London, 23 June 2011
EMA/484396/2011 Rev. 1

SUMMARY ON COMPASSIONATE USE
FOR
IV Zanamivir

International Nonproprietary Name:
Zanamivir

Procedure No. EMA/H/K/2287/CU

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

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PRODUCT INFORMATION

Name of the medicinal product for Compassionate Use:	IV Zanamivir
Company:	GlaxoSmithKline
Active substance:	Zanamivir
International Nonproprietary Name:	Zanamivir
Target Population:	Compassionate Use IV zanamivir should be considered only to treat critically ill adults and children having a life-threatening condition due to suspected or confirmed pandemic A(H1N1)v infection or infection due to seasonal influenza A or B virus and answering to the following criteria: 1. Patients not responding to either oral or inhaled authorised antiviral medicinal products, or 2. Patients for whom drug delivery by a route other than IV (e.g. oral oseltamivir or inhaled zanamivir) is not expected to be dependable or is not feasible, or 3. Patients infected with documented oseltamivir-resistant influenza virus and not suitable for therapy with inhaled zanamivir
Pharmaceutical form(s):	Solution for infusion
Strength(s):	200 mg
Route(s) of administration:	Intravenous
Packaging:	Vials
Package size(s):	1 Vial

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1 BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

Sweden notified the Agency (EMA) on 13 November 2009 and requested a CHMP opinion on the compassionate use for the above mentioned medicinal product in accordance with Article 83(3) of Regulation (EC) No 726/2004 of the European Parliament and of the council (31 March 2004), and data submitted to the Agency (EMA) by GlaxoSmithKline on 27 January 2010.

The legal basis for this application refers to:
Article 83(3) of Regulation (EC) No 726/2004 of the European Parliament and of the council (31 March 2004)

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:
Rapporteur: Bengt Ljungberg
Co-Rapporteur: Pierre Demolis
EMA Product Team Leaders: Leonor Enes, Anne-Sophie Henry-Eude, Robin Ruepp

1.2 Steps taken for the assessment of the product

- The timetable for the procedure was agreed-upon by CHMP on 19 November 2009.
- The dossier was received by the EMA on 7 December 2009.
- The Rapporteur's Quality Assessment Report was circulated to all CHMP members on 15 January 2010.
- The Rapporteur's Overview was circulated to all CHMP members on 15 January 2010.
- During the meeting held in January 2010, the CHMP agreed on the consolidated List of Questions to be sent to the company. The final consolidated List of Questions was sent to the company on 20 January 2010.
- The company submitted the responses to the CHMP consolidated List of Questions on 27 January 2010 and 3 February 2010.
- The Rapporteur circulated an updated Overview on the company's responses to the List of Questions to all CHMP members on 10 February 2010.

2 GENERAL CONDITIONS FOR THE MARKETING AUTHORISATION

2.1 Manufacturing authorisation holder

Manufacturer(s) of the active substance
Reference is made to the authorised Relenza Inhalation Powder. An additional manufacturer is:

GlaxoSmithKline R&D Limited
Gunnels Wood Road, Stevenage
Hertfordshire SG1 2NY
UK

QP declarations from both finished product manufacturers, confirming GMP compliance for the active substance, have been provided.

Manufacturer(s) of the finished product

Glaxo Operations UK Limited
Harmire Road
Barnard Castle
County Durham DL12 8DT
UK

Patheon Inc.
Ferentino Operations
Via Morolense 87
03013 Ferentino (FR)
Italy

Manufacturer responsible for import and batch release in the European Economic Area

Glaxo Operations UK Limited trading as Glaxo Wellcome Operations
Harmire Road
Barnard Castle
County Durham DL12 8DT
UK

Glaxo Wellcome Production
Zone Industrielle No. 2
23 Rue Lavoisier
Evreux, France

GlaxoSmithKline Research and Development Limited

New Frontiers Science Park
Third Avenue
Harlow, Essex CM19 5AW

GMP status of all finished product manufacturers has been confirmed.

2.2 Conditions of distribution

Medicinal product subject to special medical prescription.
IV Zanamivir should be prescribed only by clinicians skilled in the diagnosis and management of patients with potentially life-threatening illness

2.3 Conditions for update of Compassionate Use to be implemented by the company

In accordance with Article 83(4) of Regulation (EC) No 726/2004, any change or new data having an impact on the CHMP compassionate use opinion as adopted by the CHMP on 18 February 2010, related to the conditions of use, distribution and targeted population of IV Zanamivir, shall be communicated to the Agency (EMA) in order to update the CHMP Compassionate Use opinion as appropriate.

2.4 Conditions for safety monitoring to be implemented by the company

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and responsibilities defined in Articles 24(1) of the Regulation (EC) No 726/2004 referring to centrally authorised medicinal products as defined in articles 3(1) and (2) are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. Therefore the company will ensure that these pharmacovigilance rules and responsibilities are fulfilled.

'The company will submit 6-monthly, all safety information on IV Zanamivir in the format of a comprehensive Periodic Safety Update Report (PSUR), in addition to yearly PSURs, unless otherwise specified by the CHMP.

The Relenza PSURs that are being produced for all formulations of Zanamivir will include information on the intravenous formulation and the Compassionate Use programme. In its 18th February 2010 Article 83 opinion, CHMP requested use of a CRF to include capture of non-serious AEs. The Company will submit all information on serious and non-serious adverse events with IV Zanamivir available from the GSK Worldwide Clinical Safety database as an addendum to the PSUR. This addendum will consist of line listings and clinical narratives of cases of all AEs and of cases of areas of special interest, from the reporting period.

The MAH has been providing all available information on serious adverse events with IV Zanamivir available from the GSK Worldwide Clinical Safety Database in the monthly Pandemic Safety Reports (PSR) since the first PSR that covered the period 01 August 2009 to 30 September 2009. The MAH have continued to do so in all subsequent PSRs. Following MPA advice on 11 March 2010 and the conclusions of the Final Pandemic Safety Report Assessment of 17 March 2010, confirming that monthly reporting of PSRs are no longer required given the current status of the H1N1 pandemic, GSK have now submitted the final PSR covering the period 01 – 28 February 2010. No further monthly PSRs will be provided. Future reporting will now be via 6-monthly PSURs, with the next PSUR covering the period from 01 February 2010 to 31 July 2010.'

2.5 Conditions for safety monitoring to be implemented by the Member States.

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and Responsibilities defined in Articles 25 of the Regulation (EC) No 726/2004 referring to centrally authorised medicinal products as defined in articles 3(1) and (2) are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. Therefore the Member State(s) will ensure that these pharmacovigilance rules and responsibilities are fulfilled.

3 SCIENTIFIC DISCUSSION

3.1 Introduction

Zanamivir is a selective inhibitor of influenza neuraminidase (NA), the influenza virus surface enzyme. NA inhibition occurs at low zanamivir concentrations (50% inhibition at 0.64nM-7.9nM) against human influenza A and B strains. The inhibition of the enzyme encompasses all 9 NA subtypes including those that infect different animal species (50% inhibition at 0.09-95.2nM). NA catalyzes the removal of terminal N-acetylneuraminic acid from oligosaccharides. NA aids the release of newly formed virus particles from infected cells and may facilitate access of virus through mucus to epithelial cells. By the inhibition of NA, the newly formed virus particles self-aggregate at the cell surface and further spread of the progeny viruses is prevented. The activity of the drug is extracellular.

Zanamivir closely mimics the structure of the natural substrate of neuraminidase; therefore, mutations that confer resistance to oseltamivir do not necessarily demonstrate cross-resistance to zanamivir. With the widespread appearance of oseltamivir-resistant seasonal H1N1 influenza virus since late 2007, the potential utility of zanamivir in the clinical armamentarium has been recognised. The intravenous (IV) formulation of zanamivir is therefore considered important for patients in clinical scenarios where oral or oral inhaled formulations are not suitable. Intravenous zanamivir will provide both systemic and pulmonary exposure of this neuraminidase inhibitor at several hundred times the *in vitro* inhibitory concentrations.

Clinical experience with IV zanamivir administration comes from seven Phase I studies conducted in a total of 120 subjects and an ongoing compassionate use programme. The phase I studies included pharmacokinetic (PK) studies to evaluate systemic exposure following single and repeat doses, an experimental challenge study in human volunteers, a PK study to evaluate serum and pulmonary concentrations as measured in bronchoalveolar lavage (BAL) fluid following inhaled and IV doses, and a study in adults with renal impairment. In addition, results from an ongoing drug interaction study with IV zanamivir and oral oseltamivir are anticipated in Q1 2010.

No controlled efficacy studies have been conducted using the IV formulation of zanamivir to date. At this time, a Phase II safety and tolerability study (NAI113678) is ongoing and will form part of the overall clinical development programme.
As requested by the CHMP, the company submitted a dossier to support the compassionate use of IV Zanamivir formulation. The dossier was presented in accordance with Chapter 7 of Notice to Applicants Volume 2A, meaning according to CTD format.

Very limited amount of quality, non-clinical and clinical data were submitted as part of this dossier. It should therefore be kept in mind that the following assessment concerns exclusively the use of IV Zanamivir formulation in the context of the compassionate use in a specific targeted population.

3.2 Quality aspects

Introduction

IV Zanamivir formulation for compassionate use is a solution for infusion, packaged in glass vials, with rubber stoppers and aluminium overseals. The only excipients are Sodium Chloride and Water for Injections.
Relenza 5 mg/dose inhalation powder has already been authorised in 27 EU Member States via a Mutual Recognition Procedure.

Drug Substance

Zanamivir is 5-(acetylamino)-4-[(aminoiminomethyl)-amino]-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid. It has a molecular formula of $C_{12}H_{20}N_4O_7$ and a molecular weight of 332.3. Zanamivir is a white to off-white powder with solubility of approximately 18 mg/ml in water at 20°C. The drug substance zanamivir has been appropriately characterized and fully described and was already approved within the Relenza 5 mg inhalation powder Marketing Authorization Application.

For the active substance information, reference is made to the MRP approved dossier for Relenza inhalation powder. Additional information is presented below:

The manufacturer has provided satisfactory additional information to support the use of this active substance in a parenteral formulation,

The drug substance specification includes tests for description, identification, specific optical rotation, water content, acetone content, assay, impurities, and bacterial endotoxins. Impurities have been evaluated and found to be acceptable from the point of view of safety, the specific character of compassionate use taken into account.
Analytical results of three batches of the active substance conform to the specification.

Specification limits were sufficiently justified and found acceptable.

