase III study selected virus with known resistance substitutions, D198D/G, R292R/K and 4 with the most common oseltamivir resistance substitution H275Y. Resistance to zanamivir during treatment is rare and has only been previously reported in 9 immunocompromised patients and 1 immunocompetent paediatric patient. While the occurrence in 2007 to 2009 of widespread oseltamivir-resistant A(H1N1) virus carrying the H275Y substitution demonstrates the real and significant threat of an epidemic of oseltamivir-resistant virus, such a strain has not yet emerged in the postpandemic period. To conduct a clinical study exclusively in subjects with oseltamivir resistant virus would therefore not be feasible if the incidence remains at the rates observed during the most recent pandemic and post-pandemic period.

The rarity of patients in the approved indication (resistance and /or other antivirals including inhaled zanamivir not suitable to the individual patient) prevent the conduct of confirmatory studies in this specific population.

*2. Inability to provide comprehensive information due to the present state of scientific knowledge*

There is a lack of data from placebo-controlled studies to quantify the benefit of current standard of care and inability to derive conclusive evidence from a non-inferiority study. Imposing a requirement to demonstrate superiority against an established active control (standard of care) in the general population of hospitalised complicated influenza patients proves unfeasible in the present state of scientific knowledge and would likewise be inappropriate for the proposed indication that is limited to patients with highest unmet needs.

*3. Inability to collect such information because it would be contrary to medical ethics*

All approved influenza antivirals have demonstrated efficacy in placebo-controlled studies in the setting of acute uncomplicated influenza illness in which mild illness in healthy outpatients presents a different benefit-risk assessment.

Due to the standard practice of prescribing NAIs for treatment of hospitalised patients with severe/complicated influenza and the substantial associated morbidity/mortality associated with the illness, the conduct of a placebo-controlled study is considered difficult even in patients with influenza viruses that are not resistant to other NAIs. Given the lack of data from placebo-controlled studies to document the benefit of other NAIs like oseltamivir, a conclusive non-inferiority study against other NAIs like oseltamivir is also not feasible, as appropriate non-inferiority margins cannot be ascertained.

According to the recent ECDC Expert Opinion on NAIs [ECDC, 2016],

"*All EU Member States recommend NAIs, in combination with clinical supportive care, for treatment of severe, complicated or progressive illness, or for patients at high risk of complications, irrespective of vaccination status. Furthermore, influenza antivirals are being used for treatment and prophylaxis of severe influenza disease caused by zoonotic influenza strains*" , further stating that "*national recommendations regarding influenza antiviral use are available in 24 EU/EEA Member States. These policies generally recommend use of antivirals for patients with severe or progressive influenza requiring hospitalization*" .

These recommendations are generally aligned to guidance from the WHO Guidance on use of Pharmacologic Management of Pandemic Influenza and support NAIs as the widely accepted standard of care in the clinical management of patients hospitalised with severe/complicated influenza illness. Therefore, even if it were possible to conduct a randomised controlled clinical study whilst drug-resistant influenza virus was in circulation, it would not be ethical to conduct a placebo-controlled study due to the issues described above.

The totality of the above limitations prevents generation of comprehensive data for Dectova.

Therefore, recommending a marketing authorisation under exceptional circumstances is considered appropriate.

## *3.8. Conclusions*

The overall B/R of Dectova in the presently sought indication is positive.

# 4. Recommendations

## *Outcome*

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

"Dectova is indicated for the treatment of complicated and potentially life-threatening influenza A or B virus infection in adult and paediatric patients (aged ≥6 months) when:

- The patient's influenza virus is known or suspected to be resistant to anti-influenza medicinal products other than zanamivir, and/or
- Other anti-viral medicinal products for treatment of influenza, including inhaled zanamivir, are not suitable for the individual patient.

Dectova should be used in accordance with official guidance."

The CHMP therefore recommends the granting of the marketing authorisation under exceptional circumstances subject to the following conditions:

## *Conditions or restrictions regarding supply and use*

Medicinal product subject to medical prescription.

## *Other conditions and requirements of the marketing authorisation*

**Periodic Safety Update Reports**

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

**Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

## *Specific Obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances*

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

| Description | Due date |
|---|---|
| SOB 1. Title A retrospective observational chart review study to evaluate the clinical effectiveness of treatment with zanamivir 10mg/ml solution for infusion in a cohort of intensive care unit-treated (ICU) patients with complicated influenza infection<br><br>In order to evaluate the clinical effectiveness of treatment with zanamivir 10mg/ml solution for infusion in ICU-treated influenza patients, the MAH should submit the results of an observational chart review effectiveness study of IV zanamivir in ICU-treated influenza patients. | Annual reports to be submitted<br><br>Q3 2025 |
| SOB 2. Title: A prospective observational study to evaluate the clinical effectiveness of treatment with zanamivir 10 mg/ml solution for infusion in patients with complicated influenza infection<br><br>In order to evaluate the clinical effectiveness of treatment with zanamivir 10 mg/ml solution for infusion in patients with complicated influenza infection, the MAH should submit the results of a prospective observational study in patients with complicated influenza infection. | Annual reports to be submitted |

## *Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States*

Not applicable.

# Appendix

1. Divergent position to the majority recommendation

DIVERGENT POSITION DATED 28 February 2019

DECTOVA EMEA/H/C/004102/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of DECTOVA indicated for "the treatment of complicated and potentially life-threatening influenza A or B virus infection in adult and paediatric patients (aged ≥6 months) when:

- The patient's influenza virus is known or suspected to be resistant to anti-influenza medicinal products other than zanamivir, and/or
- Other anti-viral medicinal products for treatment of influenza, including inhaled zanamivir, are not suitable for the individual patient.

Dectova should be used in accordance with official guidance."

The reason for divergent opinion was the following:

Dectova was compared to oseltamivir in the randomised NAI114373 study, in hospitalised adults with influenza. This trial showed no significant difference in the clinical efficacy of Dectova and oseltamivir. Since it is unknown whether oseltamivir is efficacious in the studied population and what might be the magnitude of any such effect, superiority would have been required to established efficacy.

The marketing authorisation for Dectova in the abovementioned population would be under "exceptional circumstances". According to the Guideline on procedures for the granting of a marketing authorisation under exceptional circumstances, pursuant to article 14 (8) of Regulation (EC) No 726/2004, such a marketing authorisation may be granted if it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use, because the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence; or in the present state of scientific knowledge, comprehensive information cannot be provided; or it would be contrary to generally accepted principles of medical ethics to collect such information

While it may be agreed that for the particular conditions encompassed by the indication, it would not be anticipated that a direct demonstration of efficacy would be presented, this would neither be the only nor, arguably, the standard way of generating relevant efficacy data.

In order to establish efficacy in patients infected with virus known or suspected to be resistant to anti-influenza medicinal products other than zanamivir, an efficacy demonstration of Dectova using a relevant comparator in patients with virus susceptible to both Dectova and the comparator could have been bridged to patients with virus susceptible only to zanamivir.

Similarly, in order to establish efficacy in patients for whom other anti-viral medicinal products for treatment of influenza are not suitable, an efficacy demonstration of Dectova using a relevant comparator in patients for whom both Dectova and the comparator are suitable, could have been bridged to those only suitable for Dectova, provided that exposure to zanamivir was similar.

In summary, efficacy has not been demonstrated; furthermore, the provision of a marketing authorisation under "exceptional circumstances" is inappropriate insofar as what is lacking is a relevant demonstration of efficacy, rather than the possibility of providing a relevant demonstration of efficacy.

Kristina Dunder (Sweden)

Natalja Karpova (Latvia)

Sinan B.Sarac (Denmark)