- Stability

For stability of the active substance, reference is made to the MRP approved dossier for Relenza inhalation powder. The active substance has an approved retest period of 60 months when stored up to 30ºC. The retest period may be extended as further stability data become available.
Zanamivir is stored in double polyethylene bags inside high density polyethylene kegs.

Drug Product

- Pharmaceutical Development

Zanamivir has already been available as an inhalation powder and IV-formulation was developed as an alternative treatment option for patients considered unsuitable for currently authorised anti influenza medications The drug product is a solution for infusion in a glass vial with a rubber stopper and an aluminium overseal and is manufactured by standard manufacturing processes, including terminal sterilisation. Both excipients used – Sodium Chloride and Water for Injections – are of compendial quality.

- Adventitious Agents

Neither the excipients nor the active substance are derived from human or animal origin.

- Manufacture of the Product

The drug product is manufactured by a standard manufacturing process. The following in-process controls are applied during manufacture: pH, bioburden, filter integrity, fill weight, and visual inspection. Sterility is ensured by terminal sterilisation process. Validation of the sterilisation process has been performed.

- Product Specification

The specification presented is considered appropriate at this stage of product development. Specification tests include description (visual), identification (HPLC), zanamivir content (HPLC), drug-related impurities (HPLC), volume in container (Ph.Eur), pH, particulate matter (Ph.Eur.), bacterial endotoxins (Ph.Eur) and sterility (Ph.Eur). The analytical procedures used are well described and appropriately validated.
Batch analysis results for three batches conform to the specification.
No additional impurities to those described in the marketing application for Relenza inhalation powder are observed in the finished product.

- Stability of the Product

At the time of manufacture in November 2009, the shelf-life of 18 months was based on real time data for product manufactured at Glaxo Operations, Barnard Castle facility.

Additional stability data for up to 48 months on formulation manufactured at Glaxo Operations and for 12 months on batches manufactured at Patheon S.p.A have been presented to support the extension in shelf-life for Zanamivir Injection from 18 months to 48 months.

With regards to batches manufactured at Glaxo Operations, stability data are available for
- one batch of Zanamivir Injection 10 mg/mL stored for 48 months at 30 C/65% Relative Humidity (RH), 24 months at 40 C/75% RH and 6 months at 50 C/Amb H and for 7 days exposed to light
- one batch of Zanamivir Injection 10 mg/mL stored for 36 months at 30 C/65% RH, 6 months at 40 C/75% RH and for 7 days exposed to light
- one additional batch of Zanamivir Injection 10 mg/mL stored for 6 months at 30 C/65% RH and 40 C/75% RH, 1 month at the Freeze/Thaw cycling condition and for 7 days exposed to light.

For batches manufactured at Patheon S.p.A, stability data are available for 3 batches of Zanamivir Injection 10 mg/mL stored for 12 months at 30 C/65% Relative Humidity (RH), and 6 months at 40 C/75% RH.

Parameters tested are description, assay, drug related impurities, pH and sterility. Particulate matter is an additional test for the second batch tested (Glaxo Operations) and the batches manufactured by Patheon.
The stability data shows that Zanamivir Injection is physically and chemically stable after storage for up to 48 months when stored at 30°C/65% RH. For all tests performed at Glaxo Operations, Barnard Castle, UK and Patheon S.p.A., Ferentino, Italy, all data generated after storage were similar to those generated at the initial time point.
The stability testing completed to date supports the proposed shelf-life and storage conditions of 4 years (48 months) when stored below 30°C (86°F).

The finished product is administered as an i.v. infusion either undiluted or diluted with 0.9% sodium chloride solution for infusion. Stability after first opening and dilution and compatibility with the diluent were monitored. The stability studies focused on the critical parameters, i.e. assay and impurities. The data demonstrates the infusion is stable over the in-use period (30 minutes infusion at controlled room temperature) and if stored at 2-8°C for up to 24 hours.

Discussion on chemical, pharmaceutical and biological aspects

All relevant 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 satisfactory consistency and uniformity of all the important quality characteristics of the product. It can be reasonably concluded that the product should have a satisfactory and uniform performance in the clinic. At the time of the CHMP opinion, there were no unresolved quality issues, which could have a negative impact on the Benefit Risk balance of the product.

3.3 Non-clinical aspects

Introduction

The documentation available for zanamivir at the time of the initial application for marketing authorisation of Relenza included animal studies on the pharmacology and toxicology of zanamivir using the intravenous administration route. These were assessed in relation to the first application for marketing authorisation of Relenza and are briefly discussed below. Overall from the non-clinical point of view, these studies were considered sufficient in scope and extent to be acceptable as a basis for the present submission of an application for compassionate use of a new formulation, a new administration route and a new dose.

Non-Clinical studies performed with IV dosing

Pharmacology

Zanamivir selectively inhibits influenza virus neuraminidase with low or no activity against a range of other RNA or DNA viruses. The data submitted on primary and general pharmacology mainly originate from the time of first submission for marketing authorisation. In addition, new data in the literature,

including aspects of resistance, are considered in relation to primary pharmacology. The issue of drug resistance is discussed with particular reference to recent clinical data. The most frequent variants selected *in vitro* were E119G (glutamic acid to glycine), E119D (glutamic acid to aspartic acid) and E119A (glutamic acid to alanine). The clinical relevance of these *in vitro* resistant genotypes has not been established. In a clinical setting a case of HA and NA mutation in an influenza B isolate from an immunocompromised patient treated with zanamivir has been reported. In 2009 a novel mutation at Q136K in seasonal influenza A viruses that confers resistance to zanamivir was reported, however, this mutation has never been reported in a Relenza treated patient and not detected in *in vitro* passage in the presence of zanamivir and the possibility that this was a laboratory artefact has been discussed. Resistance in seasonal influenza A H1N1 viruses has been associated with the H274Y mutation and oseltamivir treatment. These viruses retain sensitivity towards zanamivir. In novel A/H1N1 pandemic viruses cases of oseltamivir resistance related to the H275Y NA mutation have also been reported.

The available *in vitro* and *in vivo* studies are overall sufficient for the current application and no new data has been identified that would be expected to have implications on the proposed new administration route, dose and formulation. Inhibition of neuraminidase *in vitro* by zanamivir is characterised by IC_{50} values of 0.64 to 7.9 nM against influenza A and B strains. The short half-life of zanamivir could counteract maintenance of adequate exposure for a therapeutic effect. This is considered in the proposed clinical administration frequency of twice a day.

The safety pharmacology studies previously conducted with zanamivir in rat and dog used the intravenous administration route and doses of up to 100 mg/kg. No specific or significant effects on function of major organ systems were recorded. An intravenous dose of 100 mg/kg in the mouse caused a slight increase in pentobarbitone induced sleeping time. No adverse cardiovascular effects were recorded in dog after single intravenous doses of 30 mg/kg. Although specific data on systemic exposure at this dose is lacking likely this would be lower than expected clinical. No *in vitro* electrophysiological data seems available. The potential for cardiovascular effects will be addressed in clinical studies.

Pharmacokinetics
Data on pharmacokinetics after intravenous doses are available from the time of the first submission of an application for marketing authorisation. The majority of pharmacokinetic studies with zanamivir were conducted using the intravenous route. The pharmacokinetics of zanamivir are characterised by low oral absorption, wide distribution in rat, rapid clearance and low protein binding. After an intravenous dose zanamivir is mainly eliminated in an unchanged form in the urine in mouse, rat and dog. Low amounts of the compound cross the placenta and excretion in breast milk occurs.

Toxicology
No new studies of zanamivir toxicity by the intravenous route have been conducted. Single dose intravenous studies in mouse and rat and repeated dose studies using the intravenous route are available in the rat and dog. No particular or significant primary target organ toxicity was identified in these studies. Some changes in haematological parameters were reported and in studies using continuous intravenous infusion renal vacuolation that was reversible was noted.

In the table below the margins of exposure at the no effect adverse levels in these studies are presented. Of note is that in most studies the no adverse effect level corresponded to the highest dose used, but the doses had also been identified as near possible maximum repeatable doses. Thus, the full toxicological profile of intravenous zanamivir may not have been possible to fully characterise. However, a 2 week continuous intravenous infusion study in rat has been conducted that employed doses up to 1728 mg/kg/day and that indicated development of renal effects at high doses. Further, a 2 week continuous intravenous infusion study with doses up to 6912 mg/kg/day is also available and major findings in this study were related to kidney (vacuolation of the cortical epithelium). Vacuolation in the lymph nodes and increases in urinary volume (probably related to high volume infusions) were also reported. Taken together it can be concluded that reasonable efforts to achieve maximum possible intravenous dose/exposure to provoke toxicity have been undertaken.

Studies on genotoxicity included microbial mutagenicity *in vitro* and an *in vivo* study in mouse using the intravenous route. The overall conclusion was consistent with an absence of potential genotoxicity of zanamivir. Likewise the two carcinogenicity studies by oral inhalation in mouse and rat were concluded to indicate a lack of carcinogenic potential.

A reagent (pyrazole-1H-carboxamidine) that is used during the final stage of synthesis was shown to be a weak *in vitro* mutagen while *in vivo* tests were negative. This substance was almost completely

removed and not detected in the final drug substance at a test level of 12.5 ppm (or a maximum of 15µg/day based on a dose of 600 mg bid (see further Quality Report).

Studies on reproduction toxicity using the intravenous administration route are available. In addition, a study using subcutaneous administration three times daily to maximize exposure during the day was conducted. In a revised report conclusions of the original report were clarified. At the high dose of 80 mg/kg three times daily, effects on visceral and skeletal development (incomplete ossification of skull bones and sacral vertebra arches, slightly kinked ribs, slightly dilated ureter and elongated innominate artery) were reported likely reflecting development delays. Post-implantation loss was increased from 2.9 to 4.5% in the high dose group.

A study in juvenile rats using the subcutaneous administration route did not indicate any relevant adverse effect that could be coupled to administration of zanamivir.

Specific studies on the local toxicity by intravenous administration do not appear available but in repeated dose toxicity studies no vascular irritation or haemolysis were reported. However, local tolerance in case of e.g. accidental paravenous injection has not been addressed.

Table: Interspecies comparison main intravenous studies

Species/Study	**Dose (NOAEL) (mg/kg)**	**Cmax (µg/ml)**	**$AUC_{0\text{-}tau}$ (µgxh/ml)**	**Ratio animal/human**	
				$C_{max\ animal}/C_{max\ human}$	**AUC_{animal}/AUC_{human}**
Rat (M/F) 2 week IV infusion (WPT/97/015)	432	-	660	-	4.6
Rat (M/F) 5 weeks IV (WPT/93/012)	90	-	170	-	1.2
Dog (M/F) 2 week IV infusion (WPT/94/241)	90	-	272.5	-	1.9
Dog (M/F) 5 weeks IV (WPT/93/163)	36	-	128	-	0.9
Rat (F) EFD IV days 6-15 of pregnancy (WPT/93/047)	90	281	-	7	-
Rabbit (F) EFD IV days 7-19 of pregnancy /WPT/93/095)	90	637	-	15.9	-
Rat (F) PPN SC days 6-15 of pregnancy (WD1999/00225/01)	80 TID	-	519	-	3.6
Rat juvenile (M/F) SC days 2 -42 postpartum (WPT/95/061)	90	277	-	7	-
Human (M/F)	600 mg BID	40	144	-	-

*EFD=embryo-foetal development study. PPN=peripostnatal study.

Ecotoxicity/environmental risk assessment

The introduction of an intravenous formulation of zanamivir for compassionate use is not expected to have any impact on the environmental risk potential of the compound. However, for a full approval of a new pharmaceutical form and dosage using a standard application for approval a new assessment would be expected.

Discussion on non-clinical aspects

Non-clinical studies conducted with the intravenous administration route do not indicate any specific or unique toxicity that can be coupled to the intravenous formulation and intravenous administration route. The high dose in the 5 week pivotal studies in rat and dog using intravenous administration was also the no observable adverse effect level (NOAEL) and low margins of exposure relative to expected clinical were achieved. However, the doses were limited by solubility and two 2-week continuous intravenous infusion studies in rat that employed doses up to 6912 mg/kg/day are available. No specific studies on local toxicity/tolerance have been submitted. While the potential tolerance after e.g.

an accidental paravenous injection has not been addressed, no vascular irritation or haemolysis was reported in repeated dose toxicity studies.

3.4 Clinical aspects

Introduction

To support the application of compassionate use of the zanamivir IV formulation, the company submitted the following clinical data listed in the table below:

Table: Overview of Completed Studies Evaluating IV Zanamivir

Study Number	Study Description / Design	Doses / Duration	Number of subjects	Age Range in Years (Mean)
C92-083	Randomized, double-blind, placebo-controlled, ascending dose, 4-period crossover study in healthy males	Dose: IV zanamivir 1, 2, 4, 8 and 16mg; Placebo (IV); Duration: IV infusion over 20 min; 4 periods / washout period ≥72h	Zanamivir n=8 Placebo n=8	21 – 38 (30)
C94-051, C95-014 (NAIB1003)	Open-label, single dose study in healthy and renally impaired males and females	Dose: IV zanamivir 2 or 4mg single dose; Duration: IV infusion over 20 min	Zanamivir n=17	31 – 67 (55)
NAIB1008	Randomized, double-blind, placebo-controlled, ascending dose, 3-period study in healthy males and females	Dose: IV zanamivir 50, 100, 200, 400, 600mg; Zanamivir (oral solution) 500mg±3g glucose; Placebo (IV); Duration: IV infusión over 30 min; single oral dose; 3 periods / washout period 1 wk	Zanamivir n=22 Placebo n=11	18 – 45 (25)
NAIB1009	Randomized, double-blind, placebo-controlled, multiple dose, 2-period crossover in healthy males	Dose: IV zanamivir 600mg; Placebo (IV) Duration: IV infusion over 30 min; twice daily for 5 days	Zanamivir n=12 Placebo n=12	20 – 39 (25)
NAIA1010	Randomized, double-blind, placebo-controlled, multiple dose study in healthy males inoculated with influenza A/Texas/91	Dose: IV zanamivir 600mg; Placebo (IV) Duration: IV infusion over 30 min, twice daily for 5 days	Zanamivir n=8 Placebo n=8	18 – 35 (24)
NAI106784	Open-label, two dose study in healthy males and females	Dose: IV zanamivir 100, 200, 600mg, continuous infusion 3mg/hr; Zanamivir (oral inhaled) 10mg Duration: 2 doses 12 h apart or continuous IV infusion for 12 h	Zanamivir (IV) n=37 Zanamivir (inhaled) N=6	18 – 47 (26)

Study Number	Study Description / Design	Doses / Duration	Number of subjects	Age Range in Years (Mean)
NAI108127	Open-label, single dose study in healthy and renally impaired males and females	Dose: IV zanamivir 100mg single dose Duration: IV infusion over 30 min	Zanamivir n=16	40-77 (62)

No efficacy data has been submitted, as no clinical study results using the IV formulation in influenza patients are available in patients with influenza to date.

Pharmacokinetics

Introduction

Clinical pharmacokinetic (PK) studies to evaluate systemic exposure following single and repeat doses, a PK study to evaluate serum and pulmonary concentrations as measured in bronchoalveolar lavage (BAL) fluid following inhaled and IV doses, and a study in adults with renal impairment has been performed. In addition, results from an ongoing drug interaction study with IV zanamivir and oral oseltamivir are anticipated in Q1 2010.

Dose proportionality

The pharmacokinetics of intravenously administered zanamivir were studied in healthy volunteers, after single escalating doses, 1 to 16 mg (**Study C92-083)** and 50 to 600 mg **(Study NAIB1008**), and repeated doses of 600 mg twice daily for 5 days (**Study NAIB1009**).

In study **NAIB1008** $AUC_{0\text{-}24h}$ was between 75.4 and 85.1 mg h/l and Cmax was 36.5-43.4 mg/l (N=4) after 600 mg single intravenous dose. Dose proportional increases in zanamivir AUC were demonstrated (median values illustrated in Figure PK1 and medium serum-concentration time data in figure PK2).

Figure PK1. Median AUC and Cmax vs IV Zanamivir Dose Study NAIB1008

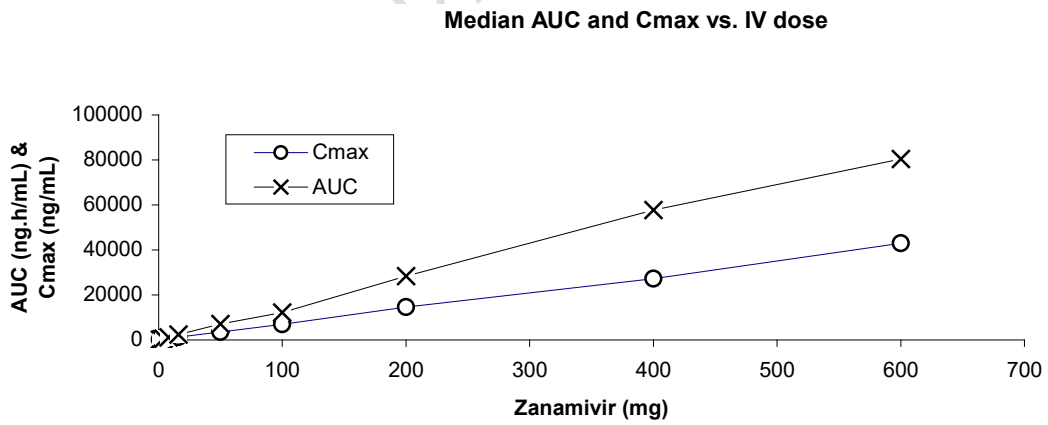
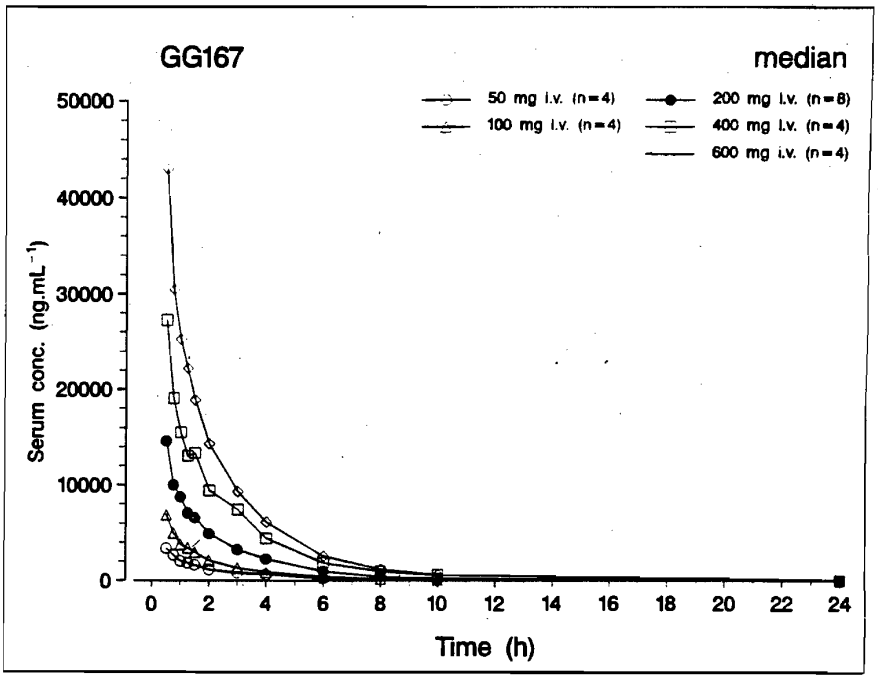


Figure PK2: Comparative medium serum-concentration time data of zanamivir (linear plot, Study NAIB1008): 50 mg – 600 mg i.v.



In study **NAIB1009** (repeat dose study) AUC_{0-12} ranged from 46.3 to 89.5 mg h/l (N=12) day 1 and from 49.1 to 100.9 mg h/l on day 5. C_{trough} levels presented as arithmetic mean (range) were 417 (174-612), 473 (196-812) and 479 (197-891) on day 3, 4 and 5 respectively. Mean accumulation ratio based on AUC was 1.05 (range 0.87 to 1.23) after twice daily dosing of 600 mg for five days.

Elimination / Excretion

Zanamivir is excreted in the urine as unchanged drug. Additionally, chromatographic profiling showed no evidence of biotransformation. These findings indicate that the drug does not undergo metabolism. Renal clearance was between 5.5 and 7.3 l/h (N=4) after 600 mg single intravenous dose in study **NAIB1008** and ranged from 4.9 to 10 l/h (N=12) in Study NAIB1009 intravenous doses of 600 mg twice daily. The half life was around 2 hours. Given its low protein binding and elimination primarily by passive renal filtration of unchanged drug it is unlikely that zanamivir would affect the elimination of other concurrently administered compounds or vice versa.

Distribution

The volume of distribution of zanamivir was 16 l, which approximates the volume of extracellular water. This is consistent with its physicochemical characteristics as a polar compound with low protein binding (<10%).

Special populations

Renal impairment

NAI108127 was a multi-centre, open-label, PK study following administration of single IV doses of zanamivir 100 mg to subjects with impaired renal function (mild, moderate and severe) and subjects with normal renal function 16 subjects in total. This study was designed to provide additional PK information at a higher dose of zanamivir compared to existing data from lower doses (2-4 mg) administered to subjects with renal impairment. The results are presented in Table PK4 and PK5 and in Figure PK6.

Table PK4 Summary of Selected Zanamivir Pharmacokinetic Parameter Estimates in NAI108127 [Geometric Mean (%CVb)]

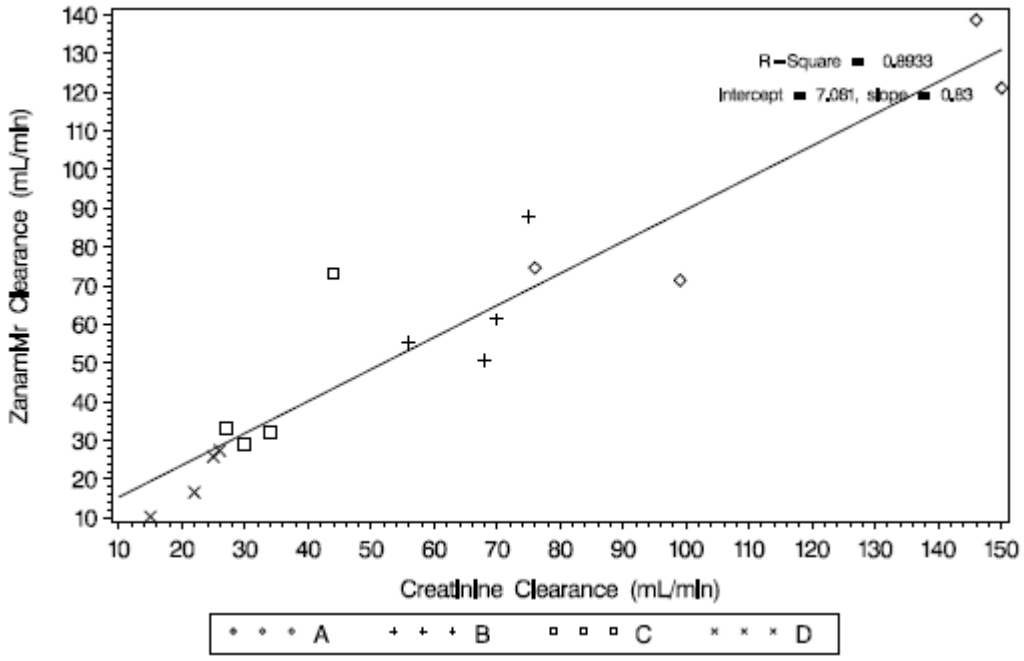
Zanamivir PK Parameter	Normal Renal Function (N = 4)	Mild Renal Impairment (N = 4)	Moderate Renal Impairment (N = 4)	Severe Renal Impairment (N = 4)
AUC(0-∞) (μg.h/mL)	17.0 (36)	26.5 (24)	42.9 (45)	89.4 (48)
AUC(0-t) (μg.h/mL)	16.8 (37)	26.1 (23)	39.8 (39)	77.6 (28)
Cmax (μg/mL)	7.29 (16)	6.93 (12)	8.50 (20)	6.96 (43)
t½ (h)	2.44 (22)	3.88 (22)	5.79 (45)	12.8 (80)
tmax[1] (h)	0.53 (0.5-0.8)	0.50 (0.50-0.5)	0.50 (0.50-0.5)	0.50 (0.50-1.0)
CL (mL/min)	97.2 (35)	62.4 (24)	38.8 (45)	18.6 (48)
Vz (L)	20.5 (18)	20.9 (12)	19.4 (12)	20.6 (34)
λz (h^{-1})	0.284 (22)	0.179 (22)	0.120 (45)	0.054 (80)
Ae (mg)[2]	89.7 (6)	75.4 (15)	74.0 (43)	61.3 (11)
CLr (mL/min)	89.0 (39)	48.2 (37)	31.0 (58)	13.2 (39)

1. Values for tmax are presented as median and range.
2. Ae denotes cumulative zanamivir recovery in urine over 24 hours for normal, mild, and moderate renal function groups and over 48 hours for severe renal impairment group.

Table PK5 Zanamivir PK Comparisons of Renally Impaired Groups with Normal Renal Function Group in NAI108127

Zanamivir PK Parameter	GLS Mean Ratio [90% CI]		
	Mild Renal Impairment vs. Normal Renal Function	Moderate Renal Impairment vs. Normal Renal Function	Severe Renal Impairment vs. Normal Renal Function
AUC(0-∞)	1.56 [0.970, 2.51]	2.53 [1.57, 4.06]	5.27 [3.27, 8.47]
AUC(0-t)	1.55 [1.04, 2.31]	2.37 [1.59, 3.53]	4.62 [3.10, 6.88]
Cmax	0.951 [0.694, 1.30]	1.17 [0.851, 1.60]	0.954 [0.697, 1.31]
t½	1.59 [0.91, 2.76]	2.37 [1.36, 4.12]	5.22 [3.00, 9.08]
CL	0.641 [0.400, 1.03]	0.399 [0.249, 0.640]	0.192 [0.120, 0.307]
Vz	1.02 [0.79, 1.32]	0.95 [0.73, 1.23]	1.00 [0.77, 1.30]
Ae[1]	0.840 [0.630, 1.12]	0.824 [0.618, 1.099]	0.683 [0.512, 0.910]
CLr	0.541 [0.319, 0.918]	0.348 [0.205, 0.590]	0.148 [0.087, 0.251]

Figure PK6 Total clearance versus creatinine clearance



Renal impairment has a significant effect on zanamivir PK. Zanamivir total clearance (ml/min) was highly correlated with creatinine clearance (CLcr, in ml/min) after IV administration:

$CL \cong 7.08 + 0.826 \bullet CLcr$ ($r^2 = 0.89$)

For IV Zanamivir administration, dosage adjustment will be required for subjects with renal impairment.

Dose adjustment in mild and moderate renal impairment follows the clearance ratios obtained (Table PK4). For severe renal impairment the group was divided in two 15-30 ml/min and <15 ml/min. Where the former receives ¼ and the latter group receives 1/10 of the normal dose.

Hepatic impairment

No effect of hepatic impairment on the pharmacokinetics of zanamivir is expected.

Paediatric population

No data is available. The company has predicted maintenance doses for infants and children >6 months with a claimed target of similar daily exposure to zanamivir based on a model for development of glomerular filtration (*Rhodin et al. 2009*). Dose reductions in paediatric subjects with renal impairment are suggested with the same degree of dose reduction as in adults.

Elderly
No data is available. Reduced clearance is expected as renal function decreases with age. Dose adjustments according to renal function are recommended but it is currently unknown whether additional dose adjustments would be needed.

Drug-drug interactions:
The potential for drug-drug interactions is considered very limited (elimination mainly through glomerular filtration, low protein binding).

Interaction study with oseltamivir
Although a drug interaction between zanamivir and oseltamivir is not anticipated, the likelihood of coadministration combined with the common route of renal clearance of both drugs warrant verification of a lack of an interaction between these agents. NAI112977 (SEA003) is an open-label, repeat-dose, drug interaction study conducted in healthy adult Thai subjects. In this study design, both intermittent (600 mg twice daily) and continuous infusion (50 mg/hour) administration of IV zanamivir will be

evaluated alone and in combination with oseltamivir 150 mg twice daily in healthy Thai subjects. The study started in July 2009 and results are anticipated in 1Q 2010.

Dose selection

Bronchoalveolar lavage (BAL) study

NAI106784 was a steady-state PK study to evaluate serum and pulmonary PK following administration of IV and inhaled zanamivir to healthy adult subjects. For IV administration of zanamivir, a range of doses was included: 600 mg, 200 mg and 100 mg twice daily for 2 doses and continuous infusion [6 mg loading dose followed by continuous infusion at 3 mg/hour for 12 hours] (n=6 subjects for each regimen). The oral inhaled regimen (10 mg twice daily for 2 doses) was included to enable benchmarking pulmonary PK exposure against an approved formulation.
Blood samples were collected to characterise systemic exposure to zanamivir and to quantify urea concentrations in blood.

BAL samples were collected 12 hours after the second dose of zanamivir (trough) for the intermittent regimens and at 2, 6, and 12 hours after the start of the continuous infusion regimen. Pulmonary concentrations of zanamivir were calculated based upon relative urea concentrations in BAL supernatant versus serum and recovered volume of BAL aspirate to derive a concentration in epithelial lining fluid. Geometric mean serum zanamivir C12 values following twice daily administration of 600 mg, 200 mg, and 100 mg IV zanamivir were 586, 252 and 114ng/ml, respectively, and many fold in excess of the IC50 values for influenza virus neuraminidase, which are typically in the range of <1 to 4 ng/ml (Table PK1).

Table PK1

Serum Zanamivir PK Parameter Estimates Following Intravenous Administration in Study NAI106784 [Geometric Mean (%CVb)]

Treatment Arm	N	Cmax (ng/mL)	AUC(0-t) (ng.h/mL)	AUC(0-12) (ng.h/mL)	Tmax[1] (h)	C12[2] (ng/mL)	t1/2 (h)
A	7	39430 (11.7)	89253 (11.6)	86630 (11.6)	0.50 (0.50-0.50)	586 (38.2)	2.89 (3.35)
B	6	21.2 (45.3)	94.9 (52.0)	175 (25.8)	1.75 (0.25-4.00)	NR[3]	NR[3]
C	6	13149 (15.0)	32607 (11.1)	31671 (10.3)	0.50 (0.50-0.50)	252 (39.0)	2.68 (16.6)
D	6	7430 (12.6)	16381 (12.6)	16386 (12.6)	0.50 (0.50-0.50)	114 (28.3)	2.23 (7.66)
E	6	574 (19.6)	7287 (19.7)	5966 (18.6)	7.00 (5.00-12.00)	525 (19.2)	2.37 (8.26)
F	6	527 (15.0)	6573 (19.4)	5356 (16.1)	6.01 (5.78-8.00)	474 (19.4)	2.13 (18.1)
G	6	499 (9.83)	6360 (10.1)	5136 (8.42)	7.00 (6.00-11.77)	459 (9.56)	2.29 (9.24)

Treatment A = Zanamivir 600mg IV q12h x 2 doses; BAL sampling 12 hours after the second dose
Treatment B = Zanamivir 10mg (2 x 5mg inhalations) via oral inhalation q12h x 2 doses; BAL sampling 12 hours after the second dose
Treatment C = Zanamivir 200mg IV q12h x 2 doses; BAL sampling 12 hours after the second dose
Treatment D = Zanamivir 100mg IV q12h x 2 doses; BAL sampling 12 hours after the second dose
Treatment E= Zanamivir Continuous Infusion x 12 hours; BAL sampling 2 hours after start of infusion
Treatment F = Zanamivir Continuous Infusion x 12 hours; BAL sampling 6 hours after start of infusion
Treatment G = Zanamivir Continuous Infusion x 12 hours; BAL sampling 12 hours after start of infusion

1. tmax was presented as median and range
2. Css for Treatments E, F, and G
3. NR: not reportable due to low serum concentrations

Table PK2

Serum, Epithelial Lining Fluid, and Nasal Fluid Zanamivir Concentration Estimates in Study NAI106784 [Median (range)]				
Treatment Arm	Zanamivir Concentration (ng/mL)			
	Serum[1]	Epithelial Lining Fluid		Nasal Fluid
		BAL1 (first BAL)	BAL2 (latter three BALs)	
A	642 (290-825) n=6	584 (336-2000) n=5	419 (216-1163) n=6	498 (212-1547) n=6
B	NS[2]	891 (116-3189) n=5	326 (89.8-760) n=6	613 (42.0-1911) n=5
C	247 (143-438) n=6	275 (143-619) n=6	146 (70.9-299) n=6	101 (58.1-296) n=6
D	117 (75-169) n=6	175 (96.8-239) n=5	74.0 (59.2-114) n=6	46.0 (20.7-98.9) n=5
E	536 (394-644) n=6	205 (178-303) n=5	141 (66.0-190) n=6	NS[2]
F	536 (423-630) n=6	349 (221-398) n=6	209 (129-259) n=6	13.4 (13.4-13.4) n=1
G	452 (389-535) n=6	403 (93.4-476) n=6	197 (187-282) n=6	51.6 (15.6-87.5) n=2

Treatment A = Zanamivir 600mg IV q12h x 2 doses; BAL sampling 12 hours after the second dose
Treatment B = Zanamivir 10mg (2 x 5mg inhalations) via oral inhalation q12h x 2 doses; BAL sampling 12 hours after the second dose
Treatment C = Zanamivir 200mg IV q12h x 2 doses; BAL sampling 12 hours after the second dose
Treatment D = Zanamivir 100mg IV q12h x 2 doses; BAL sampling 12 hours after the second dose
Treatment E= Zanamivir Continuous Infusion x 12 hours; BAL sampling 2 hours after start of infusion
Treatment F = Zanamivir Continuous Infusion x 12 hours; BAL sampling 6 hours after start of infusion
Treatment G = Zanamivir Continuous Infusion x 12 hours; BAL sampling 12 hours after start of infusion
1. C12 for Treatments A-D and Treatment G, C2 for Treatment D, and C6 for Treatment F
2. NS: No quantifiable sample

Following twice daily administration of 600 mg, 200 mg, and 100 mg IV zanamivir, median zanamivir concentrations in epithelial lining fluid were 60-65% of the serum concentrations at the corresponding time points (C12), indicating good distribution of zanamivir into the pulmonary compartment throughout the dosing interval. Median zanamivir concentrations in nasal fluid appeared to be either comparable to epithelial lining fluid concentrations (600 mg) or had a comparable range of values to epithelial lining fluid (200 mg and 100 mg) (Table PK2).

Following continuous infusion of IV zanamivir at 3 mg/hour [6 mg loading dose], median zanamivir concentrations in epithelial lining fluid ranged from 141 ng/ml to 209 ng/ml.

Following orally inhaled zanamivir 10 mg, serum zanamivir trough concentrations were below the limit of detection and the median epithelial lining fluid trough concentration was 891 ng/ml; nasal fluid concentrations of zanamivir appeared to be comparable to epithelial lining fluid concentrations.

Following orally inhaled zanamivir 10mg twice daily, epithelial lining fluid C12 concentrations were higher than following intermittent and continuous infusion IV administration. Following twice daily administration of 600 mg IV zanamivir, median zanamivir epithelial lining fluid concentrations were 47-66% of those following orally inhaled zanamivir 10 mg twice daily.

Discussion on clinical pharmacology

Choice of dose
Although the concentrations in the BAL samples is lower after intravenous administration as compared to inhaled zanamivir, the trough concentrations obtained exceeds the *in vitro* IC50 several hundred fold and therefore support the use of 600 mg twice daily in a compassionate use program. The

challenge study in healthy volunteers (see Clinical efficacy below) further supports that sufficient exposure is obtained. It is unknown whether the chosen dose is optimal and further studies are encouraged.

Pharmacokinetics
Zanamivir is primarily eliminated unchanged through glomerular filtration.
There is limited data on pharmacokinetics after intravenous administration available in healthy volunteers with or without renal impairment. Available data suggests dose proportional behaviour with no time dependency for doses up to 600 mg twice daily and that dose adjustments are required based on renal function. Dose adjustments in renal impairment are suggested for maintenance dose only. Predicted clearance and exposure with adjusted maintenance doses in adults with normal renal function and impaired renal function were provided by the company and are reflected in the conditions of use.

The company suggested that doses equal to normal renal function should be given as loading dose to all subjects, while prolonging the time to the second dose in severe renal impairment. Hence the first day the exposure will be higher for subjects with renal impairment and it is assumed that a high concentration initially is warranted. The predictions suggest that exposure in subjects with creatinine clearance <15 ml/min but >8 ml/min will have lower maintenance AUC but as the exposure during the first day/days will be higher this may be a reasonable approach.

Although total AUC is predicted to be similar in patients with severe renal impairment, these patients will have lower daily exposure during day 2-5 as compared to patients with normal renal function. Predicted concentrations are still several thousand fold above IC50 but whether the difference in plasma concentration time profile will have negative impact on efficacy is unknown. For the compassionate use program the proposed doses are considered acceptable.

No pharmacokinetic data is available in paediatric subjects. The company considered to use a model for development of glomerular filtration (Rhodin et al 2009) to predict the clearance of zanamivir. Adult zanamivir clearance is scaled by body size (allometric) and a sigmoidal maturation function based on post menstrual age. Doses are proposed to match adult exposure. Dose recommendations for infants <6 months of age have been provided. It should be noted that the proposed doses only apply to term neonates and that no dose recommendations are provided for preterm neonates.
Further, the CHMP did not agree to the proposed dose reductions in infants <6 months of age with renal impairment due to risk of inadequate exposure. For now the CHMP therefore only agreed to give dose recommendations to patients < 6 months with normal renal function for their age. In addition, the initially proposed dose adjustments in mild renal impairment did not match adult dose adjustments and were subsequently corrected.

Clinical efficacy

Intravenous zanamivir has not been evaluated in controlled efficacy studies in patients with influenza illness.

Dose-response studies and main clinical studies
For dose selection of IV zanamivir, see above under Pharmacokinetics.

Study **NAI113678** is an ongoing Phase II study in adults, adolescents and paediatrics ≥6 months of age which started in November 2009. Although primarily a study to evaluate safety and tolerability, clinical and virological data are being collected and may provide information on efficacy in a critically ill population, and will inform the design of subsequent efficacy trials. Pharmacokinetic analyses will also be conducted.

NAI113678 is an open-label, multi-centre, single-arm study currently ongoing to evaluate the safety, tolerability and pharmacokinetics of intravenous zanamivir in the treatment of hospitalized adult, adolescent and paediatric subjects with confirmed influenza infection. Approximately 200 subjects will be recruited into this study. Selected enters in Europe (FR, UK and Spain) are recruiting patients for this study.

The dosage regimen to be evaluated is 600mg twice daily for 5 days. The initial 5-day treatment course may be extended for an additional 5 days if viral shedding is determined to be ongoing or if clinical symptoms warrant further zanamivir treatment. Adult and adolescent subjects with normal renal function will receive 600mg per dose. Paediatric subjects (≥ 6 months in age, weight ≤ 37kg) will

receive a weight-adjusted dose intended to provide comparable systemic exposures to 600mg in adults. Subjects with renal impairment will receive an adjusted dose based on calculated creatinine clearance. The primary objective of the study is to assess safety and tolerability. Pharmacokinetic, virologic and clinical assessments are included as secondary endpoints. Serum pharmacokinetic assessments will be performed in a subset of subjects.

A single arm, open-label design has been selected to achieve the primary objective of providing regulatory authorities with safety data on IV zanamivir in an expedited manner. This study design also facilitates the provision of safety data on a real-time basis, if necessary. This study has been started in Nov 2009. A completion date for this study is hard to predict and will depend on the severity of the pandemic during the winter season and the number of patients hospitalised at the participating sites

Supportive studies

- NAIA1010: A Phase I human challenge study using IV zanamivir was conducted during the early development of zanamivir and available efficacy data is summarised below.

- Compassionate use: In response to the current 2009 H1N1 pandemic, the Company has been making zanamivir aqueous solution available on a compassionate-use basis for the treatment of serious influenza illness. The zanamivir solution may be administered *via* inhaled nebulised or IV routes. However, data on efficacy *via* these routes of administration are very limited.

NAIA1010 - Human challenge study in healthy volunteers (n=16)
NAIA1010 was a double blind, randomised study to examine the prophylactic antiviral activity and efficacy of repeat dose IV zanamivir 600 mg every 12 hours compared to placebo in healthy male volunteers against infection from inoculation with Influenza A/Texas/91 (H1N1) virus [*Calfee, 1999*]. Sixteen subjects were randomised to receive either IV zanamivir 600 mg every 12 hours for 5 days or placebo every 12 hour for 5 days. Subjects received Influenza A/Texas/91 (H1N1) virus suspension ($\sim 10^5$ $TCID_{50}$) intranasally (0.25 ml per nostril) four hours after the first dose of IV zanamivir. Serial nasal washings for viral load measurements, haemagglutinin antibody titres and symptom assessment scores were evaluated.

Key results: IV zanamivir had a significant prophylactic effect against an experimental challenge with influenza A as demonstrated by the low infection rate (14% vs. 100 % positive serology in placebo group), isolation of virus (0% vs. 100% in placebo group), as well as reductions in fever (14% vs. 88% in placebo group), upper respiratory tract illness (0% versus 100% in placebo group) and total symptom scores (1 vs. 44 median score in placebo group). The 600 mg dose of IV zanamivir administered every 12 hours for 5 days was well tolerated.

Compassionate use programme from May 2009 (n=273)
The zanamivir aqueous solution compassionate-use programme was initiated by GSK in May 2009 to provide IV and nebulised zanamivir on a named patient basis.

As of 30 November 2009, 283 patients have been treated with zanamivir aqueous solution, 273 of these subjects received zanamivir via the IV route. A record of age is currently unavailable for seven of the treated patients. Of the 276 patients for which age has been collected, a total of 228 were adults aged $\geq$18 years, 16 subjects were aged 13 to 17 years and 32 subjects were aged <13 years.

Clinical data are limited at this point in the programme. No PK or virology data are available at this time. Safety information is presented below. No other outcome data are available at this time. However, the Company has developed a case report form for this programme in an attempt to collect targeted outcome and safety data and implemented a structured approach to collect data from treating physicians via timely follow-up emails and phone calls. A case report describing clinical improvement in one of these patients has recently been published [*Kidd, 2009*].

Discussion on clinical efficacy

The company has provided references of available authorised methods of prevention, medical diagnosis or treatment and justification as to why the target patients cannot be treated satisfactorily by the methods reviewed, supported by clinical information or scientific literature. These articles report that in serious cases antiviral treatment may be of clinical benefit. A recent article in Lancet [*Kidd 2009]* reported a severe case of H1N1 pneumonitis in a 22 year-year-old women successfully treated

with IV zanamivir. A further case report described a 10-year-old girl undergoing immunosuppressive treatment, who was hospitalised with oseltamivir-resistant H1N1 pneumonia and improved after receiving IV zanamivir. These limited data as well as results from the human challenge healthy volunteers suggest that IV zanamivir exerts clinically significant antiviral effects against influenza H1N1 virus.

No efficacy studies have been conducted using the IV formulation of zanamivir to date. Data to demonstrate efficacy will be evaluated in future clinical studies. However, an appreciable amount of patients (n=273) have received the IV drug in the compassionate use programme initiated by GSK in May 2009. Apart from safety data with respect to SAEs and deaths, no PK, efficacy or virology data are available at this time. A total of 31 deaths have been reported, (11%), which seems low in a critically ill population. The fatality rate is, however, not possible to evaluate since no detailed data were given on the demographic and disease characteristics of these patients. The CHMP requested that all such available data should be submitted by the company. A list of authorised compassionate use applications were presented in the dossier including many EU countries (DE, DK, EL, ES, FR, IT, NL, NO, PT, RO and UK), but no information was provided on the actual use of IV zanamivir in these countries.
During the procedure, the company provided updated information on the issues stated above. As of 15 January 2010, almost 500 patients have been treated with zanamivir aqueous solution. A total of 477 patients have received IV zanamivir, of whom the majority was adults (87%). Few children aged <13 years (n=52) have been treated including only one child in the age group 6 months-<1 years. Clinical data are therefore limited. No PK or virology data are available at this time point.
Overall, 337 EU patients have been treated, which comprise 70% of the global treatment population. Most cases originated from UK (n=125), Germany (n=82), France (n=30), Spain (n=27) and Italy (n=26).

Clinical safety

Patient exposure
In clinical studies, zanamivir solution has been administered to 120 patients by the IV route, at doses up to 600mg twice daily for 5 days. However, few patients (n=20) have received the relevant dose and duration of treatment recommended in this compassionate use programme. In addition, as of 15 January 2010, 477 patients with H1N1 infection have received IV zanamivir in the compassionate use programme.

Phase I studies

Adverse events
Intravenous zanamivir has been evaluated in seven Phase I studies (Table 1 above). In total, 63 adult subjects have received single doses of IV zanamivir at doses ranging from 1 mg to 600 mg, and 57 adult subjects have received multiple doses of IV zanamivir (two doses of 100, 200 or 600 mg IV, 600 mg IV twice daily for five days, or continuous infusion for 12 hours).

From the integrated safety analysis of all studies prior to 2006, for IV zanamivir, the most commonly reported drug-related AE was headache (14% in Study NAIB1008, 25% in Study NAIB1009, and 38% in Study NAIA1010). For Study C92-083, a total of five AEs were reported; three of them were observed after zanamivir administration, but none was considered to be drug-related.

Across the IV formulation clinical studies, there were no clinically significant trends in laboratory values, ECG findings, or vital signs.

The following studies were conducted after the above integrated safety analysis was performed:

Study NAI108127 (n=16): IV zanamivir 100 mg single dose was generally well tolerated during this study including both healthy and renally impaired subjects. One subject with a prior history of coronary artery disease was withdrawn due to an SAE of myocardial infarction, which was not related to investigational product. Very few AEs were reported during the study. Only two AEs were reported in more than one subject: diarrhoea (n=3) and headache (n=3) (See further below under renal impairment).

Study NAI106784 (n=37): The overall safety profile for zanamivir inhaled every 12 hours (n=6) and IV administered as separate doses every 12 hours (n=37) to healthy subjects in this study was similar to

the previously reported safety profile for zanamivir. Zanamivir administered as a continuous infusion had a similar safety profile as that observed with the intermittent infusion. No SAEs or deaths were reported. The most commonly reported AEs were leukocytosis (6 reports), neutrophilia (5 reports), post procedural complications (5 reports), pharyngolaryngeal pain (4 reports), dizziness (4 reports), and cough (3 reports). Only three subjects reported four AEs, which were considered by the investigator to be drug-related. The drug-related AEs were abnormal T-wave on ECG, back pain, pain in extremity and headache. No severe AEs were reported.

One subject was withdrawn from the study due to an AE. Subject 1 in the zanamivir 600 mg IV q12h group (Treatment A) had a mild abnormal T wave on ECG that was considered by the investigator to be related to study drug. The subject remained asymptomatic with stable vital signs. Creatine kinase-MB and troponin tests were normal. Medical follow-up did not raise concern for ongoing cardiac ischemia. The ECG returned to baseline in 7 days. This was the only clinically significant ECG value reported during the study.

Three subjects in Study NAI106784 had clinically significant clinical laboratory values. Two subjects had increased total bilirubin and two subjects had increased white blood cell counts. All of these values resolved at follow-up.

Subjects with renal impairment
In studies C94-051 and C95-014, single IV doses of zanamivir (2 mg or 4 mg, as 20 minute infusions) were well tolerated in the 17 subjects with renal impairment.
A total of nine AEs were reported by five subjects during the study. Two of these events were thought to be possibly related to the study drug and consisted of a moderate headache (starting 23 hours post-dose and lasting 6 hours) and mild soreness in right forearm at the cannula site (approximately 4 days following dosing and lasting 24 hours). These and the seven events that were considered to be unlikely to be related to the study drug resolved completely without recourse to treatment.

There were several potentially clinically relevant deviations in the clinical chemistry and haematology screens for 12 subjects during the study, however, in all cases these deviations were associated with the medical condition of the subject at study entry and/or were not exacerbated following treatment with zanamivir. There were no potentially clinically relevant deviations in the urinalysis screens.

The study treatments were well tolerated by the subjects and, there were no clinically significant abnormalities attributable to zanamivir treatment.

In study NAI108127 (n=16), IV zanamivir was generally well-tolerated. One subject was withdrawn due to an SAE of myocardial infarction, which was not related to investigational product. Very few AEs were reported during the study. Only two AEs were reported in more than one subject: diarrhoea (three subjects) and headache (three subjects).
Four subjects had drug-related AEs, including abdominal pain, headache, and diarrhoea (one subject each) and one 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.

Effects on cardiac repolarisation
Human ECG data is available for 12 healthy male subjects receiving zanamivir 600 mg IV twice daily for 5 days versus placebo in a randomised, two-way, cross-over design (Study NAIB1009). ECG recordings showed no clinically significant changes.

Compassionate use programme 2009
Only SAEs are to be reported to the Company and no information on non-serious AEs have been received. Due to the nature of the programme, the information may be incomplete. Cumulatively, since the start of the compassionate-use programme in May 2009, and up to 15 January 2010, 477 patients have been treated with IV zanamivir, including 16 pregnant women. In all 235 AEs/SAEs were reported in 75 patients. Of these, 53 cases had a fatal outcome, 44 cases including two pregnant women, were considered not to be related to zanamivir treatment, but likely to be related to influenza or other concurrent medical conditions. Of the remaining 9 cases, the causality was unknown in 5 of them. Three cases were considered related and one was considered possibly related.

There were eight fatalities in patients less than 18 years of age. Four of these fatalities were in the <13 age category and none of these were considered to be related to zanamivir treatment. These deaths were due to underlying haemophagocytic lymphohistiocytosis following bone marrow transplantation (1 case), staphylococcus aureus sepsis or multiorgan failure in patients with ARDS due to influenza infection (2 cases), and ALL (1 case). Another four were in adolescents aged 13 to 17

years of which two were considered unrelated to zanamivir treatment. Amongst this group, a fatal incident was reported for a patient who had presented with severe influenza and acute respiratory distress syndrome (ARDS) and died from pulmonary haemorrhage; the reporting physician considered that the intravascular haemolysis and pulmonary haemorrhage were possibly related to zanamivir.

Of the 22 non-fatal cases reported, 15 were considered related/probably related/unknown causality to zanamivir. All events except one were considered serious. The majority of events was improved (n=6) or resolved (n=4) whereas two were unresolved (Stevens-Johnson syndrome, pancytopenia) and three had unknown outcome. A variety of adverse events in different body compartments were reported with no obvious pattern discernable. Hepatic events are discussed below. The events improved in three further cases (one case with sinus arrest and bradycardia, one case with rash, agitation and delirium and a case of pneumothorax and ARDS). The outcome was not reported to the company for three patients (one case with hepatocellular injury, one case of respiratory insufficiency linked to influenza A, and one case with renal failure and myocardial infarction).

The compassionate-use programme is ongoing and data collected continues to be monitored and assessed.

Hepatic events
Hepatic events have been reported in 14 patients enrolled in the compassionate-use programme. Patients with severe influenza receiving IV zanamivir through the compassionate-use programme are frequently seriously ill with many concurrent medical conditions at the time they initiate therapy. This makes evaluation of the relationship of hepatic events with zanamivir therapy difficult. Based on the information available, there is no clear pattern of events and no clear relationship between IV zanamivir and hepatic events.

The Company has further provided 14 narratives on hepatic events during IV zanamivir treatment. The following events were indicated among the diagnoses: hepatic cytolysis (3), hepatic failure (3), hepatitis (1), abnormal liver function tests (3). The remaining 4 narratives described laboratory findings of abnormal liver function tests. Three cases were fatal and hepatic events were noted although the cause of death was deemed to be sepsis, cardiac shock and vascular collapse, respectively. Causality of zanamivir was considered in 9 of the cases reporting hepatic events. In two cases, in which the reactions were considered as related to zanamivir, the events resolved. The first was hypernatraemia in a patient with acute renal failure, which resolved following appropriate treatment. The second case was liver functions tests abnormal in a patient with ultrafiltration rate of 10ml/min who was treated with 150mg twice daily. The dose was reduced to 60mg twice daily and a recovery was noted. The data suggest that hepatic dysfunction is an adverse event, which may be related with treatment with IV zanamivir.

The Company has, as of 18 January 2010, circulated a DDL concerning recent reports of hepatic cytolysis in study NAI113678: "*A single arm study to evaluate the safety and tolerability of intravenous zanamivir in the treatment of hospitalised adults, adolescents and paediatric subjects with confirmed influenza infection.*" It was observed that among the 29 subjects, enrolled to date, slight increases in base line liver function tests and low grade changes from baseline (i.e. < 1 to 2 times upper limit of normal range) have been noted in a number of study subjects, whereas substantial changes in liver function tests were noted in four subjects. Data from healthy volunteer studies did, however, not find any significant changes in liver function tests. Of note, no hepatic signals were seen in preclinical studies. It has to be considered that new safety signals may emerge with increased use and in severely ill hospitalised patient populations.

The Company continues to carefully monitor all information as it is received to gain a clearer understanding of the relationship between zanamivir therapy and hepatic events

Summary of pharmacovigilance and post-marketing surveillance

Zanamivir (Relenza) was first approved for marketing as an inhaled powder formulation in Sweden on 09 February 1999. Experience with IV zanamivir administration has been limited to a small number of clinical trials and the ongoing compassionate-use programme; therefore available pharmacovigilance and post-marketing surveillance data are limited to use of the inhaled powder.

Of the spontaneous reports received by GSK for the inhaled powder formulation, abnormal behaviour was the most commonly reported event, followed by rash, dyspnoea, nausea, headache, pyrexia, and dizziness.

The safety profile of zanamivir is under regular review, and the prescribing information for the inhaled formulation has been and will continue to be updated as new or changing information is identified. Following the receipt of post-marketing reports, bronchospasm and dyspnoea have been included as undesirable effects in the core safety information (CSI) for zanamivir, as have allergic-type reactions, including facial and oropharyngeal oedema, and skin and subcutaneous tissue disorders, including rash, urticaria, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. In addition, statements regarding respiratory AEs as well as psychiatric, neurological and behavioural symptoms have been included in the Warnings and Precautions section of the SPC.

Discussion on clinical safety

Safety information on IV zanamivir is limited to data from the phase I studies in healthy volunteers, spontaneous reports from the compassionate use programme, and the ongoing phase II study (NAI113678).

The number of patients in the phase I studies were 120, of whom only 20 have received the recommended dose of 600 mg IV twice daily for 5 days. The drug-related adverse events reported in healthy subjects and subjects with renal impairment included headache (most frequent), light-headedness, back pain, pain in the extremity, abdominal pain, diarrhoea and rash. With the exception of headache and diarrhoea, most of these events were only reported in one subject. An abnormal T-wave was observed in one subject, without any signs of a myocardial infarction. The ECG returned to baseline within one week. Of the laboratory parameters monitored some were increased including bilirubin and blood cell counts. No drug-related SAEs or deaths were reported. One SAE, myocardial infarction, occurred in a subject with a prior history of coronary artery disease. This event was not considered related to zanamivir. It can be concluded that IV zanamivir was well-tolerated in these phase I studies.

As of 15 January 2010 there are 477 patients included in the compassionate use programme who received IV zanamivir. Only SAEs were to be reported and no information on non-serious AEs is available. It is to be noted that due to the nature of the programme the information may be incomplete. Overall 235 AEs/SAEs have been reported in 75 patients and 53 had a fatal outcome (11% of the total population). Of the fatal events, 44 were considered likely to be related to influenza or other concurrent medical conditions. The causality was unknown in five of the remaining nine cases. Three cases were considered related and one was considered possibly related.

Most of the fatal cases were severely ill and had underlying chronic diseases which likely caused the fatal outcome. Hepatic dysfunction, hepatitis and acute hepatic failure were noted in three of the cases including intravascular haemolysis, DIC and multiorgan failure, cardiac shock and vascular collapse. Those were considered related as zanamivir may have contributed to the liver dysfunction. In another case of necrotising pancreatitis together with ARDS and multiorgan failure, zanamivir treatment was also discussed as a possible cause of death. All fatal cases had severe underlying diseases and most of them also complicating bacterial and/or fungal infections when treated for H1N1 influenza

Of the 22 non-fatal SAE cases reported, 15 were considered related/probably related/unknown causality to zanamivir. All events except one were considered serious. The majority of events was improved (n=6) or resolved (n=4), whereas two were unresolved (Stevens-Johnson syndrome, pancytopenia) and three had unknown outcome. The safety profile of zanamivir in a critically ill population with many complicating factors is difficult to evaluate, but based on the few serious events observed during compassionate use, the routine monitoring programme of adverse events should be

targeted to certain organs (liver, heart and lung). In particular, the Company should continue to monitor hepatic events to gain a clearer understanding of its relationship with zanamivir therapy.

The proposed routine monitoring of the patients receiving IV zanamivir including blood count with differential and a basic metabolic profile, liver associated test, urine analysis, assessment of renal function and vital signs (BT, blood pressure, heart rate, respiratory rate and oxygen saturation and baseline ECG and further ECG as medically indicated during therapy), covers all the serious adverse events observed so far.

Study NAI 113678, a phase II safety and PK study is ongoing to provide safety data on IV zanamivir in children, adolescents and adults hospitalised with influenza illness. The design of this study has been discussed with regulatory authorities (FDA, EMA, MPA) and considered acceptable. This study started in November 2009 and its completion will depend on the severity of the H1N1 pandemic during this winter season. The study will recruit approximately 200 subjects. Secondary objectives include virology and clinical measures in order to gain some knowledge of the efficacy of IV zanamivir. As of January 18, 2010, a Company letter reporting on liver related SAEs from study NAI13678 on safety and tolerability of IV zanamivir in treatment of hospitalised patients with H1N1 influenza was circulated to the investigators. In a number of the 29 patients enrolled in this study to date, slight increases in base line liver function tests were noted, while in four patients substantial changes in such tests were described and reported by the investigators as possibly related to IV zanamivir. Subsequent analyses suggest that two events were not drug-related. Through the letter, the study investigators have been alerted about hepatic events, ensuring continued real time investigations on liver events. The Company should continue to careful monitoring of hepatic events to gain a clearer understanding of its relationship with zanamivir therapy.

Based on the post-marketing experience with inhaled zanamivir, the predominant adverse events have been neuropsychiatric disorders, respiratory disorders and skin/subcutaneous tissue disorders, which therefore should be specifically monitored in the EU compassionate use programme.

3.5 Pharmacovigilance

In order to ensure the safety monitoring of the patients, the following conditions have been adopted and are annexed to the CHMP opinion on compassionate use for IV Zanamivir formulation:

Conditions for safety monitoring to be implemented by the company
In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and responsibilities defined in Articles 24(1) of the Regulation (EC) No 726/2004 referring to centrally authorised medicinal products as defined in articles 3(1) and (2) are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. Therefore the company will ensure that these pharmacovigilance rules and responsibilities are fulfilled.

'The company will submit 6-monthly, all safety information on IV Zanamivir in the format of a comprehensive Periodic Safety Update Report (PSUR), in addition to yearly PSURs, unless otherwise specified by the CHMP.

The Relenza PSURs that are being produced for all formulations of Zanamivir will include information on the intravenous formulation and the Compassionate Use programme. In its 18th February 2010 Article 83 opinion, CHMP requested use of a CRF to include capture of non-serious AEs. The Company will submit all information on serious and non-serious adverse events with IV Zanamivir available from the GSK Worldwide Clinical Safety database as an addendum to the PSUR. This addendum will consist of line listings and clinical narratives of cases of all AEs and of cases of areas of special interest, from the reporting period.

The MAH has been providing all available information on serious adverse events with IV Zanamivir available from the GSK Worldwide Clinical Safety Database in the monthly Pandemic Safety Reports (PSR) since the first PSR that covered the period 01 August 2009 to 30 September 2009. The MAH have continued to do so in all subsequent PSRs. Following MPA advice on 11 March 2010 and the conclusions of the Final Pandemic Safety Report Assessment of 17 March 2010, confirming that monthly reporting of PSRs are no longer required given the current status of the H1N1 pandemic, GSK have now submitted the final PSR covering the period 01 – 28 February 2010. No further monthly PSRs will be provided. Future reporting will now be via 6-monthly PSURs, with the next PSUR covering the period from 01 February 2010 to 31 July 2010.'

Conditions for safety monitoring to be implemented by the Member States.
In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and Responsibilities defined in Articles 25 of the Regulation (EC) No 726/2004 referring to centrally authorised medicinal products as defined in articles 3(1) and (2) are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. Therefore the Member State(s) will ensure that these pharmacovigilance rules and responsibilities are fulfilled.

Additionally, in the dossier submitted, the company proposed a "Case Report Form – Zanamivir Aqueous Solution for Compassionate Use in Serious Influenza Illness".
This form, despite not compulsory, is recommended by the CHMP in order to collect data and allow a better assessment of the use of this Zanamivir IV formulation. This form contains:

- Information on underlying diseases / conditions (e.g. ventilation support, influenza details, viral response parameters, pregnancy status)
- Information on dosing
- Concomitant medications
- Information on influenza vaccination
- Non –serious and serious adverse events
- Outcome

3.6 Conclusions

Non-clinical aspects
The non-clinical studies submitted using zanamivir intravenous dosing do not indicate any specific or unique toxicity coupled to the formulation or route of administration. Likewise studies in juvenile rats using the subcutaneous route of administration did not indicate any significant concerns for adverse effects in this population. The studies are deficient in that, in relation to the new dose, low margins of exposure to the expected clinical are evident and the full non-clinical toxicity profile may not have been identified. However, overall reasonable efforts have been made to maximize exposure including use of continuous intravenous infusion. At very high doses renal vacuolation was noted.

The CHMP pointed out that for a general full approval of a new dose, further non-clinical data would be expected to be specifically addressed according to applicable guidelines.

Clinical pharmacology
Limited data is available in adults with or without renal impairment. With the chosen dose in adults, levels in BAL samples seem to be sufficiently high and support the use of 600 mg twice daily in a compassionate use program. Whether higher or lower dose is optimal in adults is currently unknown. There are no pharmacokinetic data available in paediatric patients. The paediatric dose is chosen based on a target of similar exposure as in adults and a model for development of glomerular filtration.

Since zanamivir clearance is dependent on glomerular filtration, dose adjustments based on renal function is recommended. With the current recommendation AUC is predicted to be similar in patients with severe renal impairment they will have lower daily exposure during day 2-5 as compared to patients with normal renal function. Predicted concentrations are still several thousand-fold above IC50. Whether the difference in plasma concentration time profile will have negative impact on efficacy is unknown. For the compassionate use program the proposed doses are considered acceptable. For infants <6 months with renal impairment (in addition to immaturity of the kidneys) no dose recommendations can currently be given

Clinical efficacy
It is agreed that an unmet medical need exists for intravenous formulations of anti-influenza therapies to treat critically ill patients for whom currently available treatments are not suitable. The unmet medical need has been highlighted by the current pandemic situation, but exists also in the seasonal influenza situation. In comparison with the other neuraminidase inhibitors (oseltamivir and peramivir), zanamivir has a unique place, since it is the only available treatment option in patients with oseltamivir-resistant H1N1 influenza infection (H275Y variant).

Clinical experience with IV zanamivir in patients with influenza is currently very limited and data to demonstrate efficacy will be evaluated in future clinical studies. The ongoing study NAI113678 is a phase II safety study, but will also evaluate virologic parameters. A global compassionate use program initiated by the Company has been on-going since May 2009, but no detailed data on the therapeutic response of the patients were presented in the application dossier. The company clarified that at the present time there are only limited data on safety, whereas no data on PK and virology are available. The age distributions of the 477 patients that so far have received IV zanamivir during the pandemic, showed that the majority was adults (n=407) followed by children <13 years of age (n=52). Only one child below 1 year of age has been treated.

The Company has developed a case report form for the ongoing compassionate programme in an attempt to collect targeted outcome and safety data and implemented a structured approach to collect data from treating physicians via timely follow-up emails and phone calls. This approach is endorsed. The CRF was submitted for review as requested in the List of Questions. The CRF needs to be adjusted to ensure that data on viral response parameters, antiviral resistance, concomitant medications and vaccination status will be collected. The company has updated the CRF as requested and included a differentiation between SAES and non-serious AEs A revised CRF was submitted for review and was considered acceptable.

The CHMP considered that the compassionate use of the IV formulation of zanamivir should be restricted to critically ill patients (e.g. impaired conscious level, intubated, or those experiencing other complications of influenza such as encephalitis) in patients with severe, progressive disease on approved influenza antiviral agents or in patients considered unsuitable for treatment with approved influenza antivirals. The company modified the target population as requested.

The CHMP considered it also important that an EU compassionate use program should not impede recruitment to the ongoing safety study NAI113678. The conditions of use have been updated to state that, wherever possible, patients should be recruited into an ongoing IV zanamivir clinical study if appropriate, prior to seeking IV zanamivir via the compassionate use programme.
Furthermore, the Company will ensure that local operating companies are aware of all the active sites participating in the clinical programme in their country in order for them to communicate this information to physicians seeking IV zanamivir via the compassionate use programme if appropriate. In addition, the CHMP considered that the company should report the status of study NAI113678 in all future PSURs to ensure a continuous review of the data.

Conclusions on safety

The limited data generated for IV zanamivir to date have not revealed any clear safety signals. However, the data suggest that hepatic events may be related to IV zanamivir. These events require close monitoring. The safety information is continuously monitored as it is received. The Company has developed a case report form for the ongoing compassionate programme in an attempt to collect targeted outcome and safety data and implemented a structured approach to collect data from treating physicians via timely follow-up emails and phone calls. This approach is endorsed. In addition, the CRF records not only SAE reports, but all AE reports systematically, which should be included in monthly pandemic safety reports. The CRF further includes recording of viral parameters, data on viral resistance as well as information about concomitant medications and vaccination status.

Intravascular haemolysis, liver impairment and cardiovascular adverse events will be closely monitored.

The data generated for IV zanamivir to date have not revealed any concerning safety signals. However, data suggest that hepatic events may be related to the drug and such events must be closely monitored. At the present time data are still very limited and do not allow any firm conclusions to be drawn.

A phase II safety study is ongoing in the target population since Nov 2009. Safety data will be provided on a real-time basis, if considered necessary.

3.7 Risk/benefit assessment and recommendation

Risk-benefit assessment

The A(H1N1)v-pandemic has reached its peak in most of the EU Member states. In spite of its relatively mild clinical presentation, there are severe cases, including previously healthy children and young adults who need intensive care. In such cases, per oral antiviral therapy may not always be feasible. Thus, there is a medical need for parenteral antiviral therapy.

The zanamivir IV development program is ongoing for the treatment of influenza. No efficacy data are yet available from the studies conducted with this formulation.

It should be noted that the efficacy and safety IV zanamivir have not been established in clinical trials and that the clinical development program for zanamivir IV in the treatment of severe influenza in hospitalised patients is ongoing.

Currently, no parenteral influenza antiviral agents are approved for use. An unmet medical need exists for intravenous formulations of anti-influenza therapies to treat severely ill patients for whom currently available treatments are not suitable. The current pandemic highlights the urgent need for such a parenteral agent. In critically ill patients with oseltamivir-resistant viruses, IV zanamivir is the only available therapeutic option. An EU compassionate use programme with defined conditions for distribution and use would facilitate rapid access to the drug and a consistent EU approach with respect to the target population to be treated.

An IV formulation of zanamivir could provide benefits in that rapid and reliable systemic exposure including pulmonary exposure is achieved in patients with poor lung function precluding use of the powder for inhalation. Although the concentrations in the BAL samples is lower after intravenous administration as compared to inhaled zanamivir, the trough concentrations obtained exceeds the *in vitro* IC50 several hundred fold and therefore support the use of 600 mg twice daily in a compassionate use program. The challenge study in healthy volunteers further supports that sufficient exposure is obtained.

The recommended IV zanamivir regimen 600 mg twice daily for 5 days has been documented in 20 subjects in phase 1 trials and is, since May 2009, in use in a compassionate use programme. There have been a number of compassionate use requests in several countries, and as of 15 Jan 2010, 337 patients in Europe have been treated with IV zanamivir. At the present time and on a global base, a total of 477 compassionate use patients have been treated. No data on PK, efficacy and virology are available, except for two published case reports suggesting a successful outcome of IV zanamivir therapy. The low case fatality rate of 11% observed so far in the compassionate use programme may indicate a favourable response rate to IV zanamivir treatment, but depends on the severity of disease in the patients treated. These limited data as well as results from a challenge in healthy volunteers, suggest that IV zanamivir exerts clinically significant antiviral effects against influenza H1N1 virus.

Since renal impairment may be a significant element in critically-ill influenza patients and clearance of zanamivir is highly dependent on glomerular filtration, the Company has provided dosing instructions for health care providers for these situations. With the current recommendation total AUC is predicted to be similar in patients with severe renal impairment they will have lower daily exposure during day 2-5 as compared to patients with normal renal function. Predicted concentrations are still several thousand-fold above IC50. Whether the difference in plasma concentration time profile will have negative impact on efficacy is unknown. For the compassionate use program the proposed doses are considered acceptable.

IV zanamivir has not been administrated to pregnant or nursing mothers in clinical trials. IV zanamivir should be given to pregnant women only when the potential benefit is believed to outweigh the potential risk to the foetus.

There are no pharmacokinetic data available in paediatric patients. Few paediatric patients have received IV zanamivir in the compassionate use program so far. The company has recalculated the doses in paediatric patients based on more recent literature taking maturation of glomerular filtration into account. Simulations provided suggest that similar exposure as in adults will be obtained with the proposed doses. Doses for infants <6 months have also been included however, the suggested dose adjustment for renal impairment is not considered adequate for infants <6 months and should therefore not be included.

Only limited safety data are available on healthy adult subjects in phase I trials and during compassionate use in patients with 2009 H1N1 influenza infection. IV zanamivir was well-tolerated in the phase I studies. In the compassionate use programme only SAEs were to be reported and no information on non-serious AEs is available. SAEs were reported in 75 patients; of these, 53 cases had a fatal outcome. Only four of the deaths were considered related/possibly related to zanamivir therapy. To date no clear safety signals have been identified, except that data suggest that hepatic events may be related to the drug. However, the safety database is very limited and incomplete. The safety information is continuously monitored as it is received. Hepatic events require specific and close monitoring.

Non-clinical data available for zanamivir do not indicate any specific or unique toxicity coupled to the formulation or the intravenous route of administration. Likewise studies in juvenile rats using the subcutaneous route of administration do not indicate any significant concerns for adverse effects in this population. The studies are deficient in that, in relation to the new dose, low margins of exposure to the expected clinical exposure are evident and the full non-clinical toxicity profile may not have been identified. However, overall reasonable efforts have been made to maximize exposure including use of continuous intravenous infusion. At very high doses renal vacuolation was noted. Further, studies on reproduction toxicity have indicated some effects on visceral and skeletal development likely reflecting development delays. The recommendations for use in pregnancy and lactation reflect these concerns. For a standard full approval of a new dose, administration route and formulation the potential for local toxicity would be expected to be specifically addressed in accordance to applicable guidelines as well as the environmental risk related to use of a higher dosage. The potential for cardiovascular effects may also need to be considered further.

Even though there are major limitations to the safety and efficacy data available at this stage of drug development and the data are preliminary in nature, based upon the totality of scientific evidence available, it is reasonable to believe that IV zanamivir may be effective in patients with severe influenza. The safety profile of IV zanamivir appears benign based on the limited clinical and non-clinical data available. No new safety signal has been identified compared to the inhaled version, except that data suggest that liver events may be related to the IV formulation. The benefit-risk profile is considered positive in the context of a compassionate use programme targeted at critically ill patients with influenza infection for whom currently available treatments are not an option.

In the context of the compassionate use of IV Zanamivir for the above-mentioned targeted population and according to the conditions adopted by the CHMP, the CHMP considered that the benefits overweigh the risks.

Recommendation

As part of the Opinion, the CHMP adopted conditions of use, conditions for distribution, patients targeted and conditions for safety monitoring addressed to Member States for IV Zanamivir available for compassionate use.

References

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